UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF WISCONSIN

UNITED STATES OF AMERICA, and THE STATE OF WISCONSIN,
ex rel. DR. TOBY TYLER WATSON,

Plaintiffs,

v. Case No. 11-CV-236-JPS

JENNIFER KING VASSEL,

Defendant.

JAMES B. GOTTSTEIN DECLARATION REGARDING COMPENDIA

I, James B. Gottstein, an attorney for *Relator*, Dr. Toby Tyler Watson, hereby state as follows:

1. The purpose of this Declaration is to put in the record, Food and Drug Administration (FDA) approved "labels" and compendia listings applicable to determining medically accepted indications under 42 U.S.C. § 1396r–8(k)(6), §1396r–8(g)(1)(B)(i) for the prescriptions at issue in this action, as well as to document the status of United States Pharmacopeia-Drug Information (or its successor publications).[1]

2. Exhibit 1 is a true and correct copy of the latest FDA label for Geodon, also known as ziprasidone, revised in July, 2013. See http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020825s047,020919s032,021483s010lbl.pdf

3. Exhibit 2 is a true and correct copy of the DRUGDEX entry for Geodon, downloaded from Westlaw on November 4, 2013.

[1] Various portions of these documents have been highlighted for the Court's convenience in locating the relevant portions.

4. Exhibit 3 is a true and correct copy of the 2013 American Hospital Formulary Service (AHFS) entry for Geodon.

5. Exhibit 4 is a true and correct copy of the latest label for Risperdal, also known as risperidone, with the August 2, 2012, labeling change(s). See, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020272Orig1s065,020588Orig1s053,021444Orig1s041ltr.pdf, and http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020272s065,020588s053,021444s041lbl.pdf

6. Exhibit 5 is a true and correct copy of the DRUGDEX entry for Risperdal in 2010.

7. Exhibit 6 is a true and correct copy of the 2009 AHFS entry for Risperdal.

8. Exhibit 7 is a true and correct copy of the DRUGDEX entry for Risperdal downloaded from Westlaw on November 20, 2013.

9. Exhibit 8 is a true and correct copy of the 2013 AHFS Entry for Risperdal.

10. Exhibit 9 is a true and correct copy of the 1974-2008 Recommendation, Evidence and Efficacy Ratings for DRUGDEX.

11. Exhibit 10 is a true and correct copy of the DRUGDEX Recommendation, Evidence and Efficacy Ratings downloaded from Westlaw on November 20, 2013.

12. It is my belief after considerable investigation that United States Pharmacopeia-Drug Information is no longer published and there is no successor publication(s).

13. I created some confusion about this because I ran across information that DrugPoints had been designated a successor. However, when I followed that up that turned out not to be accurate.

14. Exhibit 11 is a true and correct copy of the Centers for Medicare & Medicaid Services February 12, 2008, decision denying compendia status for DrugPoints for Medicare purposes.

15. Exhibit 12 is a true and correct copy of e-mail correspondence between myself and counsel for the United States to get a definitive answer, which was not forthcoming.

16. In an abundance of caution, however, I am also attaching copies of the current DrugPoints entries for Geodon and Risperdal, as well as DrugPoints' rating system. Therefore,

17. Exhibit 13 is a true and correct copy of the DrugPoints entry for Geodon downloaded from Westlaw on November 4, 2013.

18. Exhibit 14 is a true and correct copy of the DrugPoints entry for Risperdal downloaded from Westlaw on October 9, 2013.

19. Exhibit 15 is a true and correct copy of the DrugPoints strength of Recommendation and Evidence ratings.

20. Dr. King's counsel has asserted that United States Pharmacopeia-Drug Information was still being published, at least as of 2006. I advised him that he probably had United States Pharmacopeia's national formulary and not the statutorily incorporated compendia. I asked for the cover page to verify what it was he had, and he has not responded.

21. Exhibit 15 is a true and correct copy of the e-mail exchange regarding this.

22. Finally, I spoke with Mr. Larson, Dr. King's lead counsel this morning about the final pretrial report and asked him if Dr. King would stipulate that AHFS and DRUGDEX are the only operative compendia at this point. Mr. Larson said Dr. King would not so stipulate because he wasn't sure that was accurate.

I state under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Dated this 25th day of November, 2013.

s/ James B. Gottstein
James B. Gottstein (Alaska Bar # 7811100)
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GEODON safely and effectively. See full prescribing information for GEODON.

GEODON (ziprasidone HCl) capsules
GEODON (ziprasidone mesylate) injection for intramuscular use
Initial U.S. Approval: 2001

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo treatment (5.1)**
- **GEODON is not approved for elderly patients with dementia-related psychosis (5.1)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions: Hyperprolactinemia (5.11)
Metabolic Changes (5.5) 07/2013

----------INDICATIONS AND USAGE----------
GEODON is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the capacity of GEODON to prolong the QT interval and may consider the use of other drugs first (5.2)
GEODON is indicated as an oral formulation for the:
Treatment of schizophrenia. (1.1)
- Adults: Efficacy was established in four 4-6 week trials and one maintenance trial in adult patients with schizophrenia (14.1)

Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder (1.2)
- Adults: Efficacy was established in two 3-week trials in adult patients with manic or mixed episodes. (14.2)

Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. (1.2)
- Adults: Efficacy was established in one maintenance trial in adult patients. (14.2)

GEODON as an intramuscular injection is indicated for the:
Acute treatment of agitation in schizophrenic patients. (1.3)
- Adults: Efficacy was established in two short-term trials in agitated patients with schizophrenia. (1.3)

----------DOSAGE AND ADMINISTRATION----------
Give oral doses with food.
• Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Dose adjustments should occur at intervals of not less than 2 days. Safety and efficacy has been demonstrated in doses up to 100 mg twice daily. The lowest effective dose should be used. (2.1)
• Acute treatment of manic/mixed episodes of bipolar I disorder: Initiate at 40 mg twice daily. Increase to 60 mg or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40-80 mg twice daily. (2.2)
• Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate: Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-80 mg twice daily. (2.2)
• Acute treatment of agitation associated with schizophrenia (intramuscular administration): 10 mg-20 mg up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Doses of 20 mg may be administered every 4 hours. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 20 mg, 40 mg, 60 mg, and 80 mg (3)
- Intramuscular injection: 20 mg/mL single-use vials (3)

----------CONTRAINDICATIONS----------
- Do not use in patients with a known history of QT prolongation (4.1)
- Do not use in patients with recent acute myocardial infarction (4.1)
- Do not use in patients with uncompensated heart failure (4.1)
- Do not use in combination with other drugs that have demonstrated QT prolongation (4.1)
- Do not use in patients with known hypersensitivity to ziprasidone (4.2)

----------WARNINGS AND PRECAUTIONS----------
- *QT Interval Prolongation*: GEODON use should be avoided in patients with bradycardia, hypokalemia or hypomagnesemia, congenital prolongation of the QT interval, or in combination with other drugs that have demonstrated QT prolongation. (5.2)
- *Neuroleptic Malignant Syndrome* (NMS): Potentially fatal symptom complex has been reported with antipsychotic drugs. Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *Tardive Dyskinesia*: May develop acutely or chronically. (5.4)
- *Metabolic Changes*: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
    - *Hyperglycemia and Diabetes Mellitus* (DM): Monitor all patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients with DM risk factors should undergo blood glucose testing before and during treatment. (5.5)
    - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
    - *Weight Gain:* Weight gain has been reported. Monitor weight gain. (5.5)
- *Rash*: Discontinue in patients who develop a rash without an identified cause. (5.6)
- *Orthostatic Hypotension*: Use with caution in patients with known cardiovascular or cerebrovascular disease. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis* has been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue Geodon at the first sign of a decline in WBC in the absence of other causative factors. (5.8)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.9)
- *Potential for Cognitive and Motor impairment*: Patients should use caution when operating machinery. (5.12)
- *Suicide*: Closely supervise high-risk patients. (5.15)

----------ADVERSE REACTIONS----------
Commonly observed adverse reactions (incidence ≥5% and at least twice the incidence for placebo) were**:**
- *Schizophrenia*: Somnolence, respiratory tract infection. (6.1)
- *Manic and Mixed Episodes Associated with Bipolar Disorder*: Somnolence, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthenia, vomiting. (6.1)
- *Intramuscular administration* (≥5% and at least twice the lowest intramuscular ziprasidone group): Headache, nausea, somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Ziprasidone should not be used in combination with other drugs that have demonstrated QT prolongation. (4.1, 7.3)
- The absorption of ziprasidone is increased up to two-fold in the presence of food. (7.9)
- The full prescribing information contains additional drug interactions. (7).

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy*: Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- *Nursing Mothers*: Breast feeding is not recommended. (8.3)
- *Pediatric Use*: Safety and effectiveness for pediatric patients has not been established. (8.4)
- *Renal Impairment:* Intramuscular ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration. (8.10)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [07/2013]

Exhibit 1

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

GEODON is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients. When deciding among the alternative treatments available for the condition needing treatment, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs [*see Warnings and Precautions (5.2)*]. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known [*see Warnings and Precautions (5.2)*]

1.1 Schizophrenia

Geodon is indicated for the treatment of schizophrenia. The efficacy of oral ziprasidone was established in four short-term (4- and 6-week) controlled trials of adult schizophrenic inpatients and in one maintenance trial of stable adult schizophrenic inpatients [*see Clinical Studies (14.1)*].

1.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

Geodon is indicated as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Efficacy was established in two 3-week monotherapy studies in adult patients [*see Clinical Studies (14.2)*].

Geodon is indicated as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder. Efficacy was established in a maintenance trial in adult patients. The efficacy of Geodon as monotherapy for the maintenance treatment of bipolar I disorder has not been systematically evaluated in controlled clinical trials [*see Clinical Studies (14.2)*].

1.3 Acute Treatment of Agitation in Schizophrenia

GEODON intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single day controlled trials of agitated schizophrenic inpatients [*see Clinical Trials (14.1)*]

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension". Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Dose Selection

GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials [*see Clinical Studies (14.1)*].

Maintenance Treatment

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically stable and then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving Geodon [*see Clinical Studies (14.1)*]. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

Acute Treatment of Manic or Mixed Episodes

Dose Selection--Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range 40 mg-80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg [*see Clinical Studies (14.2)*].

Maintenance Treatment (as an adjunct to lithium or valproate)

Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg-80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment [*see Clinical Studies (14.2)*].

2.3 Acute Treatment of Agitation in Schizophrenia

Intramuscular Dosing

The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

Intramuscular Preparation for Administration

GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.4 Dosing in Special Populations

Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. Geodon is not approved for use in children or adolescents.

Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race [*see Use in Specific Populations (8)*].

3 DOSAGE FORMS AND STRENGTHS

GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with “Pfizer” and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON Capsules

Capsule Strength (mg)	Imprint
20	**ZDX 20**
40	**ZDX 40**
60	**ZDX 60**
80	**ZDX 80**

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) [*see Dosage and Administration (2.3)*]. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

4 CONTRAINDICATIONS

4.1 QT Prolongation

Because of ziprasidone’s dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated:

- in patients with a known history of QT prolongation (including congenital long QT syndrome)
- in patients with recent acute myocardial infarction
- in patients with uncompensated heart failure

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:

- dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.
- other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning [*see Warnings and Precautions (5.2)*].

4.2 Hypersensitivity

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON is not approved for the treatment of dementia-related psychosis. *[see Boxed Warning]*

5.2 QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval [*see Contraindications (4.1), Drug Interactions (7.4)]*. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias *[see Contraindications (4)]*.

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg twice daily).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also

increase risk, or increase it in susceptible individuals**.** Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) *[see Adverse Reactions (6.2)]*.

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products *[see Indications and Usage (1)]*.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although fewer patients have been treated with GEODON, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for

symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Pooled data from short-term, placebo-controlled studies in schizophrenia and bipolar disorder are presented in Tables 1-4. Note that for the flexible dose studies in both schizophrenia and bipolar disorder, each subject is categorized as having received either low (20-40 mg BID) or high (60-80 mg BID) dose based on the subject's modal daily dose. In the tables showing categorical changes, the percentages (% column) are calculated as 100x(n/N).

Table 1: Glucose* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Schizophrenia

Mean Random Glucose Change from Baseline mg/dL (N)						
Ziprasidone						Placebo
5 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	
-1.1 (N=45)	+2.4 (N=179)	-0.2 (N=146)	-0.5 (N=119)	-1.7 (N=104)	+4.1 (N=85)	+1.4 (N=260)

*"Random" glucose measurements—fasting/non-fasting status unknown

Table 2: Glucose* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Schizophrenia

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Random Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Ziprasidone	438	77 (17.6%)
		Placebo	169	26 (15.4%)
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Ziprasidone	159	54 (34.0%)
		Placebo	66	22 (33.3%)

*"Random" glucose measurements – fasting/non-fasting status unknown

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random glucose for ziprasidone 20-40 mg BID was -3.4 mg/dL (N=122); for ziprasidone 60-80 mg BID was +1.3 mg/dL (N=10); and for placebo was +0.3 mg/dL (N=71).

Table 3: Glucose* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Bipolar Disorder

Mean Fasting Glucose Change from Baseline mg/dL (N)		
Ziprasidone		Placebo
Low Dose: 20-40 mg BID	High Dose: 60-80 mg BID	
+0.1 (N=206)	+1.6 (N=166)	+1.4 (N=287)

*Fasting

Table 4: Glucose* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone, Monotherapy Trials in Adult Patients with Bipolar Disorder

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Ziprasidone	272	5 (1.8%)
		Placebo	210	2 (1.0%)
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Ziprasidone	79	12 (15.2%)
		Placebo	71	7 (9.9%)

*Fasting

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies in schizophrenia and bipolar disorder are presented in Tables 5-8.

Table 5: Lipid* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Schizophrenia

Mean Lipid Change from Baseline mg/dL (N)							
Laboratory Analyte	Ziprasidone						Placebo
	5 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	
Triglycerides	-12.9 (N=45)	-9.6 (N=181)	-17.3 (N=146)	-0.05 (N=120)	-16.0 (N=104)	+0.8 (N=85)	-18.6 (N=260)
Total Cholesterol	-3.6 (N=45)	-4.4 (N=181)	-8.2 (N=147)	-3.6 (N=120)	-10.0 (N=104)	-3.6 (N=85)	-4.7 (N=261)

*"Random" lipid measurements, fasting/non-fasting status unknown

Table 6: Lipid* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Schizophrenia

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Triglycerides	Increase by ≥50 mg/dL	Ziprasidone	681	232 (34.1%)
		Placebo	260	53 (20.4%)

	Normal to High (<150 mg/dL to ≥200 mg/dL)	Ziprasidone	429	63 (14.7%)
		Placebo	152	12 (7.9%)
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Ziprasidone	92	43 (46.7%)
		Placebo	41	12 (29.3%)
Total Cholesterol	Increase by ≥40 mg/dL	Ziprasidone	682	76 (11.1%)
		Placebo	261	26 (10.0%)
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Ziprasidone	380	15 (3.9%)
		Placebo	145	0 (0.0%)
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Ziprasidone	207	56 (27.1%)
		Placebo	82	22 (26.8%)

***"**Random" lipid measurements, fasting/non-fasting status unknown

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random triglycerides for ziprasidone 20-40 mg BID was +26.3 mg/dL (N=15); for ziprasidone 60-80 mg BID was -39.3 mg/dL (N=10); and for placebo was +12.9 mg/dL (N=9). In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline in random total cholesterol for ziprasidone 20-40 mg BID was +2.5 mg/dL (N=14); for ziprasidone 60-80 mg BID was -19.7 mg/dL (N=10); and for placebo was -28.0 mg/dL (N=9).

Table 7: Lipid* Mean Change from Baseline in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder

Laboratory Analyte	Mean Change from Baseline mg/dL (N)		
	Ziprasidone		Placebo
	Low Dose: 20-40 mg BID	High Dose: 60-80 mg BID	
Fasting Triglycerides	+0.95 (N=206)	-3.5 (N=165)	+8.6 (N=286)
Fasting Total Cholesterol	-2.8 (N=206)	-3.4 (N=165)	-1.6 (N=286)
Fasting LDL Cholesterol	-3.0 (N=201)	-3.1 (N=158)	-1.97 (N=270)
Fasting HDL cholesterol	-0.09 (N=206)	+0.3 (N=165)	-0.9 (N=286)

*Fasting

Table 8: Lipid* Categorical Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	N	n (%)
Fasting Triglycerides	Increase by ≥50 mg/dL	Ziprasidone	371	66 (17.8%)
		Placebo	286	62 (21.7%)
	Normal to High (<150 mg/dL to ≥200 mg/dL)	Ziprasidone	225	15 (6.7%)
		Placebo	179	13 (7.3%)
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Ziprasidone	58	16 (27.6%)
		Placebo	47	14 (29.8%)
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Ziprasidone	371	30 (8.1%)
		Placebo	286	13 (4.5%)
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Ziprasidone	204	5 (2.5%)
		Placebo	151	2 (1.3%)
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Ziprasidone	106	10 (9.4%)
		Placebo	87	15 (17.2%)
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Ziprasidone	359	39 (10.9%)
		Placebo	270	17 (6.3%)
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Ziprasidone	115	0 (0%)
		Placebo	89	1 (1.1%)
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Ziprasidone	193	18 (9.3%)
		Placebo	141	14 (9.9%)
Fasting HDL	Normal (>=40 mg/dL) to Low (<40 mg/dL)	Ziprasidone	283	22 (7.8%)
		Placebo	220	24 (10.9%)

*Fasting

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Monitoring of weight is recommended. Pooled data from short-term, placebo-controlled studies in schizophrenia and bipolar disorder are presented in Tables 9-10.

Table 9: Weight Mean Changes in Short-Term (up to 6 weeks), Placebo-Controlled, Fixed-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Schizophrenia

Ziprasidone						Placebo
5 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	
Mean Weight (kg) Changes from Baseline (N)						
+0.3 (N=40)	+1.0 (N=167)	+1.0 (N=135)	+0.7 (N=109)	+1.1 (N=97)	+0.9 (N=74)	-0.4 (227)
Proportion of Patients with ≥7% Increase in Weight from Baseline (N)						
0.0% (N=40)	9.0% (N=167)	10.4% (N=135)	7.3% (N=109)	15.5% (N=97)	10.8% (N=74)	4.0% (N=227)

In long-term (at least 1 year), placebo-controlled, flexible-dose studies in schizophrenia, the mean change from baseline weight for ziprasidone 20-40 mg BID was -2.3 kg (N=124); for ziprasidone 60-80 mg BID was +2.5 kg (N=10); and for placebo was -2.9 kg (N=72). In the same long-term studies, the proportion of subjects with ≥ 7% increase in weight from baseline for ziprasidone 20-40 mg BID was 5.6% (N=124); for ziprasidone 60-80 mg BID was 20.0% (N=10), and for placebo was 5.6% (N=72). In a long-term (at least 1 year), placebo-controlled, fixed-dose study in schizophrenia, the mean change from baseline weight for ziprasidone 20 mg BID was -2.6 kg (N=72); for ziprasidone 40 mg BID was -3.3 kg (N=69); for ziprasidone 80 mg BID was -2.8 kg (N=70) and for placebo was -3.8 kg (N=70). In the same long-term fixed-dose schizophrenia study, the proportion of subjects with ≥ 7% increase in weight from baseline for ziprasidone 20 mg BID was 5.6% (N=72); for ziprasidone 40 mg BID was 2.9% (N=69); for ziprasidone 80 mg BID was 5.7% (N=70) and for placebo was 2.9% (N=70).

Table 10: Summary of Weight Change in Short-Term (up to 6 weeks), Placebo-Controlled, Flexible-Dose, Oral Ziprasidone Monotherapy Trials in Adult Patients with Bipolar Disorder:

Ziprasidone		Placebo
Low Dose: 20-40 mg BID	**High Dose*: 60-80 mg BID**	
Mean Weight (kg) Changes from Baseline (N)		
+0.4 (N=295)	+0.4 (N=388)	+0.1 (N=451)
Proportion of Patients with ≥ 7% Increase in Weight from Baseline (N)		
2.4% (N=295)	4.4% (N=388)	1.8% (N=451)

* Note that in the High Dose group, there were 2 subjects with modal 200 mg total daily dose and 1 subject with modal 100 mg total daily dose.

Schizophrenia - The proportions of patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of four 4- and 6-week placebo-controlled schizophrenia clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse reaction in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (> 7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

Bipolar Disorder – During a 6-month placebo-controlled bipolar maintenance study in adults with ziprasidone as an adjunct to lithium or valproate, the incidence of clinically significant weight gain (≥ 7% of body weight) during the double-blind period was 5.6% for both ziprasidone and placebo treatment groups who completed the 6 months of observation for relapse. Interpretation of these findings should take into consideration that only patients who adequately tolerated ziprasidone entered the double-blind phase of the study, and there were substantial dropouts during the open label phase.

5.6 Rash

In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

5.7 Orthostatic Hypotension

Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue Geodon at the first sign of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue Geodon and have their WBC followed until recovery.

5.9 Seizures

During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.11 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats *[see Nonclinical Toxicology (13.1)]*. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

5.13 Priapism

One case of priapism was reported in the premarketing database. While the relationship of the reaction to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

5.14 Body Temperature Regulation

Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.15 Suicide

The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

5.16 Patients with concomitant illnesses

Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.6),(8.7)]*

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients *[see Warnings and Precautions (5.2), (5.7)]*

5.17 Laboratory Tests

Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec. *[see Warnings and Precautions (5.2)]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. These patients include: (1) 4331 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. An additional 127 patients with bipolar disorder participated in a long-term maintenance treatment study representing approximately 74.7 patient-years of exposure to ziprasidone. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

Clinical trials for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse reactions during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone

The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Commonly Observed Adverse Reactions in Short Term-Placebo-Controlled Trials

The following adverse reactions were the most commonly observed adverse reactions associated with the use of ziprasidone (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (ziprasidone incidence at least twice that for placebo):

Schizophrenia trials (*see Table 11*)

- Somnolence
- Respiratory Tract Infection

Bipolar trials (*see Table 12)*

- Somnolence

- Extrapyramidal Symptoms which includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.
- Dizziness which includes the adverse reaction terms dizziness and lightheadedness.
- Akathisia
- Abnormal Vision
- Asthenia
- Vomiting

SCHIZOPHRENIA

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone
Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients *[See Warnings and Precautions (5.6)]*.

Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials
Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 11: Treatment-Emergent Adverse Reaction Incidence In Short-Term Oral Placebo-Controlled Trials – Schizophrenia

	Percentage of Patients Reporting Reaction	
Body System/Adverse Reaction	Ziprasidone (N=702)	Placebo (N=273)
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Chest Pain	3	2
Cardiovascular		
Tachycardia	2	1
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Nervous		
Extrapyramidal Symptoms*	14	8
Somnolence	14	7
Akathisia	8	7
Dizziness**	8	6
Respiratory		
Respiratory Tract Infection	8	3
Rhinitis	4	2
Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 5% in schizophrenia trials.
** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Dose Dependency of Adverse Reactions in Short-Term, Fixed-Dose, Placebo-Controlled Trials
An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS) - The incidence of reported EPS (which included the adverse reaction terms extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Dystonia - *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Vital Sign Changes - Ziprasidone is associated with orthostatic hypotension [*see Warnings and Precautions (5.7)*]

ECG Changes - Ziprasidone is associated with an increase in the QTc interval *[see Warnings and Precautions (5.2)]*. In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Ziprasidone
Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported reactions are included except those already listed in Table 11 or elsewhere in labeling, those reaction terms that were so general as to be uninformative, reactions reported only once and that did not have a substantial probability of being acutely life-threatening, reactions that are part of the illness being treated or are otherwise common as background reactions, and reactions considered unlikely to be drug-related. It is important to emphasize that, although the reactions reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions:

Frequent - adverse reactions occurring in at least 1/100 patients (≥1.0% of patients) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing);

Infrequent - adverse reactions occurring in 1/100 to 1/1000 patients (in 0.1-1.0% of patients)

Rare – adverse reactions occurring in fewer than 1/1000 patients (<0.1% of patients).

Body as a Whole
Frequent abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident

Cardiovascular System
Frequent tachycardia, hypertension, postural hypotension

Infrequent bradycardia, angina pectoris, atrial fibrillation

Rare first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis

Digestive System
Frequent anorexia, vomiting

Infrequent rectal hemorrhage, dysphagia, tongue edema

Rare gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena

Endocrine
Rare hypothyroidism, hyperthyroidism, thyroiditis

Hemic and Lymphatic System
Infrequent anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy

Rare thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia

Metabolic and Nutritional Disorders
Infrequent thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia

Rare BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemicreaction, hypomagnesemia, ketosis, respiratory alkalosis

Musculoskeletal System
Frequent myalgia

Infrequent tenosynovitis

Rare myopathy

Nervous System
Frequent agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy

Infrequent paralysis

Rare myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus

Respiratory System
Frequent dyspnea

Infrequent pneumonia, epistaxis

Rare hemoptysis, laryngismus

Skin and Appendages
Infrequent maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash

Special Senses
Frequent fungal dermatitis

Infrequent conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia

Rare eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis

Urogenital System
Infrequent impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria

Rare gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage

BIPOLAR DISORDER

Acute Treatment of Manic or Mixed Episodes

Adverse Reactions Associated with Discontinuation of Treatment in Short Term, Placebo-Controlled Trials
Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse reactions.

Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials
Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 12: Treatment-Emergent Adverse Reactions Incidence In Short-Term Oral Placebo-Controlled Trials – Manic and Mixed Episodes Associated with Bipolar Disorder

	Percentage of Patients Reporting Reaction	
Body System/Adverse Reaction	Ziprasidone (N=279)	Placebo (N=136)
Body as a Whole		
Headache	18	17
Asthenia	6	2
Accidental Injury	4	1
Cardiovascular		
Hypertension	3	2
Digestive		
Nausea	10	7
Diarrhea	5	4
Dry Mouth	5	4
Vomiting	5	2
Increased Salivation	4	0
Tongue Edema	3	1
Dysphagia	2	0
Musculoskeletal		
Myalgia	2	0
Nervous		
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Anxiety	5	4
Hypesthesia	2	1
Speech Disorder	2	0
Respiratory		
Pharyngitis	3	1
Dyspnea	2	1
Skin and Appendages		
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	6	3

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.

** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of this demographic factor.

INTRAMUSCULAR ZIPRASIDONE

Adverse Reactions Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone
Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

Table 13: Treatment-Emergent Adverse Reaction Incidence In Short-Term Fixed-Dose Intramuscular Trials

	Percentage of Patients Reporting Reaction		
Body System/Adverse Reaction	Ziprasidone 2 mg (N=92)	Ziprasidone 10 mg (N=63)	Ziprasidone 20 mg (N=41)
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0
Somnolence	8	8	20
Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	1	0	0

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of GEODON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following : *Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors), *[See Warnings and Precautions (5.2)]*; *Digestive System Disorders:* Swollen Tongue; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Nervous System Disorders:* Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Skin and*

subcutaneous Tissue Disorders: Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope.

7 DRUG INTERACTIONS

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

7.1 Metabolic Pathway

Approximately two-thirds of ziprasidone is metabolized via a combination of chemical reduction by glutathione and enzymatic reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase. Less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation.

7.2 In Vitro Studies

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. There is little potential for drug interactions with ziprasidone due to displacement *[See Clinical Pharmacology (12.3)]*.

7.3 Pharmacodynamic Interactions

Ziprasidone should not be used with any drug that prolongs the QT interval *[See Contraindications (4.1)]*.

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.

Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.

Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

7.4 Pharmacokinetic Interactions

- Carbamazepine

Carbamazepine is an inducer of CYP3A4; administration of 200 mg twice daily for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole

Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

- Cimetidine

Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

- Antacid

The co-administration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

7.5 Lithium

Ziprasidone at a dose of 40 mg twice daily administered concomitantly with lithium at a dose of 450 mg twice daily for 7 days did not affect the steady-state level or renal clearance of lithium. Ziprasidone dosed adjunctively to lithium in a maintenance trial of bipolar patients did not affect mean therapeutic lithium levels.

7.6 Oral Contraceptives

In vivo studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone at a dose of 20 mg twice daily did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

7.7 Dextromethorphan

Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

7.8 Valproate

A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. Ziprasidone dosed adjunctively to valproate in a maintenance trial of bipolar patients did not affect mean therapeutic valproate levels.

7.9 Other Concomitant Drug Therapy

Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

7.10 Food Interaction

The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Geodon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of ziprasidone on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed.

8.4 Pediatric Use

The safety and effectiveness of ziprasidone in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

8.6 Renal Impairment

Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg twice daily dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function *[see Clinical Pharmacology (12)]*.

8.7 Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in $AUC_{0\text{-}12}$ of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

8.8 Age and Gender Effects

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

8.9 Smoking

Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3,240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Adverse reactions reported with ziprasidone overdose included extrapyramidal symptoms, somnolence, tremor, and anxiety. *[see Adverse Reactions (6.2)]*

10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established, and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

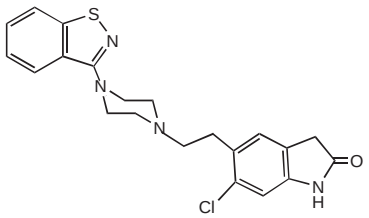
Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

GEODON is available as capsules (ziprasidone hydrochloride) for oral administration and as an injection (ziprasidone mesylate) for intramuscular use only. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$ and its molecular weight is 563.09.

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[See Dosage and Administration (2.3)]*. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

12.2 Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i s of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H_1 receptor (K_i=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM). Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

12.3 Pharmacokinetics

Oral Pharmacokinetics

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyldihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the reduction reaction is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics

Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{½}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.11)]*.

Mutagenesis

Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility

Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one maintenance trial. All trials were in adult inpatients, most of whom met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials in schizophrenia follow:

- In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg twice daily) with placebo, only the 60 mg dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.
- In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg twice daily) with placebo, both dose groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg twice daily had a numerically greater effect than 40 mg twice daily, the difference was not statistically significant.
- In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg twice daily) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg twice daily dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg twice daily to 100 mg twice daily dose range.
- In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg twice daily), none of the dose groups was statistically superior to placebo on any outcome of interest.
- A study was conducted in stable chronic or subchronic (CGI-S $\leq$5 at baseline) schizophrenic inpatients (n=294) who had been hospitalized for not less than two months. After a 3-day single-blind placebo run-in, subjects were randomized to one of 3 fixed doses of ziprasidone (20 mg, 40 mg, or 80 mg twice daily) or placebo and observed for relapse. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of $\geq$6 (much worse or very much worse) and/or scores $\geq$6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in time to relapse, with no significant difference between the different dose groups. There were insufficient data to examine population subsets based on age and race. Examination of population subsets based on gender did not reveal any differential responsiveness.

14.2 Bipolar I Disorder (Acute Mixed or Manic Episodes and Maintenance Treatment as an Adjunct to Lithium or Valproate)

Acute Manic and Mixed Episodes Associated with Bipolar I Disorder

The efficacy of ziprasidone was established in 2 placebo-controlled, double-blind, 3-week monotherapy studies in patients meeting DSM-IV criteria for bipolar I disorder, manic or mixed episode with or without psychotic features. Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in adult bipolar I disorder, manic/mixed episode follow**:** in a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg. In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone was 40 mg twice daily on Day 1. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 112 mg.

Maintenance Therapy

The efficacy of ziprasidone as adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder was established in a placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder. The trial included patients whose most recent episode was manic or mixed, with or without psychotic features. In the open-label phase, patients were required to be stabilized on ziprasidone plus lithium or valproic acid for at least 8 weeks in order to be randomized. In the double-blind randomized phase, patients continued treatment with lithium or valproic acid and were randomized to receive either ziprasidone (administered twice daily totaling 80 mg to 160 mg per day) or placebo. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase. The primary endpoint in this study was time to recurrence of a mood episode (manic, mixed or depressed episode) requiring intervention, which was defined as any of the following: discontinuation due to a mood episode, clinical intervention for a mood episode (e.g., initiation of medication or hospitalization), or Mania Rating Scale score $\geq$ 18 or a MADRS score $\geq$18 (on 2 consecutive assessments no more than 10 days apart). A total of 584 subjects were treated in the open-label stabilization period. In the double-blind randomization period, 127 subjects were treated with ziprasidone, and 112 subjects were treated with placebo. Ziprasidone was superior to placebo in increasing the time to recurrence of a mood episode. The types of relapse events observed included depressive, manic, and mixed episodes. Depressive, manic, and mixed episodes accounted for 53%, 34%, and 13%, respectively, of the total number of relapse events in the study.

14.3 Acute Treatment of Agitation in Schizophrenia

The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be "acutely agitated" and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with

scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in premarketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:

(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

16 HOW SUPPLIED/STORAGE AND HANDLING

GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with "ZDX" and the dosage strength. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON Capsules			
Package Configuration	Capsule Strength (mg)	NDC Code	Imprint
Bottles of 60	20	0049-0052-60	ZDX 20
Bottles of 60	40	0049-0054-60	ZDX 40
Bottles of 60	60	0049-0056-60	ZDX 60
Bottles of 60	80	0049-0058-60	ZDX 80
Unit dose/80	20	0049-0052-80	ZDX 20
Unit dose/80	40	0049-0054-80	ZDX 40
Unit dose/80	60	0049-0056-80	ZDX 60
Unit dose/80	80	0049-0058-80	ZDX 80

GEODON Capsules should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[see Dosage and Administration (2.3)]*. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

GEODON for Injection		
Package	Concentration	NDC Code
Single-use Vials (carton of 10 vials)	20 mg/mL	NDC-0049-3920-83

GEODON for Injection should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature] in dry form. Protect from light. Following reconstitution, GEODON for Injection can be stored, when protected from light, for up to 24 hours at 15°-30°C (59°-86°F) or up to 7 days refrigerated, 2°-8°C (36°-46°F).

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling (17.3)*.

Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

17.1 Administration with Food

Patients should be instructed to take GEODON Capsules with food for optimal absorption. The absorption of ziprasidone is increased up to two-fold in the presence of food *[see Drug Interactions (7.8) and Clinical Pharmacology (12.3)]*.

17.2 QTc Prolongation

Patients should be advised to inform their health care providers of the following: History of QT prolongation; recent acute myocardial infarction; uncompensated heart failure; prescription of other drugs that have demonstrated QT prolongation; risk for significant electrolyte abnormalities; and history of cardiac arrhythmia *[see Contraindications (4.1) and Warnings and Precautions (5.2)]*.

Patients should be instructed to report the onset of any conditions that put them at risk for significant electrolyte disturbances, hypokalemia in particular, including but not limited to the initiation of diuretic therapy or prolonged diarrhea. In addition, patients should be instructed to report symptoms such as dizziness, palpitations, or syncope to the prescriber *[see Warnings and Precautions (5.2)]*.

17.3 FDA-Approved Patient Labeling

LAB-0273-19. 1
Revised: -July 2013

PATIENT SUMMARY OF INFORMATION ABOUT

GEODON® Capsules

(ziprasidone HCl)

Information for patients taking GEODON or their caregivers

This summary contains important information about GEODON. It is not meant to take the place of your doctor's instructions. Read this information carefully before you take GEODON. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about GEODON.

What Is GEODON?

GEODON is a type of prescription medicine called a psychotropic, also known as an atypical antipsychotic. GEODON can be used to treat symptoms of schizophrenia and acute manic or mixed episodes associated with bipolar disorder. GEODON can also be used as maintenance treatment of bipolar disorder when added to lithium or valproate.

Who Should Take GEODON?

Only your doctor can know if GEODON is right for you. GEODON may be prescribed for you if you have schizophrenia or bipolar disorder.

Symptoms of schizophrenia may include:

- hearing voices, seeing things, or sensing things that are not there (hallucinations)
- beliefs that are not true (delusions)
- unusual suspiciousness (paranoia)
- becoming withdrawn from family and friends

Symptoms of manic or mixed episodes of bipolar disorder may include:

- extremely high or irritable mood
- increased energy, activity, and restlessness
- racing thoughts or talking very fast
- easily distracted
- little need for sleep

If you show a response to GEODON, your symptoms may improve. If you continue to take GEODON there is less chance of your symptoms returning. Do not stop taking the capsules even when you feel better without first discussing it with your doctor.

It is also important to remember that GEODON capsules should be taken with food.

What is the most important safety information I should know about GEODON?

GEODON is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with a diagnosis of psychosis related to dementia treated with antipsychotics are at an increased risk of death when compared to patients who are treated with placebo (a sugar pill).

GEODON is an effective drug to treat the symptoms of schizophrenia and the manic or mixed episodes of bipolar disorder. However, one potential side effect is that it may change the way the electrical current in your heart works more than some other drugs. The change is small and it is not known whether this will be harmful, but some other drugs that cause this kind of change have in rare cases caused dangerous heart rhythm abnormalities**.** Because of this, GEODON should be used only after your doctor has considered this risk for GEODON against the risks and benefits of other medications available for treating schizophrenia or bipolar manic and mixed episodes.

Your risk of dangerous changes in heart rhythm can be increased if you are taking certain other medicines and if you already have certain abnormal heart conditions. Therefore, it is important to tell your doctor about any other medicines that you

take, including non-prescription medicines, supplements, and herbal medicines. You must also tell your doctor about any heart problems you have or have had.

Who should NOT take GEODON?

Elderly patients with a diagnosis of psychosis related to dementia. GEODON is not approved for the treatment of these patients.

Anything that can increase the chance of a heart rhythm abnormality should be avoided. Therefore, do not take GEODON if:

- You have certain heart diseases, for example, long QT syndrome, a recent heart attack, severe heart failure, or certain irregularities of heart rhythm (discuss the specifics with your doctor)

- You are currently taking medications that should not be taken in combination with ziprasidone, for example, dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.

What To Tell Your Doctor Before You Start GEODON

Only your doctor can decide if GEODON is right for you. Before you start GEODON, be sure to tell your doctor if you:

- have had any problem with the way your heart beats or any heart related illness or disease
- any family history of heart disease, including recent heart attack
- have had any problem with fainting or dizziness
- are taking or have recently taken any prescription medicines
- are taking any over-the-counter medicines you can buy without a prescription, including natural/herbal remedies
- have had any problems with your liver
- are pregnant, might be pregnant, or plan to get pregnant
- are breast feeding
- are allergic to any medicines
- have ever had an allergic reaction to ziprasidone or any of the other ingredients of GEODON capsules. Ask your doctor or pharmacist for a list of these ingredients
- have low levels of potassium or magnesium in your blood

Your doctor may want you to get additional laboratory tests to see if GEODON is an appropriate treatment for you.

GEODON And Other Medicines

There are some medications that may be unsafe to use when taking GEODON, and there are some medicines that can affect how well GEODON works. While you are on GEODON, check with your doctor before starting any new prescription or over-the-counter medications, including natural/herbal remedies.

How To Take GEODON

- Take GEODON only as directed by your doctor.
- Swallow the capsules whole.
- Take GEODON capsules with food.
- It is best to take GEODON at the same time each day.
- GEODON may take a few weeks to work. It is important to be patient.
- Do not change your dose or stop taking your medicine without your doctor's approval.
- Remember to keep taking your capsules, even when you feel better.

Possible Side Effects

Because these problems could mean you're having a heart rhythm abnormality, contact your doctor ***IMMEDIATELY*** if you:

- Faint or lose consciousness
- Feel a change in the way that your heart beats (palpitations)

Common side effects of GEODON include the following and should also be discussed with your doctor if they occur:

- Feeling unusually tired or sleepy
- Nausea or upset stomach
- Constipation
- Dizziness
- Restlessness
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea
- Rash
- Increased cough / runny nose

If you develop any side effects that concern you, talk with your doctor. It is particularly important to tell your doctor if you have diarrhea, vomiting, or another illness that can cause you to lose fluids. Your doctor may want to check your blood to make sure that you have the right amount of important salts after such illnesses.

For a list of all side effects that have been reported, ask your doctor or pharmacist for the GEODON Professional Package Insert.

What To Do For An Overdose

In case of an overdose, call your doctor or poison control center right away or go to the nearest emergency room.

Other Important Safety Information

A serious condition called neuroleptic malignant syndrome (NMS) can occur with all antipsychotic medications including GEODON. Signs of NMS include very high fever, rigid muscles, shaking, confusion, sweating, or increased heart rate and blood pressure. NMS is a rare but serious side effect that could be fatal. Therefore, tell your doctor if you experience any of these signs.

Adverse reactions related to high blood sugar (hyperglycemia), sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these reactions. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Dizziness caused by a drop in your blood pressure may occur with GEODON, especially when you first start taking this medication or when the dose is increased. If this happens, be careful not to stand up too quickly, and talk to your doctor about the problem.

Before taking GEODON, tell your doctor if you are pregnant or plan on becoming pregnant. It is advised that you don't breast feed an infant if you are taking GEODON.

Because GEODON can cause sleepiness, be careful when operating machinery or driving a motor vehicle.

Since medications of the same drug class as GEODON may interfere with the ability of the body to adjust to heat, it is best to avoid situations involving high temperature or humidity.

It is best to avoid consuming alcoholic beverages while taking GEODON.

Call your doctor ***immediately*** if you take more than the amount of GEODON prescribed by your doctor.

GEODON has not been shown to be safe or effective in the treatment of children and teenagers under the age of 18 years old.

Keep GEODON and all medicines out of the reach of children.

How To Store GEODON

Store GEODON capsules at room temperature (59°-86°F or 15°-30°C).

For More Information About GEODON

This sheet is only a summary. GEODON is a prescription medicine and only your doctor can decide if it is right for you. If you have any questions or want more information about GEODON, talk with your doctor or pharmacist. You can also visit www.geodon.com.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

LAB-0272-5.0
Revised: October 2012

DRUGDEX-EV 2517

MICROMEDEX
DRUGDEX® Evaluations

Database updated September 2011

ZIPRASIDONE

0.0 Overview

1) Class
a) This drug is a member of the following class(es):
Antipsychotic
Benzisothiazoyl
2) Dosing Information
a) Ziprasidone Hydrochloride
1) Adult
a) Bipolar I disorder, Acute manic or mixed episodes, monotherapy
1) day 1, 40 mg twice daily with food; day 2, 60 or 80 mg twice daily; then adjust to 40 to 80 mg twice daily (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Bipolar I disorder, to lithium or valproate; Adjunct
1) 40 mg to 80 mg twice a day as an adjunct to lithium or valproate(Prod Info GEODON oral capsules, IM injection, 2009)
c) Schizophrenia
1) initial, 20 mg ORALLY twice a day with food; may increase dosage every 2 days up to 80 mg twice a day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
2) maintenance, 20 to 80 mg ORALLY twice a day (MAX recommended dose is 80 mg twice a day); to ensure use of the lowest effective dose, observe for improvement for several weeks before upward dosage adjustment (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
2) Pediatric

Exhibit 2

a) safety and effectiveness in pediatric patients have not been established (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

b) Ziprasidone Mesylate

1) Adult

a) Agitation, acute - Schizophrenia

1) 10 mg IM every 2 hr (MAX dose 40 mg/day) OR 20 mg IM every 4 hr (MAX dose 40 mg/day); oral ziprasidone should replace IM administration as soon as possible; IM administration for more than 3 consecutive days has not been studied (Prod Info GEODON oral capsules, IM injection, 2009)

2) Pediatric

a) safety and effectiveness in pediatric patients have not been established (Prod Info GEODON oral capsules, IM injection, 2009)

3) Contraindications

a) Ziprasidone Hydrochloride

1) concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

2) heart failure, uncompensated (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

3) hypersensitivity to ziprasidone (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

4) myocardial infarction, acute and recent (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

5) QT prolongation, including congenital long QT syndrome (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

b) Ziprasidone Mesylate

1) concomitant use with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, Class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON oral capsules, IM injection, 2009)

2) heart failure, uncompensated (Prod Info GEODON oral capsules, IM injection, 2009)

3) hypersensitivity to ziprasidone (Prod Info GEODON oral capsules, IM injection, 2009)

4) myocardial infarction, acute and recent (Prod Info GEODON oral capsules, IM injection, 2009)

5) QT prolongation, including congenital long QT syndrome (Prod Info GEODON oral capsules, IM injection, 2009)

4) Serious Adverse Effects

a) Ziprasidone Hydrochloride

1) Bone marrow depression

2) Diabetes mellitus

3) Dysphagia

4) Hyperglycemia

5) Neuroleptic malignant syndrome
6) Priapism
7) Prolonged QT interval
8) Seizure
9) Syncope
10) Tardive dyskinesia
11) Torsades de pointes

b) Ziprasidone Mesylate
1) Bone marrow depression
2) Diabetes mellitus
3) Dysphagia
4) Hyperglycemia
5) Neuroleptic malignant syndrome
6) Priapism
7) Prolonged QT interval
8) Seizure
9) Syncope
10) Tardive dyskinesia
11) Torsades de pointes

5) Clinical Applications
a) Ziprasidone Hydrochloride
1) FDA Approved Indications
a) Bipolar I disorder, Acute manic or mixed episodes, monotherapy
b) Bipolar I disorder, to lithium or valproate; Adjunct
c) Schizophrenia

b) Ziprasidone Mesylate
1) FDA Approved Indications
a) Agitation, acute - Schizophrenia

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Ziprasidone

Ziprasidone HCl
Ziprasidone Hydrochloride
Ziprasidone Mesylate

C) Physicochemical Properties

1) Molecular Weight

a) 467.42(Prod Info Geodon™, 2001)

1.2 Storage and Stability

A) Ziprasidone Hydrochloride

1) Preparation

a) Oral route

1) Oral ziprasidone hydrochloride capsules and suspension should be taken with food (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

B) Ziprasidone Mesylate

1) Preparation

a) Intramuscular route

1) Preparation

a) Reconstitute 20 milligram (mg) ziprasidone mesylate vials with 1.2 milliliters (mL) of sterile water for injection. Shake vigorously until all drug is dissolved. Reconstituted solution contains 20 mg/mL, and any unused portion should be discarded (Prod Info GEODON oral capsules, IM injection, 2009).

2) Administration

a) Ziprasidone mesylate injection should only be administered by intramuscular injection (IM) (Prod Info GEODON oral capsules, IM injection, 2009).

C) Ziprasidone Hydrochloride

1) Oral route

a) Capsule

1) Ziprasidone hydrochloride capsules should be stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

D) Ziprasidone Mesylate

1) Intramuscular route

a) Powder for Solution

1) Ziprasidone mesylate for injection, in dry form, should be protected from light and stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit). The reconstituted solution is stable for up to 7 days if refrigerated (2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit)) or for up to 24 hours between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Ziprasidone Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Bipolar I disorder, Acute manic or mixed episodes, monotherapy

1) For bipolar mania, the recommended initial dose is 40 milligrams twice daily with food. On the second day of treatment, the dose should be increased to 60 or 80 milligrams twice daily and thereafter adjusted according to tolerance and efficacy within the range of 40 to 80 milligrams twice daily (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

1.3.1.A.1.b Bipolar I disorder, to lithium or valproate; Adjunct

1) For maintenance of bipolar I with adjunctive lithium or valproate, continue the dose of ziprasidone on which the patient was initially stabilized in the range of 40 mg to 80 mg twice a day (Prod Info GEODON oral capsules, IM injection, 2009).

1.3.1.A.1.c Schizophrenia

1) For schizophrenia the initial daily dose is 20 milligrams (mg) twice daily with food. In some patients daily dosage may be adjusted up to 80 mg twice daily. Adjustments, if indicated, should occur at intervals of not less than 2 days. Efficacy in short-term clinical trials occurred with dosages between 20 to 100 mg twice daily. Initial dosages above 80 mg twice daily are not recommended and the safety of dosages above 100 mg twice daily have not been evaluated. To ensure the lowest effective dose, patients should be observed for improvement for several weeks before upward dosage adjustment (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

1.3.1.B Ziprasidone Mesylate

1.3.1.B.1 Intramuscular route

1.3.1.B.1.a Agitation, acute - Schizophrenia

1) For acute agitation in schizophrenia the recommended intramuscular dose of ziprasidone mesylate is 10 to 20 milligrams (mg) as needed to a maximum daily dose of 40 mg. The 10 mg dose may be given every 2 hours and 20 mg dose may be given every 4 hours (maximum dose=40 mg/day). Intramuscular dosing of ziprasidone for more than 3 days has not been studied. If long-term therapy is indicated, oral ziprasidone should replace intramuscular administration as soon as possible (Prod Info GEODON oral capsules, IM injection, 2009).

2) Ziprasidone 10 milligrams (mg) intramuscularly (IM) produced a rapid reduction in symptoms of acute agitation and was significantly more effective (p less than 0.01) compared to a 2 mg IM dose up to 4 hours after the first injection (Lesem et al, 2001).

1.3.2 Dosage in Renal Failure

A) Ziprasidone Hydrochloride

1) No dosage adjustment should be necessary for mild-to-moderate renal impairment. No clinically significant effect on oral ziprasidone pharmacokinetics was found in these patients (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009; Aweeka et al, 2000).

B) Ziprasidone Mesylate

1) Ziprasidone mesylate for injection should be used with caution in patients with impaired renal function as the injection contains a cyclodextrin sodium excipient that is eliminated by renal filtration (Prod Info GEODON oral capsules, IM injection, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) Ziprasidone Hydrochloride

1) No dosage adjustment is necessary for mild-to-moderate hepatic impairment (chronic and stable, Child-Pugh classification A or B); the pharmacokinetics of ziprasidone were not significantly different in subjects with mild-to-moderate liver disease (Everson et al, 2000).

1.3.4 Dosage in Geriatric Patients

A) Ziprasidone Hydrochloride

1) No dosage adjustment is thought to be necessary for elderly patients; no clinically significant difference in ziprasidone pharmacokinetics was found between healthy young and elderly volunteers (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009; Wilner et al, 2000).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Ziprasidone Hydrochloride

1) The safety and effectiveness in pediatric patients have not been established (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

2.0 Pharmacokinetics

2.2 Drug Concentration Levels

A) Ziprasidone Hydrochloride
1) Time to Peak Concentration
a) Oral: 6 to 8 hours (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)
1) The ziprasidone Cmax is achieved in approximately 6 to 8 hours after oral administration (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
2) Area Under the Curve
a) Oral, multiple-dose, 20 to 80 mg: dose-proportional (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)
1) Following multiple-dose administration within the recommended clinical dosage range, ziprasidone accumulation is predictable and dose-proportional. Steady-state concentrations are achieved within 1 to 3 days (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010) and steady-state pharmacokinetics of ziprasidone did not differ between genders (Caccia, 2000).
b) Oral, multiple-dose, cirrhosis, 20 mg: increased 13% and 34% (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)
1) In subjects with clinically significant cirrhosis who received ziprasidone 20 mg twice daily for 5 days (n=13), the AUC (0 to 12 hours) increased 13% and 34% in subjects with Child-Pugh class A and B cirrhosis, respectively compared with matched controls (n=14) (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
B) Ziprasidone Mesylate
1) Time to Peak Concentration
a) IM: 60 minutes (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)
1) Following a single IM injection of ziprasidone, the Cmax occurred in approximately 60 minutes or less (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2.3 ADME

2.3.1 Absorption

A) Ziprasidone Hydrochloride
1) Bioavailability
a) Oral: 60% (in fed state) (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)
1) Ziprasidone is considered well absorbed. Following a dose of ziprasidone 20 mg in the fed state, the absolute bioavailability was approximately 60% (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
2) Effects of Food
a) absorption increased up to 2-fold with high-calorie foods (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010; Lincoln et al, 2010)

1) In the presence of food, ziprasidone absorption is increased up to 2-fold (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010). In the fed state, following multiple doses of ziprasidone 10 to 120 mg/day, the AUC was 109.8 to 1027.9 nanograms x hr/mL (Miceli et al, 2000a).

b) Ziprasidone exposure was greatest with administration after a high-calorie meal regardless of fat content in a randomized, 6-way crossover study in patients with psychiatric disorders. Patients with various psychiatric disorders (schizophrenia, schizoaffective disorder, bipolar disorder and psychotic disorder not otherwise specified; n=16; age range, 18 to 65 years; 69% male) received ziprasidone 80 mg twice daily for more than 14 days under the following meal conditions: fasting, low calorie (250 kcal)/low fat, low calorie/high fat, medium calorie (500 kcal)/high fat, high calorie (1000 kcal)/low fat, and high calorie/high fat. Ziprasidone exposure was greatest when administered after a high-calorie meal regardless of fat content (tables). Additionally, mean trough concentrations were greater than 70 nanograms/mL following administration with either a medium calorie/high fat, high calorie/low fat, or high calorie/high fat meal, indicating sufficient concentration for clinical response prior to next dose. The trough concentrations under the other fed states fell below 70 nanograms/mL. Based on the US Food and Drug Administration requirements for bioequivalence, ziprasidone exposure was bioequivalent among fasting, low calorie/low fat, and low calorie/high fat conditions. Similarly, ziprasidone exposure was bioequivalent among the medium calorie/high fat, high calorie/low fat, and high calorie/high fat conditions; however, under these 3 meal conditions, ziprasidone exposure was almost twice the exposure compared with the fasting state (Lincoln et al, 2010):

Ziprasidone versus fasting condition ratio*
Low cal/ low fat
Low cal/ high fat
Med cal/ high fat
High cal/ low fat
High cal/ high fat
AUC
112%
122%
169%
181%
172%
Cmax
119%
134%
179%
183%
186%
Ctrough
100%
106%
177%
168%
190%

*following administration of morning dose

KEY: Med = medium; cal = calorie

c) Results of administration of ziprasidone 20 mg after either an 8 hour fast, immediately after a standard meal (50% to 60% calorie content fat), or 2 hours after a standard meal showed a 69% and 67% higher AUC and Cmax, respectively with immediate administration after a standard meal compared with the fasting state in a 3-way crossover study in healthy male volunteers (n=9; age range, 18 to 45 years). Administration 2 hours after a meal also led to greater exposure than under fasting conditions, but not to the same extent as with the high-fat/high-calorie meal (Lincoln et al, 2010).

d) Administration of a single dose of ziprasidone 20 mg, 40 mg, and 80 mg, in ascending order, after an 8 hour fast, then immediately after a standard meal (50% to 60% calorie content fat) showed ziprasidone exposure increased in a dose-proportional manner when administered immediately after a high-fat, high-calorie meal compared with the fasting state in a 6-way crossover study in healthy male volunteers (n=8; age range, 19 to 31 years). In the 20 mg, 40 mg, and 80 mg groups, compared with fasting, the AUC increased by 48%, 87%, and 101%, respective; the Cmax increased by 9%, 63%, and 97%, respectively (Lincoln et al, 2010).

e) Administration of ziprasidone 40 mg twice daily for 3 days with either a high-fat (60%) or moderate-fat (30%) meal, or after an 8-hour fast revealed the ziprasidone AUC was 104% and 79% greater with a high-fat and a moderate-fat meal, respectively compared with the fasting state in a randomized, 3-way crossover study in health volunteers (n=14; age range 18 to 45 years). Similarly, the Cmax was 84% and 98% greater, respectively compared with the fasting state. However, comparison of AUC following a high-fat meal and a moderate-fat meal indicated bioequivalent ziprasidone exposure regardless of fat content of the meal (Lincoln et al, 2010).

B) Ziprasidone Mesylate

1) Bioavailability

a) IM: 100% (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The bioavailability of ziprasidone following IM administration is 100% (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

2.3.2 Distribution

A) Distribution Sites

1) Ziprasidone Hydrochloride

a) Protein Binding

1) Albumin and alpha-1-acid glycoprotein: greater than 99% (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

a) Protein binding of ziprasidone, primarily to albumin and alpha-1-acid glycoprotein is greater than 99%. In an in vitro study, the protein binding of ziprasidone was not altered by other highly protein bound agents (warfarin, propranolol). Additionally, ziprasidone did not alter the protein binding of warfarin or propranolol in human plasma (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) Protein Binding

1) Albumin and alpha-1-acid glycoprotein: greater than 99% (Prod Info GEODON(R) oral capsules,

intramuscular injection, 2010)

a) Protein binding of ziprasidone, primarily to albumin and alpha-1-acid glycoprotein is greater than 99%. In an in vitro study, the protein binding of ziprasidone was not altered by other highly protein bound agents (warfarin, propranolol). Additionally, ziprasidone did not alter the protein binding of warfarin or propranolol in human plasma (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

B) Distribution Kinetics

1) Ziprasidone Hydrochloride

a) Volume of Distribution

1) 1.5 L/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

a) The mean apparent ziprasidone Vd is 1.5 L/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) Volume of Distribution

1) 1.5 L/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

a) The mean apparent ziprasidone Vd is 1.5 L/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Ziprasidone Hydrochloride

a) Liver: extensive (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) CYP3A4 is the predominant isoenzyme involved in ziprasidone metabolism (Prakash et al, 2000; Caccia, 2000) Ziprasidone is extensively metabolized by the CYP450 enzyme system in the liver after oral administration to 4 major metabolites (benzisothiazole sulphoxide (BITP), BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone). The S-methyl-dihydroziprasodone is rendered after reduction via aldehyde oxidase then methylation via thiol methyltransferase. In vitro studies with human liver microsomes and recombinant enzymes showed the CYP3A4 was the major metabolizing enzyme and CYP1A2 to a much lesser extent. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites. Although ziprasidone is extensively metabolized by the CYP450 enzymatic system, it is unlikely that ziprasidone will interfere with metabolism of other agents metabolized by the CYP450 system (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone does not cause clinically significant inhibition of CYP2D6 (Wilner et al, 2000a; Prakash et al, 2000).

2) Ziprasidone Mesylate

a) Liver: extensive (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) CYP3A4 is the predominant isoenzyme involved in ziprasidone metabolism (Prakash et al, 2000; Caccia, 2000). Ziprasidone is extensively metabolized by the CYP450 enzyme system in the liver after oral administration to 4 major metabolites (benzisothiazole sulphoxide (BITP), BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone). The S-methyl-dihydroziprasodone is

rendered after reduction via aldehyde oxidase then methylation via thiol methyltransferase. In vitro studies with human liver microsomes and recombinant enzymes showed the CYP3A4 was the major metabolizing enzyme and CYP1A2 to a much lesser extent. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites. Although ziprasidone is extensively metabolized by the CYP450 enzymatic system, it is unlikely that ziprasidone will interfere with metabolism of other agents metabolized by the CYP450 system (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone does not cause clinically significant inhibition of CYP2D6 (Wilner et al, 2000a; Prakash et al, 2000).

B) Metabolites

1) Ziprasidone Hydrochloride

a) benzisothiazole sulphoxide (BITP): major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

b) benzisothiazole sulphone: major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

c) ziprasidone sulphoxide: major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

d) S-methyl-dihydroziprasidone: major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) benzisothiazole sulphoxide (BITP): major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

b) benzisothiazole sulphone: major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

c) ziprasidone sulphoxide: major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

d) S-methyl-dihydroziprasidone: major, active (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2.3.4 Excretion

A) Kidney

1) Ziprasidone Hydrochloride

a) Renal Excretion (%)

1) approximately 20% with less than 1% unchanged (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

a) Approximately 20% of ziprasidone is excreted in the urine with less than 1% excreted as unchanged drug (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) Renal Excretion (%)

1) approximately 20% with less than 1% unchanged (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

a) Approximately 20% of ziprasidone is excreted in the urine with less than 1% excreted as unchanged drug (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

B) Feces

1) Ziprasidone Hydrochloride

a) approximately 66% with less than 4% unchanged (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Approximately 66% of ziprasidone is excreted in the feces with less than 4% excreted as unchanged drug (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) approximately 66% with less than 4% unchanged (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Approximately 66% of ziprasidone is excreted in the feces with less than 4% excreted as unchanged drug (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

C) Total Body Clearance

1) Ziprasidone Hydrochloride

a) 7.5 mL/min/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Following oral administration, the mean apparent total body clearance of ziprasidone is 7.5 mL/min/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) 7.5 mL/min/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Following oral administration, the mean apparent total body clearance of ziprasidone is 7.5 mL/min/kg (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2.3.5 Elimination Half-life

A) Parent Compound

1) Ziprasidone Hydrochloride

a) 7 hours, oral (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Following oral dosing within the recommended dosing range the half-life was about 7 hours (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) In subjects with clinically significant cirrhosis (Child-Pugh class A/B) who received ziprasidone 20 mg twice daily for 5 days (n=13), the half-life was 7.1 hours compared with 4.8 hours in the control group (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

3) Half-life was dose-dependent at steady-state, which was not observed with single doses. With single doses of ziprasidone 5 to 60 mg, the half-life ranged 3 to 4 hours. With multiple dosing of ziprasidone 5 mg or 20 mg twice daily, the half-life ranged from 4 to 5 hours, and with 40 mg and 60 mg twice daily, the half-life ranges were 8.8 hours and 10 hours, respectively (Miceli et al, 2000a; Miceli et al, 1995; Ereshefsky, 1996). These changes have minimal clinical relevance.

4) The half-life increased from 4 to 5 hours with 10 to 40 mg/day to 9 to 10 hours with 80 to 120 mg/day due to an additional elimination phase that becomes apparent only after repeated administration. The extended elimination period was not due to a decrease in clearance with higher doses (Caccia, 2000).

2) Ziprasidone Mesylate

a) 2 to 5 hours (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Following a single IM dose of ziprasidone, the mean elimination half-life range was 2 to 5 hours. Little accumulation was observed after 3 days of IM dosing (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Ziprasidone Hydrochloride

a) Dialyzable: No (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Ziprasidone is not removed by hemodialysis (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

2) Ziprasidone Mesylate

a) Dialyzable: No (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

1) Ziprasidone is not removed by hemodialysis (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

3.0 Cautions

Contraindications
Precautions
Adverse Reactions
Teratogenicity/Effects in Pregnancy/Breastfeeding
Drug Interactions

3.0.A) Black Box WARNING

1) Ziprasidone Hydrochloride

a) Oral (Capsule; Suspension)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Ziprasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009).

2) Ziprasidone Mesylate

a) Intramuscular (Powder for Solution)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional anti-

psychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Ziprasidone mesylate is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON oral capsules, IM injection, 2009).

3.1 Contraindications

A) Ziprasidone Hydrochloride

1) concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

2) heart failure, uncompensated (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

3) hypersensitivity to ziprasidone (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

4) myocardial infarction, acute and recent (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

5) QT prolongation, including congenital long QT syndrome (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

B) Ziprasidone Mesylate

1) concomitant use with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, Class Ia and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect (Prod Info GEODON oral capsules, IM injection, 2009)

2) heart failure, uncompensated (Prod Info GEODON oral capsules, IM injection, 2009)

3) hypersensitivity to ziprasidone (Prod Info GEODON oral capsules, IM injection, 2009)

4) myocardial infarction, acute and recent (Prod Info GEODON oral capsules, IM injection, 2009)

5) QT prolongation, including congenital long QT syndrome (Prod Info GEODON oral capsules, IM injection, 2009)

3.2 Precautions

A) Ziprasidone Hydrochloride

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

2) agranulocytosis, leukopenia, and neutropenia have been reported; risk factors include low WBC and history of drug-induced leukopenia or neutropenia; monitoring recommended; discontinue if significant WBC decline with no other causative factors or if patient has severe neutropenia (ie, ANC less than 1000/mm(3)) (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

3) bradycardia; increased risk of torsades de pointes and/or sudden death; discontinue if persistent QTc measurements greater than 500 msec (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

4) cardiac arrhythmia (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

5) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

6) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with antipsychotic agents (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

7) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

8) esophageal dysmotility and aspiration may occur, use cautiously in patients at risk for aspiration pneumonia (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

9) elderly patients, especially elderly women; increased risk of tardive dyskinesia (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

10) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) has been reported with atypical antipsychotic use; monitor for symptoms of hyperglycemia (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

11) hypokalemia or hypomagnesemia; increased risk of torsades de pointes and/or sudden death; correct hypokalemia or hypomagnesemia before starting therapy (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

12) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

13) neuroleptic malignant syndrome (NMS), potentially fatal, has been reported in association with antipsychotic drugs; immediately discontinue therapy if NMS is suspected (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

14) priapism has been reported (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

15) rash and/or urticaria have been reported; discontinue therapy upon appearance of rash for which an alternate cause cannot be determined (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

16) seizure disorder, history, or conditions that lower the seizure threshold; risk of seizures (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

17) tardive dyskinesia, potentially irreversible, may occur (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

B) Ziprasidone Mesylate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia)

(Prod Info GEODON oral capsules, IM injection, 2009)

2) agranulocytosis, leukopenia, and neutropenia have been reported; risk factors include low WBC and history of drug-induced leukopenia or neutropenia; monitoring recommended; discontinue if significant WBC decline with no other causative factors or if patient has severe neutropenia (ie, ANC less than 1000/mm(3)) (Prod Info GEODON oral capsules, IM injection, 2009)

3) bradycardia; increased risk of torsades de pointes and/or sudden death; discontinue if persistent QTc measurements greater than 500 msec (Prod Info GEODON oral capsules, IM injection, 2009)

4) cardiac arrhythmia (Prod Info GEODON oral capsules, IM injection, 2009)

5) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info GEODON oral capsules, IM injection, 2009)

6) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with antipsychotic agents (Prod Info GEODON oral capsules, IM injection, 2009)

7) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (Prod Info GEODON oral capsules, IM injection, 2009)

8) esophageal dysmotility and aspiration may occur, use cautiously in patients at risk for aspiration pneumonia (Prod Info GEODON oral capsules, IM injection, 2009)

9) elderly patients, especially elderly women; increased risk of tardive dyskinesia (Prod Info GEODON oral capsules, IM injection, 2009)

10) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) has been reported with atypical antipsychotic use; monitor for symptoms of hyperglycemia (Prod Info GEODON oral capsules, IM injection, 2009)

11) hypokalemia or hypomagnesemia; increased risk of torsades de pointes and/or sudden death; correct hypokalemia or hypomagnesemia before starting therapy (Prod Info GEODON oral capsules, IM injection, 2009)

12) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info GEODON oral capsules, IM injection, 2009)

13) neuroleptic malignant syndrome (NMS), potentially fatal, has been reported in association with antipsychotic drugs; immediately discontinue therapy if NMS is suspected (Prod Info GEODON oral capsules, IM injection, 2009)

14) priapism has been reported (Prod Info GEODON oral capsules, IM injection, 2009)

15) rash and/or urticaria have been reported; discontinue therapy upon appearance of rash for which an alternate cause cannot be determined (Prod Info GEODON oral capsules, IM injection, 2009)

16) seizure disorder, history, or conditions that lower the seizure threshold; risk of seizures (Prod Info GEODON oral capsules, IM injection, 2009)

17) tardive dyskinesia, potentially irreversible, may occur (Prod Info GEODON oral capsules, IM injection, 2009)

3.3 Adverse Reactions

3.3.1 Cardiovascular Effects

3.3.1.A Ziprasidone Hydrochloride

3.3.1.A.1 Bradyarrhythmia

a) An 18-year-old female with bipolar disorder developed symptomatic bradycardia following treatment with aripiprazole and ziprasidone. The patient was initially hospitalized for symptoms of mania and delusions, and was not on any pharmacological therapy. Upon admission, her resting heart rate was 62 beats per minute (bpm), blood pressure was 131/77 mmHg, and laboratory results of CBC, metabolic panel, liver and thyroid function tests were normal. Ziprasidone 80 mg/day was initiated to stabilize her psychotic symptoms. Fourteen hours following her second dose, the patient developed sinus bradycardia with a heart rate between 41 and 48 bpm, a blood pressure of 96/47 mmHg, and a QTc interval of 407 msec. She was asymptomatic and the cause at this time was unknown. Ziprasidone was increased to 120 mg the following day. The patient complained of being lightheaded and her heart rate fell between 31 and 35 bpm, with blood pressure of 100/60 mmHg, and a QTc interval of 410 msec. Her bradycardia resolved and she was discharged on a lower dose of ziprasidone (80 mg/day). The patient was readmitted 3 months later for treatment of psychotic symptoms due to medication nonadherence. At this time her resting heart rate was 69 bpm and her blood pressure was 127/72 mmHg. Due to nonadherence of ziprasidone, the patient was switched to aripiprazole 15 mg/day (which was increased to 20 mg/day on day 2) and lithium carbonate 600 mg twice daily for mood stabilization. The patient developed sinus bradycardia, a syncopal episode, a heart rate of 35 bpm, blood pressure of 80/42 mmHg, and a QTc interval of 444 msec. She was administered normal saline and monitored until her heart rate stabilized. Aripiprazole was discontinued following a total of 3 doses, due to the patient's recent issue of bradycardia with ziprasidone. Lithium was continued and upon discharge she had a resting heart rate of 56 bpm and blood pressure of 108/63 mmHg. Documentation of her normal resting heart rate which dropped subsequently on 2 different occasions suggested that the development of bradycardia is associated with the initiation of either ziprasidone or aripiprazole (Snarr et al, 2010).

3.3.1.A.2 Chest pain

a) Incidence: 3% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of chest pain was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

3.3.1.A.3 Hypertension

a) Incidence: 1% to 3% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Hypertension was reported frequently (at least 1%) in patients who received oral ziprasidone hydrochloride during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM

injection, 2009).

c) The incidence of hypertension reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) compared with 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.A.4 Orthostatic hypotension

a) Incidence: at least 1% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Postural hypotension was reported frequently in patients who received oral ziprasidone hydrochloride during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

c) Postural hypotension has been reported with postmarketing oral ziprasidone hydrochloride use and may be dose-dependent (Prod Info GEODON(R) oral suspension, 2009).

3.3.1.A.5 Prolonged QT interval

a) Incidence: 0.06% (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)

b) QT prolongation is dose-related. It is not yet known whether ziprasidone hydrochloride will cause torsades de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with oral ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine. During clinical trials, clinically significant QTc interval increases (defined as greater than 500 msec) occurred in 0.06% (2 out of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 out of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

1) The risk of QT prolongation and arrhythmia are increased when potassium and magnesium levels are low. Other risk factors include bradycardia, concomitant use of other drugs that prolong QTc interval, and presence of congenital prolongation of the QT interval. Baseline serum potassium and magnesium measurements should be obtained in patients who are at risk for significant electrolyte disturbances before starting ziprasidone. Before starting treatment with ziprasidone, hypokalemia and hypomagnesemia should be corrected. Electrolytes should be periodically monitored during therapy. Avoid ziprasidone in patients with histories of significant cardiovascular illness (QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia). Further evaluation, such as Holter monitor, maybe be necessary in patients who experience symptoms (dizziness, palpitations, or syncope) suggestive of torsade de pointes. If the QTc measurement consistently exceeds 500 milliseconds, then ziprasidone should be discontinued (Prod Info GEODON(R) oral

suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

c) Three case reports describe QTc prolongation following treatment with ziprasidone. The first patient, a 40-year-old male, was previously prescribed haloperidol (2.5 mg/day), quetiapine, and zuclopenthixol decanoate for psychotic disorder not otherwise specified. Haloperidol was discontinued due to lack of effect and ziprasidone 80 mg/day was initiated, which was increased to 160 mg/day three weeks later. His psychotic symptoms improved. At fourteen months into treatment with ziprasidone, his dose was increased to 240 mg/day to control psychotic exacerbation. Ten weeks following dose increase, an ECG revealed a QTc interval of 0.51 sec. Ziprasidone was decreased to 160 mg/day with initiation of haloperidol (5 mg/day) and biperidene (2 mg/day) to avoid exacerbation. QT prolongation at the subsequent 2, 16, and 20 weeks were 0.4 sec, 0.41 sec, and 0.35 sec, respectively. The second patient, a 27-year-old female with schizophrenia previously taking haloperidol and quetiapine (1200 mg/day), was switched to ziprasidone 120 mg/day due to lack of effect. Within 3 days, her dose was increased to 160 mg/day. On day 25 of treatment, an ECG revealed a QTc interval of 0.44 sec. Her dose of ziprasidone and valproic acid were steadily increased to 240 mg/day and 750 mg/day, respectively. An ECG revealed a QTc interval of 0.51 sec. Her valproic acid dose remained the same, and ziprasidone was decreased to 160 mg/day. Following the ziprasidone dose decrease, ECG testing at the first and second week of dose reduction revealed a QTc intervals of 0.41 sec and 0.38 sec, respectively. Patient three, a 45-year-old female with schizophrenia, was previously prescribed quetiapine, amisulpride, haloperidol (5 mg/day), risperidone, venlafaxine (150 mg/day), lithium (900 mg/day), and bornaprine hydrochloride (16 mg/day). Haloperidol was switched to ziprasidone (80 mg/day) due to lack of effect. An ECG revealed a QTc interval of 0.4 sec. Two days later, ziprasidone was increased to 160 mg/day and on day 10, an ECG revealed an QTc interval of 0.48 sec. Ziprasidone was discontinued. Ten days later, another ECG revealed a QTc interval of 0.42 sec. All three cases demonstrated a temporal relationship between ziprasidone and QTc prolongation (Eker et al, 2009).

d) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000).

3.3.1.A.6 Syncope

a) Incidence: 0.6% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

b) Syncope, which may be more prevalent during initial dose titrations, was reported by 0.6% of patients taking ziprasidone. Patients experiencing syncope may need further evaluation, such as Holter monitoring, to rule out torsade de pointes (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.A.7 Tachycardia

a) Incidence: 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

b) In short-term trials, the incidence of tachycardia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Tachycardia occurred frequently (at least 1% of patients) during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
d) During schizophrenia trials, a mean increase in heart rate of 1.4 beats per minute in the ziprasidone group compared with 0.2 beats per minute in the placebo group. The occurrence of tachycardia has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.A.8 Torsades de pointes

a) Incidence: rare (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Although the development of torsades de pointes, in the presence of other multiple confounding factors, has been observed rarely during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsades de pointes was not observed. Ziprasidone does have the capacity to prolong the QT/QTc interval and prolongation of the QTc interval has been associated with the development of torsade de pointes-type arrhythmias. However, the association between ziprasidone use and the possible development of torsades de pointes has yet to be determined (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In a case report of a 28-year-old female, QT prolongation occurred separately during two hospital admissions, and asymptomatic non-sustained polymorphic ventricular tachycardia occurred during the second admission while using ziprasidone concurrently with other potentially arrhythmogenic medications (lithium, ciprofloxacin, fluconazole, fluoxetine, and trazodone). Upon discontinuation of ziprasidone and the other medications, the patient's QT interval shortened. The patient had a medical history of systemic lupus erythematosus, hypothyroidism, and a complicated history of mood disorders with psychotic features, post traumatic stress disorder, and borderline personality disorder. During the first incidence of QT prolongation (600 milliseconds (msec) at 68 bpm) associated with ziprasidone, the patient was lithium toxic and hypokalemic; either of which has been associated with QT interval abnormalities and arrhythmias. Discontinuation of ziprasidone and lithium, coupled with emergency dialysis for lithium toxicity, resulted in a decrease in QT interval (440 msec at 77 bpm). Two weeks later, the patient was readmitted with complaints of chest pain and an electrocardiogram revealed prolonged QT interval (540 msec at 58 bpm). The patient experienced a gradual lowering of potassium levels and further prolongation of QT interval after the interchange of ziprasidone for olanzapine coupled with the concurrent initiation of fluconazole, ciprofloxacin, trazodone, and levetiracetam. On the third day, telemetry revealed an asymptomatic non-sustained polymorphic ventricular tachycardia. She was treated by discontinuing ziprasidone, trazodone, and fluconazole, and starting metoprolol. The QT interval remained prolonged at 455 to 480 msec for the remainder of her hospitalization with no subsequent arrhythmias (Heinrich et al, 2006).

3.3.1.B Ziprasidone Mesylate

3.3.1.B.1 Bradyarrhythmia

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Bradycardia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.B.2 Hypertension

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Hypertension was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.B.3 Orthostatic hypotension

a) Incidence: up to 5% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Postural hypotension, reported in up to 5% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.B.4 Prolonged QT interval

a) In a study of the QT/QTc prolongation effects of intramuscular ziprasidone mesylate, the mean increase in QTc from baseline to time of maximum plasma concentration following two injections of intramuscular ziprasidone mesylate (20 mg then 30 mg, given four hours apart) was 4.6 msec and 12.8 msec following the first and second injections, respectively, compared to 6 msec and 14.7 msec for the first and second injections, respectively, of haloperidol (7.5 mg then 10 mg, given four hours apart). No patients experienced a QTc interval exceeding 500 msec in this study (Prod Info GEODON oral capsules, IM injection, 2009).
b) QT prolongation is dose-related. It is not yet known whether ziprasidone mesylate will cause torsades de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone hydrochloride increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with oral ziprasidone hydrochloride than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine. During clinical trials, clinically significant QTc interval increases (defined as greater than 500 msec) occurred in 0.06% (2 out of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 out of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation (Prod Info GEODON oral capsules, IM injection, 2009).
1) The risk of QT prolongation and arrhythmia are increased when potassium and magnesium levels are low. Other risk factors include bradycardia, concomitant use of other drugs that prolong QTc interval, and presence of congenital prolongation of the QT interval. Baseline serum potassium and

magnesium measurements should be obtained in patients who are at risk for significant electrolyte disturbances before starting ziprasidone. Before starting treatment with ziprasidone, hypokalemia and hypomagnesemia should be corrected. Electrolytes should be periodically monitored during therapy. Avoid ziprasidone in patients with histories of significant cardiovascular illness (QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia). Further evaluation, such as Holter monitor, maybe be necessary in patients who experience symptoms (dizziness, palpitations, or syncope) suggestive of torsade de pointes. If the QTc measurement consistently exceeds 500 milliseconds, then ziprasidone should be discontinued (Prod Info GEODON oral capsules, IM injection, 2009).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000).

3.3.1.B.5 Syncope

a) Incidence: 0.6% (Prod Info GEODON oral capsules, IM injection, 2009)

b) Syncope, which may be more prevalent during initial dose-titrations, was reported by 0.6% of patients taking ziprasidone. Patients experiencing syncope may need further evaluation, such as Holter monitoring, to rule out torsade de pointes (Prod Info GEODON oral capsules, IM injection, 2009).

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.B.6 Tachycardia

a) During schizophrenia trials, a mean increase in heart rate of 1.4 beats per minute in the ziprasidone group compared with 0.2 beats per minute in the placebo group. The occurrence of tachycardia has been reported during postmarketing use of ziprasidone (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.1.B.7 Torsades de pointes

a) Incidence: rare (Prod Info GEODON oral capsules, IM injection, 2009)

b) Although the development of torsades de pointes, in the presence of other multiple confounding factors, has been observed rarely during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsades de pointes was not observed. Ziprasidone does have the capacity to prolong the QT/QTc interval and prolongation of the QTc interval has been associated with the development of torsade de pointes-type arrhythmias. However, the association between ziprasidone use and the possible development of torsades de pointes has yet to be determined (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.2 Dermatologic Effects

3.3.2.A Ziprasidone Hydrochloride

3.3.2.A.1 Dermal mycosis

a) Incidence: 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of fungal dermatitis was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273) (Prod Info GEODON oral capsules, IM injection, 2009).
c) The incidence of fungal dermatitis reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) (Prod Info GEODON oral capsules, IM injection, 2009).
d) Fungal dermatitis was frequently (at least 1 in 100 patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.2.A.2 Rash

a) Incidence: up to 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Development of a dose-dependent rash and/or urticaria was reported in about 5% of patients during premarketing trials with ziprasidone hydrochloride and was one of the more common reasons given for study dropouts (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of rash was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) Rash was infrequently (0.1% to 1% of patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.2.B Ziprasidone Mesylate

3.3.2.B.1 Furunculosis

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Furunculosis was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.2.B.2 Injection site pain

a) Incidence: 7% to 9% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Pain at the site of injection was reported in 7% to 9% of patients during short-term fixed-dose in-

tramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.2.B.3 Sweating symptom

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Sweating was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Ziprasidone

3.3.3.A.1 Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF DIABETES

3.3.3.B Ziprasidone Hydrochloride

3.3.3.B.1 Diabetes mellitus

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone hydrochloride, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). In some cases, ketoacidosis, hyperosmolar coma, and death have been reported in patients taking atypical antipsychotics. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic retesting. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.3.B.2 Hyperglycemia

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone hydrochloride, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). In some cases, ketoacidosis, hyperosmolar coma, and death have been reported in patients taking atypical antipsychotics. In the patients treated with atypical antipsychotics, ketoacidosis, hyperosmolar coma or death occurred. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients

with risk factors for diabetes should undergo fasting blood glucose testing, with periodic retesting. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.3.B.3 Increased prolactin level

a) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, have the potential ot increase prolactin levels; however, the clinical significance is unknown (Prod Info GEODON(R) oral suspension, 2009) (Prod Info GEODON oral capsules, IM injection, 2009).
b) A 16-year-old female developed hyperprolactinemia 2 weeks after starting treatment with ziprasidone 80 mg twice daily. Along with ziprasidone, she was taking divalproex 500 mg twice daily, which she had been receiving for an unknown period of time. Her medical history consisted of ADHD, postraumatic stress disorder, psychotic and bipolar spectrum symptoms, and oppositional defiant behavior for which she had been treated with divalproex, quetiapine, and fluoxetine. Two weeks following ziprasidone initiation, she developed galactorrhea and her prolactin level was found to be 68.6 nanogram/mL (normal range, 1.4 to 24.2 nanogram/mL). Ziprasidone was discontinued and aripiprazole 2 mg/day was implemented. Known causes of galactorrhea were investigated and excluded. Three weeks later, her galactorrhea had subsided and her prolactin level was within the normal range (Raza & Haq, 2010).
c) Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Anon, 1996a; Kerwin & Taylor, 1996). The changes are transient and return to baseline within 12 hours of ziprasidone administration (Miceli et al, 2000; Goff et al, 1998a).

3.3.3.B.4 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.B.5 Weight gain

a) Incidence: 0.4% to 10% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Weight gain was reported in 0.4% and 0.4% of patients on ziprasidone-treated and placebo-treated patients, respectively (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Based on 4 short-term clinical trials (4 to 6 week duration) related to schizophrenia, incidence of weight gain amounting to 7% or more of baseline body weight was 10% for subjects receiving oral ziprasidone hydrochloride compared with 4% for those receiving placebo. Median weight gain of 0.5 kg and 0 kg occurred in the ziprasidone and placebo groups, respectively. Data collected during long-term therapy showed mean weight gain from baseline to be 1.4 kg for patients with initial low BMI (less than 23), no mean weight change for those with normal BMI (23 to 27), and 1.3 kg weight loss for patients

with initially high BMI (greater than 27) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

d) Compared to other atypical antipsychotics in a systemic review, ziprasidone is associated with a low risk of weight gain (Kingsbury et al, 2001; Taylor & McAskill, 2000).

3.3.3.C Ziprasidone Mesylate

3.3.3.C.1 Diabetes mellitus

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone mesylate, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). In some cases, ketoacidosis, hyperosmolar coma, and death have been reported in patients taking atypical antipsychotics. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.3.C.2 Hyperglycemia

a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone mesylate, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). In some cases, ketoacidosis, hyperosmolar coma, and death have been reported in patients taking atypical antipsychotics. In the patients treated with atypical antipsychotics, ketoacidosis, hyperosmolar coma or death occurred. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.3.C.3 Increased prolactin level

a) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, have the potential ot increase prolactin levels; however, the clinical significance is unknown (Prod Info GEODON oral capsules, IM injection, 2009). Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Anon, 1996a; Kerwin & Taylor, 1996). The changes are transient and return to baseline within 12 hours of ziprasidone administration (Miceli et al, 2000; Goff et al, 1998a).

3.3.3.C.4 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.C.5 Weight gain

a) Compared to other atypical antipsychotics in a systemic review, ziprasidone is associated with a low risk of weight gain (Kingsbury et al, 2001; Taylor & McAskill, 2000).

3.3.4 Gastrointestinal Effects

3.3.4.A Ziprasidone Hydrochloride

3.3.4.A.1 Abdominal pain

a) Incidence: at least 1% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Abdominal pain was frequently (at least 1 in 100 patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.2 Constipation

a) Incidence: 9% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of constipation was 9% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 8% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.3 Diarrhea

a) Incidence: 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of diarrhea reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 4% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of diarrhea was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 4% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.4 Dysphagia

a) Incidence: 0.1% to 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
b) Esophageal dysmotility and aspiration have been reported with antipsychotic use, and should be used with caution in patients at risk for aspiration pneumonia (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) The incidence of dysphagia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) Dysphagia was infrequently (0.1% to 1% of patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.5 Edema of the tongue

a) Incidence: 0.1% to 3% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of tongue edema reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
c) Tongue edema was infrequently (0.1% to 1% of patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON(R) oral capsules, IM injection, 2007).
d) The rare occurrence of swollen tongue has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.6 Excessive salivation

a) Incidence: 4% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of increased salivation reported in short-term trials of patients with bipolar mania was 4% for ziprasidone hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of increased salivation and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.7 Indigestion

a) Incidence: 8% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of dyspepsia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.8 Loss of appetite

a) Incidence: 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of anorexia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273). (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Anorexia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of anorexia and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.9 Nausea

a) Incidence: 10% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of nausea reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) compared with 7% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of nausea was 10% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.10 Vomiting

a) Incidence: 1% to 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of vomiting reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 2% for placebo-treated patients

(n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Vomiting was frequently (at least 1 in 100 patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day and was one of the more common reasons given for study dropouts during the bipolar mania trials (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.A.11 Xerostomia

a) Incidence: 4% to 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of dry mouth reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 4% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of dry mouth was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of dry mouth and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B Ziprasidone Mesylate

3.3.4.B.1 Abdominal pain

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Abdominal pain was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.2 Constipation

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Constipation was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.3 Diarrhea

a) Incidence: up to 3% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Diarrhea was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of

ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.4 Dysphagia

a) Esophageal dysmotility and aspiration have been reported with antipsychotic use, and should be used with caution in patients at risk for aspiration pneumonia (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.5 Indigestion

a) Incidence: 1% to 3% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Dyspepsia was reported in 1% to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.6 Loss of appetite

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Anorexia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.7 Nausea

a) Incidence: 4% to 12% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Nausea was reported in 4%, 8% and 12% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate 2 mg, 10 mg, and 20 mg, respectively (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.8 Rectal hemorrhage

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Rectal Hemorrhage was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.4.B.9 Vomiting

a) Incidence: up to 3% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Vomiting was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5 Hematologic Effects

3.3.5.A Ziprasidone Hydrochloride

3.3.5.A.1 Agranulocytosis

a) Agranulocytosis, including fatal cases, has been related to antipsychotic drugs in clinical trials (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5.A.2 Bone marrow depression

a) Bone marrow suppression, including leukopenia, neutropenia, and cases of thrombocytopenia, some fatal, have occurred with antipsychotic use in clinical studies and reported in postmarketing surveillance. Patients with preexisting low white blood cell (WBC) count or a history of drug-induced leukopenia or neutropenia should have complete blood counts measured frequently and ziprasidone hydrochloride therapy should be discontinued if WBC counts decline without the presence of other contributive factors. Additionally, if severe neutropenia occurs (absolute neutrophil count less than 1000 cells per cubic millimeter), ziprasidone hydrochloride should be discontinued and WBC counts should be monitored until the patient has fully recovered (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5.A.3 Leukopenia

a) Incidence: 0.1% to 1% (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)
b) Leukopenia was reported infrequently (0.1% to 1%) in patients who received oral ziprasidone hydrochloride during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009).

3.3.5.A.4 Neutropenia

a) Neutropenia has been related to antipsychotic drugs in clinical trials (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5.A.5 Thrombocytopenia

a) Incidence: less than 0.1% (Prod Info GEODON(R) oral suspension, 2009)
b) Thrombocytopenia was reported rarely (less than 0.1%) in patients who received oral ziprasidone hydrochloride during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009).

3.3.5.B Ziprasidone Mesylate

3.3.5.B.1 Agranulocytosis

a) Agranulocytosis, including fatal cases, has been related to antipsychotic drugs in clinical trials (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5.B.2 Bone marrow depression

a) Bone marrow suppression, including leukopenia, neutropenia, and cases of thrombocytopenia, some fatal, have occurred with antipsychotic use in clinical studies and reported in postmarketing surveillance. Patients with preexisting low white blood cell (WBC) count or a history of drug-induced leukopenia or neutropenia should have complete blood counts measured frequently and ziprasidone hydrochloride therapy should be discontinued if WBC counts decline without the presence of other contributive factors. Additionally, if severe neutropenia occurs (absolute neutrophil count less than 1000 cells per cubic millimeter), ziprasidone should be discontinued and WBC counts should be monitored until the patient has fully recovered (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5.B.3 Leukopenia

a) Leukopenia has been related to antipsychotic drugs, such as ziprasidone, in clinical trials (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.5.B.4 Neutropenia

a) Neutropenia has been related to antipsychotic drugs in clinical trials (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.6 Hepatic Effects

3.3.6.A Ziprasidone Hydrochloride

3.3.6.A.1 Increased liver enzymes

a) No overt cases of hepatotoxicity have been reported. Occasional rises in liver enzymes have been reported with ziprasidone use but have not been clinically significant (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996).
b) Ziprasidone was discontinued in 2 patients in a clinical trial because of abnormal laboratory results. One patient had elevated gamma-glutamyl transpeptidase (GGT) and serum glutamic-pyruvic transaminase (SGPT/ALT) after 7 days of treatment with ziprasidone 10 milligrams/day. The other patient showed elevations of both serum glutamic-oxaloacetic transaminase (SGOT/AST) and SGPT/ALT after

8 days of treatment with ziprasidone 40 milligrams/day. Both patients had elevated GGT values at baseline. At follow-up, all values had returned or were returning to normal (Goff et al, 1998a).

3.3.6.B Ziprasidone Mesylate

3.3.6.B.1 Increased liver enzymes

a) No overt cases of hepatotoxicity have been reported. Occasional rises in liver enzymes have been reported with ziprasidone use but have not been clinically significant (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996).

3.3.8 Musculoskeletal Effects

3.3.8.A Ziprasidone Hydrochloride

3.3.8.A.1 Myalgia

a) Incidence: 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of myalgia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Myalgia was frequently observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.8.A.2 Rhabdomyolysis, following correction of hyponatremia secondary to psychogenic polydipsia

a) Rhabdomyolysis, possibly complicated by ziprasidone therapy, was observed in one patient following the correction of hyponatremia secondary to psychogenic polydipsia. The 50-year-old Caucasian male had begun ziprasidone therapy (40 mg twice daily) for the treatment of chronic paranoid schizophrenia three weeks before presenting with hyponatremia secondary to psychogenic polydipsia. Following the discontinuation of ziprasidone and the correction of hyponatremia via sodium chloride 0.9% administration and oral water restriction, the man developed rhabdomyolysis secondary to hyponatremia correction which manifested as an unexplained increase in serum alanine and aspartate aminotransferase levels and total serum creatine kinase elevated to 67,259 International units/L. Following resolution of rhabdomyolysis, ziprasidone therapy was reinitiated at a dose of 80 mg twice daily with no recurrence of increased serum creatine kinase levels. While the author notes that hyponatremia secondary to psychogenic polydipsia or its correction was most likely the primary cause of rhabdomyolysis in this pa-

tient, he also asserts that a review of the literature allows supposition that the development of rhabdomyolysis may have been complicated by the prior use of ziprasidone. The use of the Naranjo probability scale indicated a possible relationship between the use of ziprasidone and the subsequent development of rhabdomyolysis (Zaidi, 2005).

3.3.9 Neurologic Effects

3.3.9.A Ziprasidone Hydrochloride

3.3.9.A.1 Akathisia

a) Incidence: 8% to 10% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of akathisia reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) compared with 5% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of akathisia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) Akathisia was one of the more common reasons given for study dropouts during the bipolar mania trials (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.2 Anxiety

a) Incidence: 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of anxiety reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 4% for placebo-treated patients (n=136). Anxiety was one of the more common reasons given for study dropouts during the bipolar mania trials(Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of anxiety and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.3 Asthenia

a) Incidence: 5% to 6% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

b) The incidence of asthenia reported in short-term trials of patients with bipolar mania was 6% for ziprasidone hydrochloride-treated subjects (n=279) compared with 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of asthenia was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of tremor and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.4 Behavior showing reduced motor activity

a) Incidence: bipolar mania, less than 10%; schizophrenia, less than 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Hypokinesia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Hypokinesia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.5 Disturbance in speech

a) Incidence: 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of speech disorder reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.6 Dizziness

a) Incidence: bipolar mania, 16%; schizophrenia, 8% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of dizziness and lightheadedness reported in short-term trials of patients with bipolar mania was 16% for ziprasidone hydrochloride-treated subjects (n=279) compared with 7% for placebo-treated patients (n=136). Dizziness was one of the more common reasons given for study dropouts during the bipolar mania trials (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of dizziness and lightheadedness was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 6% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injec-

tion, 2009).
d) Dizziness may be more prevalent during initial ziprasidone hydrochloride dose titrations and is dose-dependent. Patients experiencing continued dizziness may need further evaluation, such as Holter monitoring, to rule out torsade de pointes (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.7 Dystonia

a) Incidence: bipolar mania, less than 10%; schizophrenia, less than 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with greater severity) with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Dystonia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials, and was one of the more common reasons given for study dropouts during the bipolar mania trials. Dystonia was frequently (at least 1% of patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of dystonia and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.8 Extrapyramidal disease

a) Incidence: bipolar mania, 31%; schizophrenia, 14% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of extrapyramidal symptoms (EPS) reported in short-term trials of patients with bipolar mania was 31% for ziprasidone hydrochloride-treated subjects (n=279) compared with 12% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of extrapyramidal symptoms (EPS) was 14% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 8% for placebo-treated subjects (n=273). However, objectively collected data on the Simpson-Angus Rating Scale for EPS and the Barnes Akathisia Scale did not generally indicate a difference between the ziprasidone hydrochloride and placebo groups in these trials (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) In clinical trial adverse effect reports for ziprasidone hydrochloride, the manufacturer defines ex-

trapyramidal symptoms to collectively include the following: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis, and twitching (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.A.9 Headache

a) Incidence: 18% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of headache reported in short-term trials of patients with bipolar mania was 18% for ziprasidone hydrochloride-treated subjects (n=279) compared with 17% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.10 Hypesthesia

a) Incidence: 1% to 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of hypesthesia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Hypesthesia was frequently (greater than 1% of patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

3.3.9.A.11 Increased muscle tone

a) Incidence: bipolar mania, less than 10%; schizophrenia, less than 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Hypertonia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Hypertonia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of hypertonia and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.12 Insomnia

a) Incidence: rare (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON oral

capsules, IM injection, 2009)
b) Insomnia has been reported rarely as part of the postmarketing surveillance of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.13 Neuroleptic malignant syndrome

a) Incidence: rare (Murty et al, 2002)
b) The use of antipsychotic drugs, such as ziprasidone hydrochloride, has been associated with the development a potentially fatal syndrome referred to as neuroleptic malignant syndrome (NMS). Signs and symptoms include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability, elevated creatinine phosphokinase, myoglobinuria, and acute renal failure. If NMS is suspected, discontinue ziprasidone hydrochloride and other nonessential drugs, provide aggressive symptomatic treatment and monitoring, and treat any serious medical problems. Rechallenge antipsychotic treatment with caution, and carefully monitor the patient for symptoms of NMS. Development of NMS has been reported with reintroduction of antipsychotic therapy in a patient with a history of the syndrome (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Neuroleptic malignant syndrome (NMS) has been reported rarely as part of the postmarketing surveillance of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) Neuroleptic malignant syndrome (NMS) developed in a 49-year-old female patient after receiving ziprasidone (20 to 60 mg twice daily) for the treatment of recurrent psychotic depression. Symptoms included agitation, disorganized thoughts, sweating, tachycardia, hypertension, elevated liver enzymes, and hyponatremia. Although there was no evidence of fever or muscle rigidity, a diagnosis of rhabdomyolysis secondary to NMS was made. All medications were stopped and the symptoms resolved over the next 6 days following aggressive treatment including intravenous hydration and electrolyte replacement (Murty et al, 2002).

3.3.9.A.14 Paresthesia

a) Incidence: at least 1% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Paresthesia was frequently (occurred in at least 1 of 100 people) reported in oral ziprasidone hydrochloride-treated patients during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.15 Seizure

a) Incidence: 0.4% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Seizures were reported in 0.4% of ziprasidone-treated patients during clinical trials, although con-

founding factors may have contributed to the occurrence in many of these cases (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.16 Somnolence

a) Incidence: bipolar mania, 31%; schizophrenia, 14% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of somnolence reported in short-term trials of patients with bipolar mania was 31% for ziprasidone hydrochloride-treated subjects (n=279) compared with 12% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of somnolence was 14% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 7% for placebo-treated subjects (n=273). The frequency of somnolence appears to be dose-dependent (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) Somnolence may be more prevalent during initial ziprasidone hydrochloride dose titrations and is dose-dependent. During short-term clinical trials, 0.3% discontinued therapy due to somnolence (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.17 Spasmodic movement

a) Incidence: bipolar mania, less than 10%; schizophrenia, less than 5% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Twitching occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Twitching was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.18 Spasmodic torticollis

a) A case report described tardive cervical dystonia in a 50-year-old woman following ziprasidone use. The patient, who was diagnosed with atypical depression, was initiated on ziprasidone 80 mg/day. Prior to ziprasidone initiation, she had not been prescribed any antidepressant medications. After 4 months of treatment, she presented with involuntary neck movements. Ziprasidone was gradually discontinued in 20-mg/day increments over 4 days. However, the cervical dystonia persisted and became worse. She was initiated on clonazepam 12.5 mg/day which was titrated to 150 mg/day, but there was no improvement. Patient and family history showed no serious diseases. Physical examination revealed neck extension and head tilt caused by patterned, repetitive and spasmodic contraction of her neck muscles. Brain and cervical MRI and other biochemical tests were all normal. A diagnosis of tardive cervical dystonia with torticollis was made after ruling out causes of secondary dystonia and family history of dystonia. She was treated with botulinum toxin type A injections in 4 muscles of her neck and spinal area. The treatment was repeated 4 times at 1-month intervals. The patient experienced a significant improvement

in neck pain and head deviation after the fourth injection with no recurrence of tardive symptoms after 5 months of follow-up (Kutlu et al, 2009).

3.3.9.A.19 Summary

a) Neuroleptic malignant syndrome, including fatalities, has been reported with the use of antipsychotic drugs (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009). A case report described NMS in a 49-year-old woman following ziprasidone use (Murty et al, 2002). During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms of dystonia can occur at low doses but most often occur with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute dystonia. Acute and chronic tardive dyskinesia and extrapyramidal syndrome have been reported. Extrapyramidal symptoms include the following: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis, and twitching. Somnolence, dizziness, headache, and akathisia have also been commonly reported with ziprasidone use. If symptoms of NMS develop, ziprasidone should be discontinued and the patient should be closely monitored. If extrapyramidal symptoms are observed, consideration should be given to discontinuing the drug (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.A.20 Tardive dyskinesia

a) Incidence: rare (Prod Info GEODON oral capsules, IM injection, 2009; Prod Info GEODON(R) oral suspension, 2009)
b) The use of antipsychotic drugs, such as ziprasidone mesylate, is a risk factor for the development of tardive dyskinesia, potentially irreversible. The risk of developing the syndrome increases with duration of treatment and total cumulative dose. The incidence of the syndrome appears to be highest among the elderly, particularly women. However, any patient may be at risk to develop the syndrome, even after a comparatively brief treatment period at a low dose. Partial or complete resolution may occur with discontinuation of the antipsychotic drug. The goal should be the smallest dose for the shortest duration with periodic treatment reassessment (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Tardive dyskinesia has been reported rarely as part of the postmarketing surveillance of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) Tardive dyskinesia developed in a 70-year-old woman 9 weeks following the initiation of ziprasidone therapy (100 mg/day) for the treatment of major depression with mood-congruent psychotic features. Symptoms included repetitive, involuntary jaw and toe movements (Keck et al, 2004).

3.3.9.A.21 Tremor

a) Incidence: bipolar mania, less than 10%; schizophrenia, less than 5% (Prod Info GEODON(R) oral

suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Tremor occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Tremor was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 mg/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of tremor and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B Ziprasidone Mesylate

3.3.9.B.1 Akathisia

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Akathisia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.2 Anxiety

a) Incidence: up to 2% (Prod Info GEODON(R) oral suspension, 2009)
b) Anxiety was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral suspension, 2009).

3.3.9.B.3 Asthenia

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Asthenia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.4 Disturbance in speech

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Speech disorder was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.5 Dizziness

a) Incidence: 3% to 10% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Dizziness was reported in 3% to 10% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.6 Dystonia

a) During the first few days of treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with greater severity) with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.7 Extrapyramidal disease

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Extrapyramidal syndrome was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).
See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.B.8 Headache

a) Incidence: 3% to 13% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Headache was reported in 3% to 13% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.9 Insomnia

a) Incidence: up to 3% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Insomnia, reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.10 Neuroleptic malignant syndrome

a) Incidence: rare (Murty et al, 2002)
b) The use of antipsychotic drugs, such as ziprasidone hydrochloride, have been associated with the development a potentially fatal syndrome referred to as Neuroleptic malignant syndrome (NMS). Signs and symptoms include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability, elevated creatinine phosphokinase, myoglobinuria, and acute renal failure. If NMS is suspected, discontinue ziprasidone hydrochloride and other nonessential drugs, provide aggressive symptomatic treatment and monitoring, and treat any serious medical problems. Rechallenge antipsychotic treatment with caution, and carefully monitor the patient for symptoms of NMS. Development of NMS

has been reported with reintroduction of antipsychotic therapy in a patient with a history of the syndrome (Prod Info GEODON(R) oral suspension, 2009).

c) Neuroleptic malignant syndrome (NMS) has been reported rarely as part of the postmarketing surveillance of oral and intramuscular ziprasidone (Prod Info GEODON(R) oral suspension, 2009).

d) Neuroleptic malignant syndrome (NMS) developed in a 49-year-old female patient after receiving ziprasidone (20 to 60 mg twice daily) for the treatment of recurrent psychotic depression. Symptoms included agitation, disorganized thoughts, sweating, tachycardia, hypertension, elevated liver enzymes, and hyponatremia. Although there was no evidence of fever or muscle rigidity, a diagnosis of rhabdomyolysis secondary to NMS was made. All medications were stopped and the symptoms resolved over the next 6 days following aggressive treatment including intravenous hydration and electrolyte replacement (Murty et al, 2002).

3.3.9.B.11 Paresthesia

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)

b) Paresthesia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.12 Seizure

a) Incidence: 0.4% (Prod Info GEODON oral capsules, IM injection, 2009)

b) Seizures were reported in 0.4% of ziprasidone-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.13 Somnolence

a) Incidence: 8% to 20% (Prod Info GEODON oral capsules, IM injection, 2009)

b) Somnolence was reported in 8%, 8%, and 20% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate 2 mg, 10 mg, and 20 mg, respectively (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.9.B.14 Tardive dyskinesia

a) Incidence: rare (Prod Info GEODON oral capsules, IM injection, 2009)

b) The use of antipsychotic drugs, such as ziprasidone mesylate, is a risk factor for the development of tardive dyskinesia, potentially irreversible. The risk of developing the syndrome increases with duration of treatment and total cumulative dose. The incidence of the syndrome appears to be highest among the elderly, particularly women. However, any patient may be at risk to develop the syndrome, even after a comparatively brief treatment period at a low dose. Partial or complete resolution may occur with discontinuation of the antipsychotic drug. The smallest dose for the shortest duration should be the goal, with periodic treatment reassessment (Prod Info GEODON oral capsules, IM injection, 2009).

c) Tardive dyskinesia has been reported rarely as part of the postmarketing surveillance of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009).

3.3.10 Ophthalmic Effects

3.3.10.A Ziprasidone Hydrochloride

3.3.10.A.1 Abnormal vision

a) Incidence: 3% to 6% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of abnormal vision reported in short-term trials of patients with bipolar mania was 6% for ziprasidone hydrochloride-treated subjects (n=279) compared with 3% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of abnormal vision was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
d) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of abnormal vision and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.10.A.2 Oculogyric crisis

a) A case report describes a 28-year-old female who experienced oculogyric crisis following administration of ziprasidone (80 mg/day) for the treatment of schizophrenia. At 15 years of age, the patient was diagnosed with schizophrenia and was treated with haloperidol with poor response. At the age of 24 years, the patient developed upward deviation of the eyes and blepharospasm for 2 hours which occurred 2 to 3 times per week. She had no loss of consciousness, visual hallucinations, torticollis, or opisthotonus. Haloperidol was switched to ziprasidone 80 mg/day with no further occurrences for the next 7 months. However, this movement returned with a frequency of up to 3 episodes per month while on ziprasidone. An EEG revealed no epileptic issues. Clonazepam (1 mg/day) was then initiated with significant improvement in movement disorder, and she remained free of oculogyric crisis for 8 months. Three days upon discontinuation of clonazepam, movement disorder returned (Viana Bde et al, 2009).
b) Oculogyric crisis developed in an 11-year-old boy after receiving ziprasidone 20 milligrams (mg) twice daily for the treatment of pervasive developmental disorder and psychotic symptoms. Six weeks following initiation of ziprasidone therapy, the child had a sudden onset of dystonic upward deviation of the eyes. Ziprasidone was discontinued and the patient was treated with oral diphenhydramine 50 mg every 4 hours. Symptoms subsided within 30 minutes of the first dose and completely resolved within 24 hours (Ramos et al, 2003).

3.3.12 Psychiatric Effects

3.3.12.A Ziprasidone Hydrochloride

3.3.12.A.1 Mania

a) Summary

1) There have been several case reports of mania/hypomania associated ziprasidone use, including rare reports during postmarketing use (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009; Brieger, 2004; Baldassano et al, 2003).

b) Incidence: rare (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Hypomania developed in a 40-year-old man on two occasions following the initiation and reinitiation of ziprasidone therapy for the treatment bipolar schizoaffective disorder. Hypomania developed eight days after ziprasidone (100 milligrams (mg)/day) was initiated with ongoing venlafaxine (150 mg/day) and valproate (1200 mg/day) therapy. Symptoms included decreased need for sleep, recklessness, talkativeness, high self-esteem, and racing thoughts. Ziprasidone was stopped on day 10 after a worsening of symptoms. However, 6 weeks later, the patient was restarted on ziprasidone treatment (120 mg/day) and again developed a hypomanic episode after eight days of treatment. A dysphoric mood rather than euphoric mood marked this episode and ziprasidone was again discontinued. Symptoms of hypomania resolved within 24 hours on both occasions (Brieger, 2004).

d) Four cases of mania related to the initiation of ziprasidone administration have been reported in bipolar patients. Three of the cases occurred in males 25, 26 and 45 years of age and the other case occurred in a 29-year-old female. In each case, the patient was receiving multiple psychotropic medications prior to ziprasidone administration. Each patient received an initial ziprasidone dose of 20 milligrams (mg) twice a day. Manic symptoms occurred within 3 to 7 days in each of the male patients at this dosage. With the woman patient, ziprasidone dosage was increased to 100 mg/day over a period of 5 days and on the fifth day of treatment, she developed manic symptoms. Within 3 to 7 days of dosage reduction or discontinuation of ziprasidone, all of the patient's manic symptoms improved. The authors speculated that ziprasidone's potent inhibition of noradrenergic and serotonergic reuptake sites may play a role in the observed switch from bipolar depression to mania (Baldassano et al, 2003).

3.3.12.B Ziprasidone Mesylate

3.3.12.B.1 Agitation

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)

b) Agitation was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.12.B.2 Personality disorder

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Personality disorder was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.14 Reproductive Effects

3.3.14.A Ziprasidone Hydrochloride

3.3.14.A.1 Orgasm disorder

a) A 50-year-old female experienced spontaneous orgasms following initiation of ziprasidone treatment. The patient had not been sexually active for the past 10 years, and had been suffering from symptoms of prolonged depression, decreased need for sleep, racing thoughts, rapid speech, increased goal-directed activities, and suicidal ideation. Following medication trials and evaluation, a diagnosis of bipolar II disorder was confirmed. A mood-stabilizing agent, oral ziprasidone 20 mg twice daily, was initiated. Within one week, she experienced abrupt onset sexual arousal and spontaneous orgasms 10 to 15 times daily, and each episode lasted for approximately 30 seconds to 1 minute. Extrapyramidal symptoms, specifically mild torticollis, also progressed over the following 3 days. Upon feeling a sensation of swollen tongue and throat which did not obstruct breathing, she sought emergency medical attention. Ziprasidone was discontinued. Her extrapyramidal symptoms resolved within 1 day and spontaneous orgasms resolved within 3 days. At follow-up, oxcarbazepine was initiated which was effective and well tolerated by the patient (Boora et al, 2010).

3.3.14.A.2 Priapism

a) Incidence: rare (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) Although no causal relationship has been established, rare postmarketing reports of priapism with ziprasidone use have been observed and one case was reported during premarketing trials. Surgical intervention may be required in severe cases (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) An African American male developed priapism on two occasions after receiving risperidone and again after receiving ziprasidone for the treatment of schizophrenia. Following risperidone treatment (4 milligrams (mg) twice daily), the man developed an erection lasting 13 hours, which resolved upon irrigation of the corpora with phenylephrine 200 micrograms. Following discontinuation of risperidone, the patient developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 mg twice daily. This erection lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the ziprasidone was discontinued and the priapism quickly resolved (Reeves et al, 2002).

3.3.14.B Ziprasidone Mesylate

3.3.14.B.1 Dysmenorrhea

a) Incidence: up to 2% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Dysmenorrhea was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.14.B.2 Priapism

a) Incidence: up to 1% (Prod Info GEODON oral capsules, IM injection, 2009)
b) Priapism, reported in up to 1% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use. Surgical intervention may be required in severe cases (Prod Info GEODON oral capsules, IM injection, 2009).

3.3.15 Respiratory Effects

3.3.15.A Ziprasidone Hydrochloride

3.3.15.A.1 Cough

a) Incidence: 3% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of increased cough was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.15.A.2 Dyspnea

a) Incidence: 1% to 2% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of dyspnea reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) Dyspnea was frequently (at least 1 in 100 patients) observed during premarketing schizophrenia clinical trials (n=3834) at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.15.A.3 Pharyngitis

a) Incidence: 3% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)

b) The incidence of pharyngitis reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.15.A.4 Respiratory tract infection

a) Incidence: 8% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of respiratory tract infection was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.15.A.5 Rhinitis

a) Incidence: 4% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) In short-term trials, the incidence of rhinitis was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of rhinitis and the dose of ziprasidone hydrochloride (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.16 Other

3.3.16.A Ziprasidone Hydrochloride

3.3.16.A.1 Accidental injury

a) Incidence: 4% (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009)
b) The incidence of accidental injuries reported in short-term trials of patients with bipolar mania was 4% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).
c) In short-term trials, the incidence of accidental injuries was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

3.3.16.A.2 Death

a) Results of a population-based, retrospective, cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Pair-wise comparisons were made between atypical and no antipsychotic use and conventional andatypical antipsychotic use. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community vs long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31; 95% confidence interval (CI), 1.02 to 1.7); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55; 95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

b) Results of a population-based, retrospective, cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multivariable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional compared with atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional compared with atypical drug therapy was greatest when higher (above median) doses were used (mortality ratio, 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio, 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multivariable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

c) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of

age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk (RR) of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.9). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.A.3 Serotonin syndrome

a) A 50-year-old female with schizophrenia developed serotonin-syndrome 4 hours after receiving her second dose of ziprasidone 40 mg. Fourteen days prior to receiving ziprasidone, she had been admitted to the hospital with agitation, auditory hallucinations, and delusions of persecution. She was initiated on quetiapine 400 mg/day, valproate sodium 1000 mg/day, and lorazepam 4 mg/day. On day 9, she had fluctuating consciousness, and a laboratory workup revealed an increase in total valproic acid at 167 mcg/mL (normal range, 50 to 100 mcg/mL) and free valproic acid at 27 mcg/mL (normal range, 5 to 10 mcg/mL), with all other laboratory values normal. All medications were discontinued. Consciousness returned 4 days later; however, all her original psychotic symptoms remained. Ziprasidone was initiated and 4 hours following her second 40 mg dose, she became severely restless, agitated, and disoriented to time and place. Physical examination revealed hypertension, tachycardia, hyperhidrosis, hyperrelexia, ataxia, and flushing. Her body temperature was 35.8 C, and she showed no focal neurological signs or rigidity. Ziprasidone was discontinued and all symptoms, including disorientation subsided within 24 hours. Quetiapine 600 mg/day was initiated and the patient was discharged 8 days later with no further psychotic symptoms. A diagnosis of full-blown serotonin syndrome was made based on the Sternbach criteria (Lin et al, 2010).

3.3.16.B Ziprasidone Mesylate

3.3.16.B.1 Death

a) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of resi-

dence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Government Department of Health and Ageing Therapeutic Goods Administration, 2006)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled studies of ziprasidone use during pregnancy in humans; however, animal studies have shown developmental toxicity with potential teratogenic effects with ziprasidone administration. In humans, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. Therefore, ziprasidone should be used during pregnancy only if the maternal benefit justifies the fetal risk (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

5) Literature Reports

a) There are no adequate and well-controlled studies of ziprasidone use in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

b) Developmental toxicity, including possible teratogenic effects, was reported in animal studies. An increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney changes) were observed in rabbits administered ziprasidone doses of 30 mg/kg/day (3 times the maximum recommended human dose (MRHD) on a mg/m(2) basis) during organogenesis. In rats, embryofetal toxicity (ie, decreased fetal weights, delayed skeletal ossification) was observed following ziprasidone doses up to 160 mg/kg/day (8 times the MRHD on a mg/m(2) basis), but no evidence of teratogenicity was noted (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) It is not known whether ziprasidone or its metabolites are excreted in human milk; therefore, breastfeeding in women who are receiving ziprasidone is not recommended (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.C Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001e; Duenas-Laita et al, 1999d; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular injection, oral capsule,

2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.D Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.E Amisulpride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval, such as amisulpride, is contraindicated (Prod Info Solian(R), 1999d; Prod Info Geodon(R), 2002o).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as amisulpride, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002n).

3.5.1.F Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.G Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.H Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002b; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.I Arsenic Trioxide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs, such as arsenic trioxide, which are also known to prolong the QTc interval (Prod Info Geodon(R), 2002d; Prod Info Trisenox(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as arsenic trioxide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less

than that observed with thioridazine (Prod Info Geodon(R), 2002c).

b) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.J Arsenic Trioxide

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes

2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999e), haloperidol (O'Brien et al, 1999d), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001e), quetiapine (Owens, 2001k), sultopride (Lande et al, 1992f), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.

7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001a).

3.5.1.K Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of

ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including astemizole (Prod Info Geodon(TM), 2002e).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and astemizole is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.L Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.M Azithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone can prolong the QT interval in a dose-related manner which can lead to torsade de pointes, ventricular tachycardia, and sudden death (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010). QT prolongation and torsades de pointes have been reported during postmarketing use of azithromycin (Prod Info ZMAX(R) extended release oral suspension, 2009). Therefore, due to the potential for additive effects on the QT interval, coadministration of ziprasidone and other drugs that prolong the QT interval, such as azithromycin, should be avoided (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ziprasidone with drugs that prolong the QT interval, such as azithromycin, may result in additive effects on the QT interval and an increased risk of cardiotoxicity.

Therefore, concomitant use of azithromycin and ziprasidone should be avoided (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.N Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001; Owens, 2001; Prod Info Orap(R), 1999a; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999; Ravin & Levenson, 1997).

3.5.1.O Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.P Carbamazepine

1) Interaction Effect: decreased ziprasidone plasma concentrations
2) Summary: Ziprasidone is metabolized primarily by CYP3A4. The concomitant use of carbamazepine (a CYP3A4 inducer) 200 mg twice daily for 21 days decreased the ziprasidone AUC by approximately 35%. Therefore, caution should be used when carbamazepine and ziprasidone are coadministered due to the potential for reduced ziprasidone plasma concentrations (Prod Info GEODON(R) oral capsules, IM injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing carbamazepine to a patient who takes ziprasidone. Concomitant use of carbamazepine and ziprasidone has resulted in decreased ziprasidone plasma concentrations (Prod Info GEODON(R) oral capsules, IM injection, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated ziprasidone metabolism by carbamazepine

3.5.1.Q Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloral hydrate (Prod Info Geodon(TM), 2002i; Young et al, 1986).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and chloral hydrate is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.R Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloroquine (Prod Info Geodon(TM), 2002f). Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Aralen(R), 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and chloroquine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.S Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.T Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001f), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.U Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002c; Owens, 2001a; Prod Info Orap(R), 1999c). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999b).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997a).

3.5.1.V Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including clarithromycin (Prod Info Geodon(TM), 2002k; Prod Info Biaxin(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and clarithromycin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.W Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.X Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.Y Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001e; Duenas-Laita et al, 1999d; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.Z Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.AA Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(R), 2002u).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as dolasetron, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002t).

3.5.1.AB Doxepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.AC Dronedarone

1) Interaction Effect: an increased risk of torsade de pointes
2) Summary: Due to the potential for additive effects on the QT interval prolongation and increased risk of torsade de pointes, the concomitant use of dronedarone and ziprasidone is contraindicated (Prod Info MULTAQ(R) oral tablets, 2011).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dronedarone and ziprasidone is contraindicated due to the potential for additive effects on the QT interval and an increased risk of torsade de pointes (Prod Info MULTAQ(R) oral tablets, 2011).
7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.AD Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including ziprasidone, is contraindicated (Prod Info Inapsine(R), 2001; Prod Info Geodon(TM), 2002o).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as droperidol and ziprasidone, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002n).

3.5.1.AE Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including enflurane (Prod Info Geodon(R), 2002k; Owens, 2001g).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as enflurane, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002j).

3.5.1.AF Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Though no formal drug interaction studies have been done, ziprasidone should not be co-administered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002l). Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AG Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002b; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AH Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002u). Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluconazole, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002v).

3.5.1.AI Fluoxetine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002v; Prod Info Prozac(R), 2001).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002w).

3.5.1.AJ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002m; Prod Info Foscavir(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as foscarnet, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AK Gatifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including gatifloxacin (Prod Info Geodon(TM), 2002p).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and gatifloxacin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AL Gemifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between ziprasidone and gemifloxacin, which may prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving ziprasidone (Prod Info Factive(R), 2003; Prod Info Geodon(R), 2002ac).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of ziprasidone with a drug that may prolong the QT interval, such as gemifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AM Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because ziprasidone may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with ziprasidone is contraindicated (Prod Info Halfan(R), 1998; Prod Info Geodon(TM), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halofantrine, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AN Haloperidol

1) Interaction Effect: an increased risk of QT prolongation
2) Summary: Coadministration of ziprasidone with drugs that prolong the QT interval (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010), such as haloperidol (Prod Info HALDOL(R) immediate release IM injection, 2010), is not recommended due to the potential for additive QT prolonging effects. In a direct comparison study in patient volunteers, QTc prolongation was observed with administration of ziprasidone or haloperidol (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of ziprasidone with drugs that prolong the QT interval (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010), such as haloperidol (Prod Info HALDOL(R) immediate release IM injection, 2010), is not recommended due to the potential for additive QT

prolonging effects (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In a direct comparison study in patient volunteers, QTc prolongation was observed with administration of ziprasidone or haloperidol. The increase in mean QTc change from baseline was 9 to 14 msec greater following administration of oral ziprasidone compared with haloperidol and 3 other comparator drugs (risperidone, olanzapine, and quetiapine); however, the QTc change observed with ziprasidone was 14 msec less than the increase seen with thioridazine administration (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

3.5.1.AO Haloperidol

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). Coadministration of ziprasidone with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Geodon(R), 2002g).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as haloperidol, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993; Wilt et al, 1993). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).
c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal

ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002f).

3.5.1.AP Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Prod Info Geodon(R), 2002y; Owens, 2001i).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halothane, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002x).

3.5.1.AQ Hydromorphone

1) Interaction Effect: an increase in CNS or respiratory depression
2) Summary: The concomitant use of hydromorphone and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including respiratory depression, hypotension, profound sedation, and coma. When administering hydromorphone and an antipsychotic together, dose reduction of one or both of the medications should be considered (Prod Info EXALGO(R) extended release oral tablets, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of hydromorphone and other CNS depressants, such as antipsychotics, may result in respiratory depression, hypotension, profound sedation, and coma. When con-

comitant use is required, dose reduction of one or both medications should be considered (Prod Info EXALGO(R) extended release oral tablets, 2010).
7) Probable Mechanism: additive effects

3.5.1.AR Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AS Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001e; Duenas-Laita et al, 1999d; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AT Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.AU Iloperidone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Iloperidone should be

avoided in patients with significant cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncompensated heart failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).

7) Probable Mechanism: additive effects on the QT interval

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.AV Imipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).

7) Probable Mechanism: additive cardiac effects

3.5.1.AW Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including isoflurane (Prod Info Geodon(R), 2002q; Owens, 2001h).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isoflurane, is contraindicated.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal

ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002p).

3.5.1.AX Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including isradipine (Prod Info Geodon(TM), 2002h; Prod Info DynaCirc(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isradipine, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002g).

3.5.1.AY Lapatinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.AZ Levofloxacin

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no formal drug interaction studies have been done, ziprasidone should not be co-administered with other drugs which are also known to prolong the QTc interval, including levofloxacin (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004; Prod Info Levaquin, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and levofloxacin is not recommended.
7) Probable Mechanism: additive QT prolongation effects

3.5.1.BA Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as ziprasidone that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with ziprasidone as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002e).

3.5.1.BB Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including lidoflazine, is contraindicated (Prod Info Geodon(TM), 2002x).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as lidoflazine, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BC Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002b; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).

7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BE Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including mefloquine (Prod Info Geodon(TM), 2002r; Davis et al, 1996).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and mefloquine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BF Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BG Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets,

2006), quetiapine (Owens, 2001d), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992a), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BH Methadone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Ziprasidone use is associated with dose-related QT interval prolongation. Due to the potential for additive effects on QT interval prolongation, concurrent use of methadone and ziprasidone is contraindicated (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BI Metoclopramide

1) Interaction Effect: an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome
2) Summary: Concomitant use of metoclopramide with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as tardive dyskinesia or neuroleptic malignant syndrome, and is contraindicated (Prod Info REGLAN(R) oral tablets, 2009). If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions. Injection of diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of metoclopramide with antipsychotic agents is contraindicated (Prod Info REGLAN(R) oral tablets, 2009). If concurrent therapy is required, monitor patients for signs

and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome. Injection of diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).
7) Probable Mechanism: unknown

3.5.1.BJ Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant use of milnacipran and an antipsychotic may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of serotonin syndrome develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated (Prod Info SAVELLA(R) oral tablets, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in hypertension and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of serotonin syndrome develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment (Prod Info SAVELLA(R) oral tablets, 2010).
7) Probable Mechanism: additive serotonergic effect

3.5.1.BK Moxifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including moxifloxacin (Prod Info Geodon(TM), 2002s).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and moxifloxacin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BL Nilotinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BM Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.BN Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including octreotide, is contraindicated (Prod Info Geodon(TM) ziprasidone, 2002a).
3) Severity: contraindicated
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as octreotide, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BO Pazopanib

1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Both pazopanib (Prod Info VOTRIENT(R) oral tablets, 2009) and ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2009) have been associated with QT interval prolongation and torsades de pointes. Due to the potential for additive effects on the QT interval, avoid the concomitant use of ziprasidone and other QT-prolonging drugs (Prod Info GEODON(R) oral capsules, IM injection, 2009), such as pazopanib.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid the concomitant use of ziprasidone and other medications that prolong the QT interval (Prod Info GEODON(R) oral capsules, IM injection, 2009), such as pazopanib (Prod Info VOTRIENT(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval

3.5.1.BP Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and pentamidine is contraindicated (Prod Info Geodon(TM) ziprasidone, 2002b). Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as pentamidine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BQ Pimozide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including pimozide (Prod Info Geodon(TM), 2002z).

3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and pimozide is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BR Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BS Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001e; Duenas-Laita et al, 1999d; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BT Posaconazole

1) Interaction Effect: increased ziprasidone plasma concentrations and increased risk of QT interval prolongation
2) Summary: The metabolism of ziprasidone, a CYP3A4 substrate, may be inhibited by concomitant administration of posaconazole, a strong CYP3A4 inhibitor. Increased ziprasidone plasma concentrations can lead to QT interval prolongation and torsade de pointes. Prolongation of the QT interval and rare cases of torsade de pointes have also been reported in patients receiving posaconazole. Therefore, concomitant use of posaconazole and CYP3A4 substrates that prolong the QT interval is contraindicated (Prod Info NOXAFIL(R) oral suspension, 2010).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of posaconazole with CYP3A4 substrates that prolong the QT interval, such as ziprasidone, is contraindicated due to the potential for increased ziprasidone plasma concentrations, thereby increasing the risk for QT interval prolongation and torsades de pointes (Prod Info NOXAFIL(R) oral suspension, 2010).
7) Probable Mechanism: inhibition of CYP3A4-mediated ziprasidone metabolism by posaconazole

3.5.1.BU Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BV Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001e; Duenas-Laita et al, 1999d; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BW Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including probucol (Prod Info Geodon(TM), 2002aa). Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as probucol, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BX Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BY Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001e; Duenas-Laita et al, 1999d; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic

is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BZ Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CA Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets,

2006), quetiapine (Owens, 2001f), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CB Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002b; Prod Info Tambocor(R) flecainide acetate, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CC Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.CD Quetiapine

1) Interaction Effect: an increased risk of QT prolongation
2) Summary: Coadministration of ziprasidone with drugs that prolong the QT interval (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010), such as quetiapine (Prod Info SEROQUEL(R) oral tablets, 2010), is not recommended due to the potential for additive QT prolonging effects. In a direct comparison study in patient volunteers, QTc prolongation was observed with administration of ziprasidone or quetiapine (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of ziprasidone with drugs that prolong the QT interval (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010), such as quetiapine (Prod Info SEROQUEL(R) oral tablets, 2010), is not recommended due to the potential for additive QT prolonging effects (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In a direct comparison study in patient volunteers, QTc prolongation was observed with administration of ziprasidone or quetiapine. The increase in mean QTc change from baseline was 9 to 14 msec greater following administration of oral ziprasidone compared with quetiapine and 3 other comparator drugs (risperidone, olanzapine, and haloperidol); however, the QTc change observed with ziprasidone was 14 msec less than the increase seen with thioridazine administration (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

3.5.1.CE Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CF Ranolazine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Concurrent use of ranolazine and ziprasidone may result in an increased risk of QT interval prolongation due to additive effects (Prod Info Ranexa(R) extended-release oral tablets, 2009). Therefore, caution is warranted when these drugs are administered concomitantly.

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of ranolazine and ziprasidone may increase the risk of QT interval prolongation (Prod Info Ranexa(R) extended-release oral tablets, 2009). Therefore, caution is warranted when co-administering ranolazine and ziprasidone.
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CG Saquinavir

1) Interaction Effect: increased risk of QT interval prolongation and torsades de pointes
2) Summary: The concomitant use of ziprasidone and ritonavir-boosted saquinavir is contraindicated as both drugs have the potential for prolongation of the QT interval (Prod Info GEODON(R) oral suspension, 2009). Concomitant use of ritonavir-boosted saquinavir and ziprasidone should be considered only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either ziprasidone or ritonavir-boosted saquinavir or both (Prod Info INVIRASE(C) oral capsules, tablets, 2010).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of ziprasidone and other drugs that prolong the QT interval, such as ritonavir-boosted saquinavir, is contraindicated (Prod Info GEODON(R) oral suspension, 2009). These drugs may be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either ziprasidone or ritonavir-boosted saquinavir or both (Prod Info INVIRASE(C) oral capsules, tablets, 2010).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CH Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.CI Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Brown & Levin, 1998a; Prod Info Geodon(R), 2002i).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as sertindole is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001c).
c) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002h).

3.5.1.CJ Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.CK Sparfloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including sparfloxacin (Prod Info Geodon(TM), 2002q).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and sparfloxacin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CL Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the co-administration of ziprasidone and other drugs known to prolong the QTc interval, including spiramycin, is not recommended (Prod Info Geodon(TM) ziprasidone, 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as spiramycin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CM Sultopride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Lande et al, 1992e; Montaz et al, 1992a; Harry, 1997a; Prod Info Geodon(R), 2002aa).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that prolong the QT interval, such as sultopride, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992d; Montaz et al, 1992; Harry, 1997).
b) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002z).

3.5.1.CN Sunitinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, caution should be used when sunitinib and ziprasidone are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info SUTENT(R) oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of sunitinib and ziprasidone may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info SUTENT(R) oral capsules, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.CO Tacrolimus

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including tacrolimus (Prod Info Geodon(TM), 2002t).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and tacrolimus is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CP Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.CQ Telavancin

1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: In clinical trials, prolongation of the QT interval was observed with telavancin use (Prod Info VIBATIV IV injection, 2009). Ziprasidone has also been associated with QT interval prolongation. Due to the potential for serious additive effects on the QT interval, ziprasidone should not be used concomitantly with other drugs that prolong the QT interval (Prod Info GEODON(R) oral capsules, IM injection, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for serious additive QT prolongation effects, ziprasidone should not be used with other drugs that also prolong the QT interval (Prod Info GEODON(R) oral capsules, IM injection, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In 3 clinical trials, QTc prolongation greater than 60 msec was observed in 1.5% (15 of 2062) of patients treated with telavancin 10 mg/kg compared with 0.6% (6 of 2062) patients treated with vancomycin. In these studies, 21% (214 of 1029) of telavancin-treated patients and 16% (164 of 1033) of vancomycin-treated patients received concomitant medications known to prolong QTc. Of the patients experiencing QTc prolongation of greater than 60 msec, 9 telavancin-treated patients and 1 vancomycin-treated patient received concomitant medications known to prolong the QTc interval, and less than 1% in each group did not receive a concomitant medication known to prolong the QTc interval. A separate analysis revealed 1 telavancin-treated patient and 2 vancomycin-treated patients experienced a QTc greater than 500 msec. No patients experienced a cardiac adverse event attributed to QTc prolongation (Prod Info VIBATIV IV injection, 2009).

b) In a randomized, double-blind, multiple-dose, positive- and placebo-controlled, parallel study, maximum QTc prolongation of 11.6 msec (upper 90% confidence limit (CL), 16 msec) and 15.1 msec (upper 90% CL, 20 msec) was observed in patients treated with telavancin 7.5 mg/kg and 15 mg/kg, respectively, compared with 21.6 msec (upper 90% CL 26 msec) in the positive-control group. Healthy subjects (n=160) were randomized to telavancin 7.5 mg/kg, telavancin 15 mg/kg, positive control, or placebo infused over 60 min once daily for 3 days. At the end of the infusion, the mean maximum baseline-corrected, placebo-corrected QTc prolongation estimate for telavancin 10 mg/kg (based on interpolation of the data from patients treated with telavancin 7.5 mg/kg and 15 mg/kg) was 12 to 15 msec compared with 22 msec for the positive control. One hour after infusion, the maximum QTc prolongation for telavancin-treated patients was 6 to 9 msec compared with 15 msec for the positive control (Prod Info VIBATIV IV injection, 2009).

3.5.1.CR Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Prod Info Geodon(TM), 2002d; Owens, 2001b).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as telithromycin, is contraindicated.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less

than that observed with thioridazine (Prod Info Geodon(R), 2002b).

3.5.1.CS Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002y; Owens, 2001j; Prod Info Orap(R), 1999e). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.CT Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Tetrabenazine causes a small increase in the corrected QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, ziprasidone) should be avoided (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with ziprasidone or other drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info XENAZINE(R) oral tablets, 2008). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CU Tetrabenazine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CV Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CW Toremifene

1) Interaction Effect: an increased risk of Torsade de pointes
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, the concomitant use of mesoridazine with toremifene is contraindicated (Prod Info GEODON(R)

oral capsules, intramuscular injection, 2010; Prod Info FARESTON(R) oral tablets, 2011).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, the concomitant use of mesoridazine with toremifene is contraindicated (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010; Prod Info FARESTON(R) oral tablets, 2011).
7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.CX Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CY Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001f), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CZ Trimipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.DA Vandetanib

1) Interaction Effect: an increased risk of QT interval prolongation and Torsades de pointes
2) Summary: Vandetanib can prolong the QT interval in a concentration-dependent manner. Torsades de pointes, ventricular tachycardia, and sudden death have been reported in patients taking vandetanib. The concomitant administration of vandetanib and other drugs that prolong the QT interval should be avoided. If these drugs must be coadministered, monitor ECG more frequently. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds. Dosing can then be resumed at a reduced dose (Prod Info CAPRELSA(R) oral tablets, 2011).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of vandetanib and drugs that prolong the QT interval as it may result in additive effects on the QT interval and an increased risk of Torsades de pointes and ventricular tachycardia. If these agents must be given together, monitor ECG more frequently. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and can then resume at a reduced dose (Prod Info CAPRELSA(R) oral tablets, 2011).
7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.DB Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including vasopressin

(Prod Info Geodon(TM), 2002w; Jacoby & Wiegman, 1990).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as vasopressin, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Ziprasidone prolongs the QTc and an increased risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002ab).

3.5.1.DC Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including zolmitriptan (Prod Info Geodon(R), 2002s; Prod Info Zomig(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as zolmitriptan, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002r).

3.5.1.DD Zotepine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval,

such as zotepine, is contraindicated (Prod Info Geodon(R), 2002m; Sweetman, 2003).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that prolong the QT interval, such as zotepine, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon(R), 2002l).

b) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2003).

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Ziprasidone Hydrochloride

1) Therapeutic

a) Physical Findings

1) Improvement in signs and symptoms of schizophrenia or manic or mixed episodes associated with bipolar disorder are indicative of efficacy.

2) Toxic

a) Laboratory Parameters

1) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below (None Listed, 2004):

a) Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control (None Listed, 2004).

b) Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat testing should be done more frequently as clinically indicated (None Listed, 2004).

2) Perform CBC (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010; Prod Info GEODON(R) oral suspension, 2009) with differential frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia or neutropenia.

3) Serum potassium and magnesium levels should be performed at baseline and periodically, especially in patients prone to electrolyte disturbances (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010; Prod Info GEODON(R) oral suspension, 2009).

b) Physical Findings

1) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below (None Listed, 2004):

a) Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease prior to treatment and review annually with patient (None Listed, 2004).

b) Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter (None Listed, 2004).

c) Measure waist circumference at baseline and annually thereafter (None Listed, 2004).

d) Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension (None Listed, 2004).

2) Examine patient for tardive dyskinesia before initiation and then annually. Patients at high risk for tardive dyskinesia (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment (Marder et al, 2004).

3) Closely monitor patients for suicidality during therapy due to the increased risk of suicide attempts in patients with schizophrenia or bipolar disorder (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010; Prod Info GEODON(R) oral suspension, 2009).

B) Ziprasidone Mesylate

1) Therapeutic

a) Physical Findings

1) Reduction of acute agitation in schizophrenia patients is indicative of efficacy.

2) Toxic

a) Laboratory Parameters

1) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below (None Listed, 2004):

a) Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control (None Listed, 2004).

b) Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat

testing should be done more frequently as clinically indicated (None Listed, 2004).

2) Perform CBC (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010) with differential frequently during the first few months of therapy in patients with a history of a clinically significant low WBC or drug-induced leukopenia or neutropenia.

3) (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

4) Serum potassium and magnesium levels should be performed at baseline, and periodically, especially in patients prone to electrolyte disturbances (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

b) Physical Findings

1) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below (None Listed, 2004):

a) Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease, prior to treatment and review annually with patient (None Listed, 2004).

b) Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter (None Listed, 2004).

c) Measure waist circumference at baseline, and annually thereafter (None Listed, 2004).

d) Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension (None Listed, 2004).

2) Examine patient for tardive dyskinesia before initiation and then annually. Patients at higher risk for tardive dyskinesia (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment (Marder et al, 2004).

3) Monitor orthostatic vital signs, especially during the initial dose-titration period, in the elderly, in patients with renal or hepatic impairment, in patients predisposed to hypotension, including those with dehydration and hypovolemia, or known cerebrovascular disease, or cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities) (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010)

4) Closely monitor patients for suicidality during therapy due to the increased risk of suicide attempts in patients with schizophrenia (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

4.2 Patient Instructions

A) Ziprasidone (By mouth)

Ziprasidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to ziprasidone, or if you have severe

heart failure or have recently had a heart attack. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome) or if you are using certain medicines that prolong the QT interval in the heart (such as amiodarone, disopyramide, dofetilide, quinidine, procainamide, sotalol, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, gatifloxacin, moxifloxacin, sparfloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus). This medicine should not be used in elderly patients who have a mental illness called dementia-related psychosis.

How to Use This Medicine:

Capsule

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

It is best to take this medicine with food or milk at the same time every day. Swallow the capsule whole. Do not break, crush, or chew it.

Keep using this medicine for the full treatment time, even if you feel better after the first few doses.

This medicine comes with patient instructions. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are using medicines to lower blood pressure (such as atenolol, lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®).

Tell your doctor if you are using a diuretic or "water pill" (such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®), carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®).

Tell your doctor if you are also using levodopa (Dopart®, Larodopa®), bromocriptine (Parlodel®), pramipexole (Mirapex®), ropinirole (Requip®), cabergoline (Dostinex®), or apomorphine (Apokyn®).

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold

and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have blood or bone marrow problems, prolactin-dependent breast cancer, diabetes, trouble with swallowing, or a history of seizures or neuroleptic malignant syndrome (NMS). Tell your doctor if you have any kind of blood vessel or heart problems, including low blood pressure, heart failure, a low amount of blood, a slow heartbeat, a history of a heart attack or stroke, or low potassium or magnesium levels in your blood. Also, tell your doctor if you have had thoughts of hurting yourself or others.

This medicine can cause changes in the heart rhythm, such as a condition called QT prolongation. It may change the way your heart beats and cause fainting or serious side effects. Contact your doctor right away if you have any symptoms of heart rhythm problems, such as fast, pounding, or irregular heartbeats.

Stop using this medicine and check with your doctor right away if you have any of the following symptoms while using this medicine: convulsions (seizures), difficulty with breathing, a fast heartbeat, a high fever, high or low blood pressure, increased sweating, loss of bladder control, severe muscle stiffness, unusually pale skin, or tiredness. These could be symptoms of a serious condition called neuroleptic malignant syndrome (NMS).

Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you have any of the following symptoms while using this medicine: lip smacking or puckering; puffing of the cheeks; rapid, worm-like movements of the tongue; uncontrolled chewing movements; or other uncontrolled movements of the arms and legs.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. Check with your doctor right away if you have increased thirst or increased urination, or if you have any questions.

This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

This medicine should not be used to treat mental disorders in elderly patients who have dementia. Using this medicine to treat this condition could increase the risk for serious side effects, including death. Make sure the doctor knows if the person who will be using this medicine has forgetfulness or confusion related to aging (such as Alzheimer's disease or dementia).

This medicine may make you dizzy, drowsy, have trouble with thinking, or have trouble with controlling body movements. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert, well-coordinated, or able to think well.

Dizziness, lightheadedness, or fainting may occur, especially when you get up suddenly from a lying or sitting position. Getting up slowly may help. If this problem continues or gets worse, check with your doctor.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if

you are too hot and cannot cool down.
This medicine may cause some people to be agitated, irritable, or display other abnormal behaviors. It may also cause some people to have suicidal thoughts and tendencies. If you or your caregiver notice any of these side effects, tell your doctor right away.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments. Blood tests may be needed to check for unwanted effects.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Chest pain.
Chills, cough, runny or stuffy nose, sore throat, and body aches.
Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.
Fast, slow, pounding, or uneven heartbeat.
Fever, sweating, confusion, or muscle stiffness.
Increased thirst, hunger, or urination.
Lightheadedness, dizziness, or fainting.
Mood or behavioral changes, or thoughts of hurting yourself or others.
Neck muscle spasm, throat tightness, difficulty with swallowing or breathing, or sticking out of the tongue.
Painful, prolonged erection of your penis (in males).
Problems with balance or walking.
Seizures.
Severe diarrhea, nausea, vomiting, or stomach pain.
Skin rash.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:
Anxiety or restlessness.
Changes in vision.
Constipation, diarrhea, nausea, or upset stomach.
Dry mouth.
Headache.
Sleepiness or unusual drowsiness.
Tiredness.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Ziprasidone (Injection)

Ziprasidone

Treats agitation (excessive movement, tension, or anxiety) in a person who has schizophrenia.

When This Medicine Should Not Be Used:

You should not receive this medicine if you have had an allergic reaction to ziprasidone, or if you have severe heart failure or have recently had a heart attack. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome) or if you are using certain medicines that prolong the QT interval in the heart (such as amiodarone, disopyramide, dofetilide, procainamide, quinidine, sotalol, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, gatifloxacin, moxifloxacin, sparfloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus). This medicine should not be used in elderly patients who have a mental illness called dementia-related psychosis.

How to Use This Medicine:

Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.

A nurse or other trained health professional will give you this medicine.

Your doctor will give you a few doses of this medicine until your condition improves, and then switch you to an oral medicine that works the same way. If you have any concerns about this, talk to your doctor.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are using medicines to lower blood pressure (such as atenolol, lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®).

Tell your doctor if you are using a diuretic or "water pill" (such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®), carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®).

Tell your doctor if you are using levodopa (Dopart®, Larodopa®), bromocriptine (Parlodel®), pramipexole (Mirapex®), ropinirole (Requip®), cabergoline (Dostinex®), or apomorphine (Apokyn®).

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have kidney disease, blood or bone marrow problems, prolactin-dependent breast cancer, diabetes, trouble with swallowing, or a history of seizures or neuroleptic malignant syndrome (NMS). Tell your doctor if you have any kind of blood vessel or heart problems, including low blood pressure, heart failure, a low amount of blood, a slow heartbeat, a history of a heart attack or stroke, or low potassium or magnesium levels in your blood. Also, tell your doctor if you have had thoughts of hurting yourself or others.

This medicine can cause changes in the heart rhythm, such as a condition called QT prolongation. It may change the way your heart beats and cause fainting or serious side effects. Contact your doctor right away

if you have any symptoms of heart rhythm problems, such as fast, pounding, or irregular heartbeats.

Check with your doctor right away if you have any of the following symptoms while using this medicine: convulsions (seizures), difficulty with breathing, a fast heartbeat, a high fever, high or low blood pressure, increased sweating, loss of bladder control, severe muscle stiffness, unusually pale skin, or tiredness. These could be symptoms of a serious condition called neuroleptic malignant syndrome (NMS).

Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you have any of the following symptoms while using this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

This medicine should not be used to treat mental disorders in elderly patients who have dementia. Using this medicine to treat this condition could increase the risk for serious side effects, including death. Some side effects are more likely to happen in elderly people who have memory problems or reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has forgetfulness or confusion related to aging (such as Alzheimer's disease or dementia).

This medicine may make you dizzy, drowsy, have trouble with thinking, or have trouble with controlling body movements. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert, well-coordinated, or able to think well.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your urine or blood sugar more often. Check with your doctor right away if you have increased thirst or increased urination, or if you have any questions.

This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

Dizziness, lightheadedness, or fainting may occur, especially when you get up suddenly from a lying or sitting position. Getting up slowly may help. If this problem continues or gets worse, check with your doctor.

This medicine may cause you to become overheated more easily than usual. Be careful when exercising, or when you are outdoors in hot or humid weather.

This medicine may cause some people to be agitated, irritable, or display other abnormal behaviors. It may also cause some people to have suicidal thoughts and tendencies. If you or your caregiver notice any of these side effects, tell your doctor right away.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments. Blood tests may be needed to check for unwanted effects.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Chills, cough, runny or stuffy nose, sore throat, and body aches.

Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.

Fast, slow, pounding, or uneven heartbeat.

Fever, sweating, confusion, or muscle stiffness.
Increased thirst, hunger, or urination.
Lightheadedness, dizziness, or fainting.
Mood or behavioral changes, or thoughts of hurting yourself or others.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Painful, prolonged erection of your penis (in males).
Problems with balance or walking.
Red or black stools.
Seizures.
Severe diarrhea, nausea, vomiting, or stomach pain.
Skin rash.
Trouble with swallowing or talking, sticking out of the tongue, or spasm of the neck muscles.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:
Anxiety or restlessness.
Headache.
Pain where the shot was given.
Sleepiness or unusual drowsiness.
Tiredness.
Trouble with sleeping.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Ziprasidone

1) Current users of atypical antipsychotic drugs (including ziprasidone) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly in-

creased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

2) General (atypical agents): patients resistant to standard antipsychotic agents; patients with therapy-limiting extrapyramidal symptoms, other adverse effects.

3) Specific: comparisons of ziprasidone with clozapine, risperidone, olanzapine, and sertindole in refractory patients are needed to determine potential advantages. Disadvantages of ziprasidone: prolongation of QT/QTc interval, shorter half-life, twice-daily dosing usually required (olanzapine, sertindole may be given once daily).

B) Ziprasidone Hydrochloride

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

C) Ziprasidone Mesylate

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) Ziprasidone Hydrochloride

1) Mechanism of Action

a) The exact mechanism of action of ziprasidone hydrochloride is unknown; however, it is proposed that ziprasidone exerts action as a psychotropic agent for schizophrenia by antagonism of dopamine type 2 and serotonin type 2 receptors. The activity of ziprasidone is primarily through the parent drug and unchanged ziprasidone represents about 44% of total drug-related material in the serum. The exact mechanism in bipolar disorder is unknown. In vitro, ziprasidone demonstrated high binding affinity for dopamine D2 and D3, serotonin 5HT2A, 5HT2C, 5HT1A, 5HT1D, and alpha(1)-adrenergic receptors. Moderate binding affinity to the histamine H1 receptor was also demonstrated. Some side effects of ziprasidone may be explained by antagonistic effects at 5HT2, histamine H1 (somnolence), and alpha(1)-adrenergic (orthostatic hypotension) receptors (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

B) Ziprasidone Mesylate

1) Mechanism of Action

a) The exact mechanism of action of ziprasidone hydrochloride is unknown; however, it is proposed that ziprasidone exerts action as a psychotropic agent for schizophrenia by antagonism of dopamine type 2 and serotonin type 2 receptors. The activity of ziprasidone is primarily through the parent drug and unchanged ziprasidone represents about 44% of total drug-related material in the serum. The exact mechanism in bipolar disorder is unknown. In vitro, ziprasidone demonstrated high binding affinity for dopamine D2 and

D3, serotonin 5HT2A, 5HT2C, 5HT1A, 5HT1D, and alpha(1)-adrenergic receptors. Moderate binding affinity to the histamine H1 receptor was also demonstrated. Some side effects of ziprasidone may be explained by antagonistic effects at 5HT2, histamine H1 (somnolence), and alpha(1)-adrenergic (orthostatic hypotension) receptors (Prod Info GEODON(R) oral capsules, intramuscular injection, 2010).

4.5 Therapeutic Uses

4.5.A Ziprasidone

4.5.A.1 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B Ziprasidone Hydrochloride

4.5.B.1 Bipolar I disorder, Acute manic or mixed episodes, monotherapy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated as monotherapy for the treatment of acute manic or mixed episodes in patients with bipolar disorder, with or without psychotic features (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009; Keck et al, 2003)

c) Adult:

1) Ziprasidone was more effective than placebo for treating acute bipolar mania. In a randomized, double-blind, multicenter, placebo-controlled trial, 210 bipolar inpatients, currently in a manic or mixed episode, underwent single-blind placebo treatment for a one-week washout and were then randomized 2:1 to receive ziprasidone (n=140) or placebo (n=70) for 3 weeks. Ziprasidone, given with meals, was started at 40 milligrams (mg) twice daily on day 1, raised to 80 mg twice daily on day 2, and then adjusted if necessary during the trial to a final range of 80 to 160 mg/day. Data from 131 ziprasidone-treated patients and 66 placebo-treated patients were used for determining efficacy. On the 11-item Mania Rating Scale, a significantly greater improvement with ziprasidone compared to placebo was evident by day 2 (p less than 0.003) and remained apparent throughout the study (p less than 0.001 at the end of weeks 1, 2, and 3). By the end of the study, significant differences between the groups, favoring ziprasidone over placebo, were evident on the Clinical Global Impressions (CGI) severity scale, the CGI improvement scale, the Positive and Negative Syndrome Scale, and the Global Assessment of Functioning Scale. Fifty percent of patients receiving ziprasidone and 35% receiving placebo were classified

as responders (p less than 0.05). In the ziprasidone group, 6.4% of patients (9 of 140) withdrew because of adverse events, compared to 4.3% (3 of 70) of the placebo group. None of the treatment-related adverse events in either group was serious. The most commonly occurring adverse events were somnolence (ziprasidone vs placebo: 37% vs 13%), headache (21% vs 19%), dizziness (22% vs 10%), and akathisia (11% vs 6%). Movement disorders were uncommon. No change in weight was associated with ziprasidone treatment. Ziprasidone treatment showed a mean prolongation in QT(c) interval of 11 milliseconds (msec). No patient had a QT(c) interval of 500 msec or higher (Keck et al, 2003).

4.5.B.2 Bipolar I disorder, to lithium or valproate; Adjunct

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or valproate (Prod Info GEODON oral capsules, IM injection, 2009)

c) Adult:

1) As adjunctive therapy to lithium or valproate in the treatment of bipolar I disorder, ziprasidone (n=127) was superior to placebo (n=112) in increasing the time to recurrence of a mood episode (depressive, manic, or mixed) in a placebo-controlled trial of patients who met DSM-IV criteria for bipolar I disorder. Eligible patients were required to be stabilized on ziprasidone plus lithium or valproate for at least 8 weeks prior to randomization. The primary endpoint was time to recurrence of a mood episode requiring clinical intervention, including discontinuation of treatment, initiation of medication or hospitalization, or a Mania Rating Scale score 18 or higher or a MADRS (Montgomery-Asberg Depression Rating Scale) score of 18 or higher on 2 consecutive assessments within 10 days (Prod Info GEODON oral capsules, IM injection, 2009).

4.5.B.3 Schizoaffective disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Oral ziprasidone has been shown to be effective in the short term treatment of patients with an acute episode of schizoaffective disorder (Keck et al, 2001).

c) Adult:

1) Significant dose-related improvements on all primary efficacy variables (BPRS total, BPRS Core, CGI-S and BPRS Manic scores) were observed in patients receiving ziprasidone compared to placebo in 2 multicenter double-blind placebo-controlled clinical trials (n=115). Inclusion criteria consisted of hospitalized patients with an acute exacerbation of schizoaffective disorder, bipolar or depressive subtype. Patients were required to have a minimum duration of illness of at least 6 months or 1 year. In one study patients were randomized to receive ziprasidone 20 milligrams (mg) twice daily or placebo for 4 weeks. In the second study, patients were randomized to receive ziprasidone 40 mg twice daily, 80 mg twice daily or placebo for 6 weeks. The incidence of individual adverse events was generally low in all treatment groups (Keck et al, 2001).

4.5.B.4 Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class I

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Ziprasidone has been associated with positive and negative symptom improvement with relatively low incidence of extrapyramidal symptoms (Reeves & Harrigan, 1996; Harrigan et al, 1996; Citrome, 1997a; Kerwin & Taylor, 1996a; Anon, 1996b).

Clinical trials have demonstrated that ziprasidone decreases the rate of relapse in patients with chronic, stable schizophrenia (Prod Info GEODON(R) oral suspension, 2009; Arato et al, 2002; Prod Info GEODON oral capsules, IM injection, 2009).

Patients with acute exacerbation of schizophrenia or schizoaffective disorder receiving ziprasidone had significant improvement in positive, negative, and depressive symptoms within one week compared with placebo (Daniel et al, 1999; Diaz-Marsa et al, 2009).

c) Adult:

1) Results of the Ziprasidone Extended Use in Schizophrenia (ZEUS) study indicate that ziprasidone treatment decreased the rate of relapse in patients with chronic, stable schizophrenia. In this randomized, double-blind, placebo-controlled study, markedly ill (score of 5 or lower on the Clinical Global Impression Severity scale) patients with chronic, stable schizophrenia in extended-stay, inpatient settings received twice daily doses of ziprasidone 40 milligrams (mg)/day (n=72), ziprasidone 80 mg/day (n=68), ziprasidone 160 mg/day (n=67) or placebo (n=71) for up to 1 year. Patients were allowed to receive anticholinergics, lorazepam, and temazepam, but no other psychotropic medications were permitted during the study. The likelihood of relapse at 1 year was significantly lower in patients treated with ziprasidone 40 mg/day (43%), 80 mg/day (35%) or 160 mg/day (36%) as compared with placebo (77%) (p=0.002, p less than 0.001, p less than 0.001, respectively). Of the ziprasidone-treated patients who relapsed during the study, most (61/71) did so in the first 6 months. However, of patients who stayed in the study for at least 6 months only 9% (10/110) of patients in the ziprasidone groups eventually re-

lapsed, as compared with 42% (8/19) of placebo-treated patients (p=0.001). Patients in all three ziprasidone treatment groups showed significantly better improvements in negative symptoms as compared with placebo beginning at week 16 and continuing until the end of the study. Ziprasidone was generally well tolerated, however, one patient had a grand mal seizure and another experienced extrapyramidal symptoms during treatment (Arato et al, 2002).

2) In a double-blind, randomized, placebo-controlled trial, patients with acute exacerbation of schizophrenia or schizoaffective disorder receiving ziprasidone had significant improvement in positive, negative, and depressive symptoms within one week compared with placebo. Patients were randomized to ziprasidone 80 milligrams (mg) per day (n=106, mean age 36.8 years old), ziprasidone 160 mg per day (n=104, mean age 35.8 years old) or placebo (n=92, mean age 37.2 years old) for 6 weeks. All patients presented with baseline Positive and Negative Syndrome Scale (PANSS) scores of at least 60 (mean of 98.2, 95.8 and 97.3 in the 80-mg, 180-mg, and placebo groups, respectively), and remained hospitalized for the first 14 days of the study. Depressive symptoms were present at baseline in 50% of all patients per Montgomery Asberg Depression Rating Scale (MADRS). PANSS, Brief Psychiatric Rating Scale, Clinical Global Impression-Improvement, and Positive and Negative Syndrome Scale-Negative scores decreased significantly in each of the ziprasidone groups compared with placebo (p=0.05). Ziprasidone patients identified with depressive symptoms at baseline had significant improvement in MADRS scores (p=0.05). All differences became apparent at week 1, and were maintained at week 6. Extrapyramidal symptoms were reported in 1% of placebo patients, 2% of ziprasidone 80 mg patients, and 7% of ziprasidone 160 mg patients (Daniel et al, 1999).

3) In a case series of 196 inpatients with acute exacerbation of schizophrenia or schizoaffective disorder, ziprasidone significantly reduced symptoms within one week of initiation. Patients (mean age 38.4 years old, 60.1% male) were moderately ill at baseline, with mean Brief Psychiatric Rating Scale (BPRS) score of 58.3 and mean Clinical Global Impession-Severity (CGI-S) score of 5.3. Mean initial ziprasidone dose was 136.9 milligrams (mg) per day; at discharge the mean dose was 186.3 mg per day, and at that point 75% of patients were taking at least 160 mg per day, with 45% of patients taking a dose above 160 mg per day. Response to treatment, defined as at least 30% reduction in ratings scores, was noted in 74% (95% confidence interval (CI), 68% to 80%) of patients via BPRS criteria, and 67% (95% CI, 61% to 74%) of patients via CGI-S score at hospital discharge (average length of stay 23.4 days). Effects became statistically significant compared with baseline at week one, and persisted throughout follow-up. Daily doses between 120 mg per day and 240 mg per day were associated with greater likelihood of response compared with doses below 120 mg per day (odds ratio, 3.7; 95% CI, 1.5 to 8.8). Common side effects were sedation (16.3%), somnolence (7.1%), restlessness (6.1%), akathisia (4.1%), insomnia (3.1%), anxiety (2.5%), tremor (2.6%) and parkinsonism (1%); no events were considered severe (Diaz-Marsa et al, 2009).

4) Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the 2 dose groups in a 52-week, placebo-controlled trial (n=294). Inpatients were randomized to receive ziprasidone 20 milligrams (mg) twice daily, 40 mg twice daily, 80 mg twice daily or placebo (Prod Info GEODON(R) oral suspension, 2009; Prod Info GEODON oral capsules, IM injection, 2009).

4.5.C Ziprasidone Mesylate

4.5.C.1 Agitation, acute - Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class I

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intramuscular ziprasidone mesylate is effective for the treatment of acute agitation in schizophrenic patients (Prod Info GEODON oral capsules, IM injection, 2009)

In an open-label three-day study (n=21), intramuscular (IM) ziprasidone significantly improved mean Brief Psychiatric Rating Scale (BPRS) and Behavioral Activity Rating Scale (BARS) scores from baseline in elderly patients with schizophrenia-related acute psychotic agitation (Barak et al, 2006)

c) Adult:

1) The efficacy of intramuscular ziprasidone mesylate for the treatment of acute agitation in schizophrenia was established in two double-blind, randomized, single-day trials. Acutely agitated schizophrenic patients with a score of 3 or higher on at least three Positive and Negative Syndrome Scale (PANSS) items (anxiety, tension, hostility, and excitement) received either a control dose (2 milligrams) or a higher dose of ziprasidone. In the first study, patients (n=79) received 20 mg or 2 mg of intramuscular ziprasidone up to four times in 24 hours at intervals of at least 4 hours. The higher dose of ziprasidone was statistically superior to the control dose as assessed by the area under the curve (AUC) of the Behavioral Activity Rating Scale (BARS) at 0 to 4 hours and by the Clinical Global Impression (CGI) severity rating at 4 hours and at endpoint. In the second study, patients (n=117) received 10 mg or 2 mg of intramuscular ziprasidone up to four times in 24 hours at intervals of at least 2 hours. The 10 mg dose of ziprasidone was statistically superior to the 2 mg dose as assessed by the AUC of the BARS at 0 to 2 hours , but not by the CGI severity rating (Prod Info GEODON oral capsules, IM injection, 2009).

2) In an open-label three-day study (n=21), intramuscular (IM) ziprasidone significantly improved mean Brief Psychiatric Rating Scale (BPRS) and Behavioral Activity Rating Scale (BARS) scores from baseline in elderly patients with schizophrenia-related acute psychotic agitation. Patients (mean age, 71.4 +/- 1.3 years (yr); range, 60 to 81 yr) hospitalized with acute psychosis related to schizophrenia (diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria) were eligible for enrollment. Concomitant use of other psychotropic medications was not permitted. Following hospitalization and screening procedures (1 to 6 hours), patients received three days of flexible-dose IM ziprasidone (10 or 20 mg initially, followed by 10 to 20 mg every 12 hours as needed; not to exceed 40 mg per day). After three days of ziprasidone therapy, the mean BPRS score significantly decreased by 26.8 points from 76.9 +/- 2.4 points at baseline to 50.1+/- 1.9 points at study completion (p=0.001). Additionally, the mean BARS score (measure of agitation) decreased from 5.8 +/- 0.16 points at baseline to 2.14 points after the 6th injection at study completion (p=0.001). Reported adverse events included acute urinary retention (1 patient), blurred vision (1 patient), and sedation (1 patient) (Barak et al, 2006).

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of ziprasidone was 120 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

4.6.B Clozapine

4.6.B.1 Schizophrenia

a) Ziprasidone was as effective as clozapine in the treatment of adults with schizophrenia resistent or intolerant to multiple cycles of antipsychotic therapy, according to an 18-week, randomized, double-blind, flexible-dose, equivalence MOZART trial (Monitoring Oral Ziprasidone As Rescue Therapy; n=147). Patients diagnosed with DSM-IV schizophrenia and resistant or intolerant to 6 weeks of antipsychotic therapy, with baseline Clinical Global Impression Severity (CGI-S) scale score of at least 4, and a Positive and Negative Syndrome Scale (PANSS) score of at least 80 were included in the study. At baseline patients had a mean total PANSS score was 107 and CGI-S score of 5.2. Following a 1- to 7-day washout period and a 3-day placebo run-in period, patients were randomized to receive either ziprasidone (n=73) or clozapine (n=73). Ziprasidone therapy was initiated with 80 milligrams (mg)/day divided in 2 doses for 3 days, then flexibly dosed 80 to 160 mg/day. Clozapine was initiated with 25 mg/day titrated to 300 mg/day over 10 days, maintained for 1 week, then flexibly dosed 250 to 600 mg/day. Concomitant benzodiazepines, anticholinergic drugs, and propranolol was permitted. Clinical equivalence was defined as 13.5 points on the PANSS total score to yield an effect size of 0.45. The rate of premature discontinuation from the trial was similar in both groups (28 patients in each group (38.4%)) mainly due to adverse events. In an intent-to-treat analysis with last observation carried forward, the PANSS total score change from baseline was -25 +/- 22 (95% CI, -30.2 to -19.8) in ziprasidone-treated patients compared with -24.5 +/- 22.5 (95% CI, -29.7 to -19.2) in clozapine-treated patients, with no significant difference seen between treatment groups, yielding a baseline to endpoint effect size of 1.41 and 1.38, respectively. There were no significant differences between treatment groups in an analysis of subscale PANSS positive, negative, and general psychopathology, and in CGI-S score improvement. Treatment-emergent adverse events occurred in 71% (n=52) of ziprasidone-treated patients and in 79.5% (n=58) of clozapine-treated patients. There were significant decreases from baseline in median fasting total cholesterol, LDL-C, and triglycerides in ziprasidone-treated patients (p less than 0.05) (Sacchetti et al, 2009).

4.6.C Haloperidol

4.6.C.1 Chronic schizophrenia

a) Ziprasidone was as effective as haloperidol in treating overall symptomatology, was more effective in the treatment of negative symptoms, and was better tolerated, in the long-term treatment of outpatients with stable schizophrenia. In a 28-week, double-blind, flexible-dose, parallel-group clinical trial, ziprasidone and haloperidol both improved overall symptomatology in 227 patients with chronic or sub-chronic schizophrenia. Patients who received ziprasidone had a significantly higher rate of improvement in the treatment of negative symptoms (48% of patients showed improvement) compared to patients who received haloperidol (33% of patients showed improvement). For patient assessment, the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and the Montgomery-Asberg Depression Rating Scale (MADRS) were used at baseline and weeks 3, 6, 16, and 28. In the ziprasidone group, patients received a starting dose of 40 milligrams per day (mg/d) on the first 2 days and 80 mg/d on day 3. The ziprasidone dose could be increased to a maximum of 120 mg/d in the second week and up to 160 mg/d in the third week. For the haloperidol group, patients received a starting dose of 5 mg/d, which could be increased to a maximum of 10 mg/d during the second week and 15 mg/d during the third week of treatment. At week 28, the mean doses of ziprasidone and haloperidol were 116.5 mg/d and 8.6 mg/d, respectively. Adverse events were evaluated using the Simpson-Angus scale, the Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (AIMS). Adverse events were reported in 85% of patients in the haloperidol group and 77% in the ziprasidone group; twice as many patients receiving haloperidol (16%) compared to ziprasidone (8%) discontinued the study due to treatment-related adverse events. There was also a distinct difference in the percentage of patients who developed movement disorders; 41% in the haloperidol group compared to 15% in the ziprasidone group, although this difference was not statistically significant (Hirsch et al, 2002).

4.6.C.2 Schizophrenic episode, acute

a) Acute exacerbations: ziprasidone 160 mg daily, haloperidol 15 mg daily comparable in efficacy (reduction of BPRS scores). Ziprasidone 4 to 40 mg/day less effective (Anon, 1996).

b) Ziprasidone 160 milligrams (mg) and haloperidol 15 mg were both effective in improving overall psychopathology in patients with an acute exacerbation of schizophrenia or schizoaffective disorder (Goff et al, 1998). In a double-blind, dose-ranging study, patients received either haloperidol 15 mg/day (n=17), or ziprasidone 4 mg (n=19), ziprasidone 10 mg (n=17), ziprasidone 40 mg (n=17), or ziprasidone 160 mg (n=20). Despite 46 patients failing to complete the study, intention-to-treat analysis showed a trend toward significance for the ziprasidone dose response on the Brief Psychiatric Rating scale (p=0.08) and a statistically significant dose response for the Clinical Global Impression (CGI) scale (p less than 0.001). Changes in the CGI severity score were significantly changed from baseline as compared to the ziprasidone 4 mg group for both the haloperidol group (p less than 0.01) and the ziprasidone 160 mg group (p=0.001). Study termination was due to 18 patients having a lack of efficacy (4 in the haloperidol group), 7 due to liver transaminase elevations in ziprasidone groups, and 23 for unrelated reasons.

c) In hospitalized patients, the mean reductions in BPRS total, BPRS agitation items, and CGI were statistically greater after INTRAMUSCULAR (IM) ziprasidone than IM haloperidol, and this continued following conversion to oral treatment. The study was a multicenter, 7-day, randomized, open-label, parallel-group study in 7 countries (n=132). Patients received either an initial dose of ziprasidone 10 milligrams (mg) IM, followed by up to 3 days of flexible-dose IM ziprasidone (5 mg to 20 mg every 4 to 6 hours

prn) and continued with oral treatment (80 mg to 200 mg/day) to day 7 (n = 90), or haloperidol IM (2.5 mg to 10 mg) on entry, followed by 2.5 mg to 10 mg IM every 4 to 6 hours prn up to 3 days followed by oral haloperidol 10 mg/day to 80 mg/day to day 7 (n = 32). Ziprasidone was associated iwth a lower incidence of movement disorders compared to haloperidol (Brook et al, 2000).

4.6.D Olanzapine

4.6.D.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.D.2 Schizophrenia

a) In a randomized, double-blind trial (n=269), six-week courses of OLANZAPINE and ZIPRASIDONE had comparable efficacy for treatment of schizophrenia or schizoaffective disorder (DSM-IV), while the side effects profile of ziprasidone appeared to be more favorable with respect to metabolic indicators but less favorable related to QT interval prolongation. Enrollees were acutely ill, recently admitted inpatients. During the first week, subjects received fixed doses of study drugs: olanzapine 5 milligrams (mg) on days 1 and 2 and 10 mg/day on days 3 to 7 (n=133); ziprasidone 40 mg twice daily on days 1 and 2 and 80 mg twice daily on days 3 to 7 (n=136). Dosing was flexible over weeks 2-6 (olanzapine 5 to 15 mg/day; ziprasidone 40 to 80 mg twice daily); overall median daily doses were 12.4 mg for olanzapine and 138.6 mg for ziprasidone (the latter in 2 divided doses daily). Efficacy measures included the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) severity and improvement scales, Positive and Negative Syndrome Scale, and the Calgary Depression Scale for Schizophrenia. At study end, there were no significant differences on any rating scale between improvements in the olanzapine group and those in the ziprasidone group. At endpoint, 36.8% of the olanzapine group and 48.5% of the ziprasidone group had discontinued. Overall, 39.8% and 46.3% of the olanzapine and ziprasidone groups, respectively, had experienced adverse events that were considered treatment related. No between-group differences were seen related to dyskinesia, dystonia, or extrapyramidal symptoms. Weight gain amounted to approximately 3.5

kilograms (kg) and 1 kg for olanzapine- and ziprasidone-treated patients, respectively (p less than 0.0001). Total cholesterol, low- density lipoprotein cholesterol, and triglycerides increased by approximately 10%, 13%, and 25%, respectively, in the group receiving olanzapine; all the same measures decreased slightly in the ziprasidone group (p less than 0.0001; p=0.0004; p less than 0.003, respectively). Fasting serum insulin increased by median 3.3 and 0.25 micro- units/milliliter in the olanzapine and ziprasidone groups, respectively (p=0.051). Prolongation of the QTc interval amounted to 0.52 and 6.08 milliseconds for the same 2 groups, respectively (p less than 0.05) (Simpson et al, 2004).

b) A multicenter, randomized, double-blind, parallel-group, 28 week study (n=548) found that olanzapine therapy resulted in significantly greater psychopathology improvement and higher response and completion rates compared to ziprasidone, while ziprasidone therapy was superior for weight change and lipid profile. Patients with schizophrenia were randomized to receive olanzapine (n=277) 10 to 20 mg/day or ziprasidone (n=271) 80 to 160 mg/day. The primary efficacy measure, the Positive and Negative Syndrome Scale total score, showed that the olanzapine group had significantly greater improvement than the ziprasidone group (p less than 0.001). The olanzapine group also showed significant improvement from baseline to endpoint compared to ziprasidone in the Positive and Negative Syndrome subscales: positive symptoms, negative symptoms, general psychopathology, cognition, and excitability (all p less than 0.0001 except for negative symptoms p=0.003). Patients were allowed to take benzodiazepines or hypnotic monotherapy during the study, but were removed from the study if they required more than two concurrent benzodiazepine hypnotic medications. Significantly more patients in the ziprasidone group required at least one dose of a benzodiazepine compared to the olanzapine group (53.5% versus 40.4%; p=0.003). Response was defined as a 30% improvement in the Positive and Negative Syndrome Scale total score at endpoint, and the rate was significantly higher for the olanzapine group compared to the ziprasidone group (58.6% versus 42.5%) (p less than 0.001). There was no significant difference in exacerbation of symptoms between the two groups, which was defined as a decrease in the Positive and Negative Syndrome Scale total score by 20% or more and a decrease in the Clinical Global Impression severity of illness score of 1 point or more after week 8 (14.6% olanzapine and 25.3% ziprasidone; p=0.06). Significantly more patients in the olanzapine group (59.6%) than in the ziprasidone group (42.4%) completed the study (p less than 0.001). Reasons for discontinuation were only significant for lack of efficacy (olanzapine 7.2% versus ziprasidone 13.7%; p=0.02) and aggravation of psychosis (olanzapine 1.4% versus ziprasidone 4.4%; p=0.05). There were significantly greater increases in body weight and levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (all p less than 0.001) and a significantly greater decrease in high-density lipoprotein cholesterol (p=0.001) in the olanzapine group than in the ziprasidone group (Breier et al, 2005).

4.6.E Perphenazine

4.6.E.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160

mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F Quetiapine

4.6.F.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.G Risperidone

4.6.G.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI),

0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

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Product Information: Geodon(R), ziprasidone capsules. Pfizer, Inc., New York, NY, 2002k.

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Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002ab.

Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002b.

Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002c.

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Product Information: Geodon(R), ziprasidone for injection. Pfizer Inc., New York, NY, 2002s.

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Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002g.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002h.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002i.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002l.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002m.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002n.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002o.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002t.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002u.

Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002z.

Product Information: Geodon(R), ziprasidone. Pfizer Inc., NY, NY, 2002a.

Product Information: Geodon(R), ziprasidone. Pfizer Inc., NY, NY, 2002ac.

Product Information: Geodon(R), ziprasidone. Pfizer Inc., NY, NY, 2002y.

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Product Information: PCE(R), erythromycin particles in tablets. Abbott Laboratories, North Chicago, IL, 1997.

Product Information: Propulsid(R), cisapride. Janssen Pharmaceutica, Titusville, NJ, 2000.

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END OF DOCUMENT

TOC

Ziprasidone

Class: 28:16.08.04 Atypical Antipsychotics

Special Alerts:

[Posted 02/22/2011] **ISSUE:** FDA notified healthcare professionals that the Pregnancy section of drug labels for the entire class of antipsychotic drugs has been updated. The new drug labels now contain more and consistent information about the potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy.

The symptoms of EPS and withdrawal in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays.

BACKGROUND: Antipsychotic drugs are used to treat symptoms of psychiatric disorders such as schizophrenia and bipolar disorder.

RECOMMENDATION: Healthcare professionals should be aware of the effects of antipsychotic medications on newborns when the medications are used during pregnancy. Patients should not stop taking these medications if they become pregnant without talking to their healthcare professional, as abruptly stopping antipsychotic medications can cause significant complications for treatment. For more information visit the FDA website at:http://www.fda.gov/Safety/MedWatch/SafetyInformation andhttp://www.fda.gov/Drugs/DrugSafety.

Introduction

Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.(1)(4)(10)(11)(29)

Uses

Psychotic Disorders

Schizophrenia

Ziprasidone is used for the symptomatic management of schizophrenia.(1) Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse.(29) Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia.(29) Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile. (29)(70)(71)(72)

Exhibit 3

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents.(1) (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.(2)(3)(5)

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings.(1)(2)(3)(7) Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.(1)(2)(3)(7)

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks).(1)(6) Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.(12)

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior).(1) The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings.(1) Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.(1)

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Bipolar Disorder

Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder.(1)(73)(74) According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).(69)

Efficacy of ziprasidone in the treatment of acute manic and mixed episodes has been demonstrated in 2 short-term (3 weeks' duration), double-blind, placebo-controlled trials in patients who met the DSM-IV criteria for bipolar I disorder and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features).(1)(73)(74) The

principal rating instruments used for assessing manic symptoms in these trials were the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C) with items grouped as the Manic Syndrome subscale (e.g., elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation Subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment), and impaired insight, and the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response. (1)(73)(74)

- In the first 3-week, placebo-controlled trial, ziprasidone hydrochloride was given at an initial dosage of 40 mg twice daily on the first day and 80 mg twice daily on the second day; dosage adjustment in 20-mg twice daily increments within a dosage range of 40–80 mg twice daily was then permitted for the remainder of the study. (1)(73) The mean daily dosage of ziprasidone hydrochloride in this study was 132 mg. (1)(73) In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of ziprasidone hydrochloride 40 mg twice daily on the first day; subsequent dosage titration in 20-mg twice daily increments within a dosage range of 40–80 mg twice daily was permitted. (1)(74) The mean daily dosage of ziprasidone hydrochloride in this study was 112 mg daily.(1)(74) Ziprasidone was found to be superior to placebo in the reduction of the MRS total score and the CGI-S score in both of these studies.(1)(73)(74)

- For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate.(75) For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy.(75) For further information on the management of bipolar disorder, see Uses: Bipolar Disorder in Lithium Salts 28:28.

- The manufacturer states that efficacy of ziprasidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) or for prophylactic use in patients with bipolar disorder.(1)

Dosage and Administration

Supplementary dosing info/calc

Administration

Ziprasidone hydrochloride is administered orally twice daily with food.(1) Ziprasidone mesylate is administered only by IM injection.(1)

The commercially available lyophilized powder of ziprasidone mesylate for injection must be reconstituted prior to administration by adding 1.2 mL of sterile water for injection to single-dose vials of ziprasidone to provide a solution containing 20 mg/mL.(1) Other solutions should not be used to reconstitute ziprasidone mesylate injection, and the drug should not be admixed with other drugs.(1) The vials should then be shaken vigorously to ensure complete dissolution.(1) Strict aseptic technique must be observed since the drug contains no preservative.(1) Following reconstitution, ziprasidone mesylate for injection is stable for 24 hours when protected from light and stored at 15–30°C or for up to 7 days when refrigerated at 2–8°C.(1) Ziprasidone mesylate injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.(1)

Dosage

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Dosage of ziprasidone hydrochloride is expressed in terms of the hydrochloride monohydrate.(1)(12) Dosage of ziprasidone mesylate is expressed in terms of ziprasidone.(1)

Schizophrenia

Oral Dosage

For the symptomatic management of schizophrenia, the recommended initial adult dosage of ziprasidone hydrochloride is 20 mg orally twice daily.(1) Dosage may be increased after a minimum of 2 days at each dosage up to a maximum recommended dosage of 80 mg twice daily.(1)(12) To ensure use of the lowest effective dosage, however, it is recommended that patients be observed for several weeks prior to upward titrations of ziprasidone dosages.(1) While a relationship between dosage and antipsychotic effect has not been established, the effective dosage of ziprasidone hydrochloride in clinical studies generally ranged from 20–100 mg twice daily.(1) The manufacturer states that dosages exceeding 80 mg twice daily generally are not recommended, and safety of ziprasidone hydrochloride in dosages exceeding 100 mg twice daily has not been established.(1)

The optimum duration of ziprasidone therapy currently is not known, but maintenance therapy with ziprasidone hydrochloride 20–80 mg twice daily has been shown to be effective for up to 52 weeks.(1) However, the manufacturer states that no additional benefit has been demonstrated for ziprasidone hydrochloride dosages beyond 20 mg twice daily.(1) Patients responding to ziprasidone therapy should continue to receive the drug as long as clinically necessary and tolerated, but at the lowest possible effective dosage,(12) and the need for continued therapy with the drug should be reassessed periodically.(1)

IM Dosage

For the prompt control of acute agitation in patients with schizophrenia, the recommended initial adult IM dose of ziprasidone is 10–20 mg given as a single dose.(1) Depending on patient response, doses of 10 or 20 mg may be repeated every 2 or 4 hours, respectively, up to a maximum cumulative dose of 40 mg daily.(1)

Oral therapy should replace IM therapy as soon as possible.(1) Safety and efficacy of administering ziprasidone mesylate IM injection for longer than 3 consecutive days have not been evaluated.(1) Because there is no experience regarding the safety of administering ziprasidone mesylate IM injection to patients with schizophrenia who already are receiving oral ziprasidone hydrochloride, the concomitant use of oral and IM formulations of ziprasidone is not recommended by the manufacturer.(1)

Bipolar Disorder

Oral Dosage

For the management of acute manic and mixed episodes associated with bipolar disorder (with or without psychotic features), the recommended initial adult dosage of ziprasidone

hydrochloride is 40 mg orally twice daily on the first day of therapy.(1) Dosage should then be increased to 60 or 80 mg twice daily on the second day of therapy.(1) Subsequent dosage adjustments based on efficacy and tolerability may be made within a dosage range of 40–80 mg twice daily. (1) In the flexible-dosage clinical trials, the mean daily dosage of ziprasidone hydrochloride was approximately 120 mg.(1)(74)(75)

The optimum duration of ziprasidone hydrochloride therapy for bipolar disorder currently is not known.(1) While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone beyond 3 weeks.(1) Therefore, the manufacturer states that clinicians who elect to use ziprasidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.(1)

Special Populations

No special population dosage recommendations at this time.(1)

Cautions

Contraindications

Known history of QT prolongation (including congenital long QT syndrome), recent acute myocardial infarction, or uncompensated heart failure.(1) (See Prolongation of QT Interval under Warnings/Precautions: Warnings, in Cautions.) Concomitant therapy with other drugs that prolong the QT interval.(1) (See Drug Interactions: Drugs that Prolong QT Interval.) Known hypersensitivity to ziprasidone.(1)

Warnings/Precautions

Warnings

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Increased Mortality in Geriatric Patients with Dementia-related Psychosis

Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo.(1)(68) Analyses of seventeen placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6 - to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo.(1)(68) Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group.(1)(68) Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.(1)(68) The manufacturer states that ziprasidone is not approved for the treatment of patients with dementia-related

psychosis.(1) (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Prolongation of QT Interval

Prolongation of the QT interval can result in an occurrence of ventricular arrhythmias (e.g., torsades de pointes) and/or sudden death.(1) In one study, oral ziprasidone prolonged the QT interval on ECG by a mean of 9–14 msec more than that observed in patients receiving risperidone, olanzapine, quetiapine, or haloperidol, but approximately 14 msec less than that observed in patients receiving thioridazine.(1) In a study evaluating the QT/QT_c prolongation effect of IM ziprasidone, the mean increase in QT_c from baseline following 2 IM injections of ziprasidone (20 mg, then 30 mg, which is 50% higher than the recommended therapeutic dose) or haloperidol (7.5 mg, then 10 mg), given 4 hours apart, was 12.8 or 14.7 msec, respectively.(1) Therefore, although torsades de pointes was not associated with ziprasidone therapy when the drug was administered at recommended dosages in premarketing clinical studies, experience with the drug is too limited to rule out the possibility that ziprasidone may be associated with a greater risk of sudden death than other antipsychotic agents.(1) Patients at particular risk of torsades de pointes and/or sudden death include those with bradycardia, hypokalemia, or hypomagnesemia, those receiving concomitant therapy with other drugs that prolong the QT_c interval, and those with congenital prolongation of QT_c interval.(1) The manufacturer states that ziprasidone should be avoided in patients with congenital prolongation of the QT interval or a history of cardiac arrhythmias and in those receiving concomitant therapy with other drugs that prolong the QT_c interval.(1) (See Cautions: Contraindications and see Drug Interactions: Drugs that Prolong QT Interval.)

Baseline serum potassium and magnesium concentrations should be determined in patients at risk for substantial electrolyte (i.e., potassium, magnesium) disturbances, particularly those receiving concomitant diuretic therapy, and hypokalemia or hypomagnesemia should be corrected prior to initiating ziprasidone.(1) Clinical and ECG monitoring of cardiac function, including appropriate ambulatory ECG monitoring (e.g., Holter monitoring), is recommended during ziprasidone therapy in patients with symptoms that could indicate torsades de pointes (e.g., dizziness, palpitations, syncope).(1) Ziprasidone therapy should be discontinued if the QT_c interval exceeds 500 msec.(1)

Neuroleptic Malignant Syndrome

Although no cases have been confirmed to date in patients receiving ziprasidone, neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, may occur in patients receiving antipsychotic agents.(1)(12) For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia

Like other antipsychotic agents, use of ziprasidone may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements.(1) Although emergence of tardive dyskinesia was not specifically evaluated in clinical studies of ziprasidone, use of the drug was associated with either no change or small reductions in the Abnormal Involuntary Movement Scale (AIMS) scores from baseline in one year-long study of the drug.(4) However, differences among antipsychotic agents in their potential to cause

tardive dyskinesia have not been established definitively.(1) For additional information on tardive dyskinesia, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus

Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents (e.g., clozapine, olanzapine, quetiapine, risperidone).(1)(13)(14)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)(40)(41)(42)(43)(47) While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether ziprasidone also is associated with this increased risk.(1)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(27)(28)(66) Although there have been few reports of hyperglycemia or diabetes in patients receiving ziprasidone, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.(1)(16)(20)(25)(60)(61)(62)(63)(64)(65)

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available.(1)(13)(14)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25) While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.(15)(26)(27)(28)(29)(30)(31)(33)(34)(35)(36)(37)(38)(39)(44)(45)(46)(48)(49)(50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60)(61)(62)(63)(64)(65)(66)

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment.(1)(13)(14)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25) Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing.(1)(13)(14)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25) In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.(1)(13)(14)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(47)

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions

Rash

Rash and/or urticaria, possibly related to dose and/or duration of therapy, occurred in about 5% of patients in clinical studies and have necessitated discontinuance of the drug in about 17% of these patients.(1) Adjunctive treatment with antihistamines or steroids and/or drug discontinuance may be required.(1) Discontinue ziprasidone if alternative etiology of rash cannot be identified.(1)

General Precautions

Cardiovascular Effects

Orthostatic hypotension, particularly during initial dosage titration period, has been reported.(1) Use with caution in patients with known cardiovascular or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).(1)

Nervous System Effects

Seizures occurred in about 0.4% of patients receiving ziprasidone in controlled clinical trials.(1) Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients).(1)

Although not reported in clinical studies with ziprasidone, disruption of the body's ability to reduce core body temperature has been associated with use of other antipsychotic agents.(1) Use caution when ziprasidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).(1)

GI Effects

Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents.(1) Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia).(1) (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Suicide

Attendant risk with psychotic illnesses; closely supervise high-risk patients.(1) Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.(1)

Sexual Dysfunction

One case of drug-induced priapism reported in clinical studies of ziprasidone.(1)

Other Metabolic and Endocrine Effects

Prolactin concentrations exceeding 22 ng/mL were reported in about 20% of patients receiving ziprasidone in phase II or III clinical studies compared with about 4, 46, or 89% of those receiving placebo, haloperidol, or risperidone, respectively.(7)

Median weight gain of 0.5 kg occurred in patients receiving ziprasidone compared with no median weight change in those receiving placebo.(1)(7) In clinical studies, ziprasidone reportedly caused less weight gain than clozapine, olanzapine, quetiapine, or risperidone.(4)(10)(11)(12)

For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions: Warnings, in Cautions.

Specific Populations

Pregnancy

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Category C.(1) (See Users Guide.)

Lactation

Not known whether ziprasidone is distributed into milk; use in nursing women is not recommended.(1)

Pediatric Use

Safety and efficacy not established in children younger than 18 years of age.

Geriatric Use

No substantial differences in safety of oral ziprasidone relative to younger adults have been observed in clinical studies.(1) Ziprasidone mesylate IM injections have not been systematically evaluated in geriatric patients.(1) Lower initial dosages, slower titration, and more careful monitoring during the initial dosing period may be advisable in some geriatric patients.(1) (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment

Commercially available ziprasidone mesylate injections contain sulfobutylether β-cyclodextrin sodium, an excipient that is cleared by renal filtration.(1) Therefore, ziprasidone injection should be used with caution in patients with renal impairment.(1)

Common Adverse Effects

Adverse effects occurring in more than 5% of patients with schizophrenia receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (14%) and respiratory tract infection (8%).(1)

Adverse effects occurring in more than 5% of patients with schizophrenia receiving IM ziprasidone 10 or 20 mg and at a frequency twice that reported among those receiving IM ziprasidone 2 mg include somnolence (20%), headache (13%), and nausea (12%).(1)

Adverse effects occurring in more than 5% of patients with bipolar mania receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%).(1)(73)(74)

Drug Interactions

Go to **Drug Interactions**

Drugs that Prolong QT Interval

Potential pharmacologic interaction (additive effect on QT interval prolongation; concomitant use contraindicated) when ziprasidone is used with drugs that are known or consistently observed to prolong the QT_c interval (e.g., dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate [no longer commercially available in the US], dolasetron mesylate, probucol, tacrolimus).(1) Ziprasidone also is contraindicated in patients receiving drugs shown to cause QT prolongation as an effect and for which this effect is described in the full prescribing information as a contraindication or a boxed or bolded warning.(1)(See Cautions: Contraindications and Prolongation of QT Interval under Warnings/Precautions: Warnings in Cautions.)

Hypotensive Agents

Potential pharmacologic interaction (additive hypotensive effects).(1)

Other CNS Agents

Potential pharmacologic interaction(1) (additive sedative effects).(12)

Levodopa and Dopamine Agonists

Potential pharmacologic interaction (antagonistic effects).(1)

Drugs Affecting Hepatic Microsomal Enzymes

Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 isoenzyme; potential pharmacokinetic interaction (altered metabolism).(1) Inhibitors or inducers of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 isoenzymes: pharmacokinetic interaction unlikely.(1)

Protein-bound Drugs

Pharmacokinetic interaction unlikely.(1)

Description

Ziprasidone is a benzisothiazolyl piperazine-derivative antipsychotic agent that is chemically unrelated to other currently available antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent.(1)(4)(10)(11)(29) The exact mechanism of antipsychotic action of ziprasidone has not been fully elucidated but, like that of other atypical antipsychotic agents (e.g., olanzapine, risperidone), may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors.(1)(8)(9) As with other drugs that are effective in bipolar disorder, the precise mechanism of antimanic action of ziprasidone has not been fully elucidated.(1) Antagonism of various other receptors (e.g., histamine H_1 receptors, α_1-adrenergic receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with ziprasidone.(1)

Ziprasidone is extensively metabolized in the liver principally via reduction by aldehyde oxidase with minimal excretion of unchanged drug in urine (less than 1%) or feces (less than 4%).(1) About one-third of ziprasidone's metabolic clearance is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme.(1) Ziprasidone did not inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4 isoenzymes in vitro.(1)

Advice to Patients

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Importance of reading manufacturer's patient information.(1)

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs That Prolong QT Interval) or OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus).(1)

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with ziprasidone, avoid driving, operating machinery, or performing hazardous tasks while taking ziprasidone until gain experience with the drug's effects.(1)

Importance of taking medication exactly as prescribed by the clinician.(1)

Importance of women informing clinicians immediately if they are or plan to become pregnant or plan to breast-feed.(1)

Importance of informing patients of other important precautionary information. (See Cautions.)

Additional Information

Overview® (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ziprasidone Hydrochloride				
Routes	**Dosage Forms**	**Strengths**	**Brand Names**	**Manufacturer**
Oral	Capsules	20 mg	Geodon®,	Pfizer
		40 mg	Geodon®,	Pfizer
		60 mg	Geodon®,	Pfizer
		80 mg	Geodon®,	Pfizer

Ziprasidone Mesylate				
Routes	**Dosage Forms**	**Strengths**	**Brand Names**	**Manufacturer**
Parenteral	For injection, for IM use only	20 mg (of ziprasidone)	Geodon®,	Pfizer

Comparative Pricing

This pricing information is subject to change at the sole discretion of DS Pharmacy. This pricing information was updated 04/2011. For the most current and up-to-date pricing information, please visithttp://www.drugstore.com. Actual costs to patients will vary depending on the use of specific retail or mail-order locations and health insurance copays.

Geodon 20MG Capsules (PFIZER U.S.): 60/$478.01 or 180/$1402.96

Geodon 40MG Capsules (PFIZER U.S.): 60/$482.99 or 180/$1407.94

Geodon 60MG Capsules (PFIZER U.S.): 60/$574.97 or 180/$1687.92

Geodon 80MG Capsules (PFIZER U.S.): 60/$574.97 or 180/$1687.92

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RISPERDAL® safely and effectively. See full prescribing information for RISPERDAL®.

RISPERDAL® (risperidone) tablets, for oral use
RISPERDAL® (risperidone) oral solution
RISPERDAL® M-TAB® (risperidone) orally disintegrating tablets
Initial U.S. Approval: 1993

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

•Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
•RISPERDAL® is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Metabolic Changes (5.5) September 2011

----------INDICATIONS AND USAGE----------

RISPERDAL® is an atypical antipsychotic indicated for:

- Treatment of schizophrenia (1.1)
- As monotherapy or adjunctive therapy with lithium or valproate, for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder (1.2)
- Treatment of irritability associated with autistic disorder (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Recommended daily dosage:

	Initial Dose	Target Dose	Effective Dose Range
Schizophrenia: adults (2.1)	2 mg	4 to 8 mg	4 to 16 mg
Schizophrenia: adolescents (2.1)	0.5 mg	3 mg	1 to 6 mg
Bipolar mania: Adults (2.2)	2 to 3 mg	1 to 6 mg	1 to 6 mg
Bipolar mania: in children and adolescents (2.2)	0.5 mg	1 to 2.5 mg	1 to 6 mg
Irritability associated with autistic disorder (2.3)	0.25 mg (Weight < 20 kg) 0.5 mg (Weight ≥20 kg)	0.5 mg (<20 kg) 1 mg (≥20 kg)	0.5 to 3 mg

- Severe Renal or Hepatic Impairment in Adults: Use a lower starting dose of 0.5 mg twice daily. May increase to dosages above 1.5 mg twice daily at intervals of at least one week. (2.4)
- Oral Solution: Can be administered directly from calibrated pipette or mixed with beverage (water, coffee, orange juice, or low-fat milk. (2.6)
- M-TAB Orally Disintegrating Tablets: Open the blister only when ready to administer, and immediately place tablet under tongue. Can be swallowed with or without liquid. (2.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)
- Oral solution: 1 mg per mL (3)
- Orally disintegrating tablets: 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to RISPERDAL® (4)

----------WARNINGS AND PRECAUTIONS----------

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis: RISPERDAL® is not approved for use in patients with dementia-related psychosis. (5.2)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation of RISPERDAL® and close monitoring. (5.3)
- Tardive dyskinesia: Consider discontinuing RISPERDAL® if clinically indicated. (5.4)
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
  - *Hyperglycemia and Diabetes Mellitus:* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.5)
  - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
  - *Weight Gain:* Significant weight gain has been reported. Monitor weight gain. (5.5)
- Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. (5.6)
- Orthostatic hypotension: For patients at risk, consider a lower starting dose and slower titration. (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts in patients with a history of clinically significant low white blood cell count (WBC). Consider discontinuing RISPERDAL if a clinically significant decline in WBC occurs in the absence of other causative factors. (5.8)
- Potential for cognitive and motor impairment: Use caution when operating machinery. (5.9)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.10)

----------ADVERSE REACTIONS----------

The most common adverse reactions in clinical trials (≥5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. Increase the RISPERDAL® dose up to double the patient's usual dose. Titrate slowly. (7.1)
- Fluoxetine, paroxetine, and other CYP 2D6 enzyme inhibitors increase plasma concentrations of risperidone. Reduce the initial dose. Do not exceed a final dose of 8 mg per day of RISPERDAL®. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: MM/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. ***[See Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

1.1 Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia. Efficacy was established in 4 short-term trials in adults, 2 short-term trials in adolescents (ages 13 to 17 years), and one long-term maintenance trial in adults *[see Clinical Studies (14.1)]*.

1.2 Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in 2 short-term trials in adults and one short-term trial in children and adolescents (ages 10 to 17 years) *[see Clinical Studies (14.2)]*.

Adjunctive Therapy

RISPERDAL® adjunctive therapy with lithium or valproate is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in one short-term trial in adults *[see Clinical Studies (14.3)]*.

1.3 Irritability Associated with Autistic Disorder

RISPERDAL® is indicated for the treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Efficacy was established in 3 short-term trials in children and adolescents (ages 5 to 17 years) *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

Table 1. Recommended Daily Dosage by Indication

	Initial Dose	Titration (Increments)	Target Dose	Effective Dose Range
Schizophrenia: adults (2.1)	2 mg	1 to 2 mg	4 to 8 mg	4 to 16 mg
Schizophrenia: adolescents (2.2	0.5 mg	0.5 to 1 mg	3 mg	1 to 6 mg
Bipolar mania: adults (2.2)	2 to 3 mg	1mg	1 to 6mg	1 to 6 mg
Bipolar mania: children and adolescents (2.2)	0.5 mg	0.5 to 1mg	1 to 2.5 mg	1 to 6 mg
Irritability in autistic disorder (2.3)	0.25 mg Can increase to 0.5 mg by Day 4: (body weight less than 20 kg) 0.5 mg Can increase to 1 mg by Day 4: (body weight greater than or equal to 20 kg)	After Day 4, at intervals of > 2 weeks: 0.25 mg (body weight less than 20 kg) 0.5 mg (body weight greater than or equal to 20 kg)	0.5 mg: (body weight less than 20 kg) 1 mg: (body weight greater than or equal to 20 kg)	0.5 to 3 mg

Severe Renal and Hepatic Impairment in Adults: use a lower starting dose of 0.5 mg twice daily. May increase to dosages above 1.5 mg twice daily at intervals of at one week or longer

2.1 Schizophrenia

Adults

Usual Initial Dose

RISPERDAL® can be administered once or twice daily. Initial dosing is 2 mg per day. May increase the dose at intervals of 24 hours or greater, in increments of 1 to 2 mg per day, as tolerated, to a recommended dose of 4 to 8 mg per day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4 mg to 16 mg per. However, doses above 6 mg per day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. In a single study supporting once-daily dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg per day has not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Adolescents

The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or

1 mg per day, as tolerated, to a recommended dose of 3 mg per day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 mg to 6 mg per day, no additional benefit was observed above 3 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance Therapy

While it is unknown how long a patient with schizophrenia should remain on RISPERDAL®, the effectiveness of RISPERDAL® 2 mg per day to 8 mg per day at delaying relapse was demonstrated in a controlled trial in adult patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years *[see Clinical Studies (14.1)]*. Both adult and adolescent patients who respond acutely should generally be maintained on their effective dose beyond the acute episode. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that after an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or treating patients with concomitant antipsychotics.

2.2 Bipolar Mania

Usual Dose

Adults

The initial dose range is 2 mg to 3 mg per day. The dose may be adjusted at intervals of 24 hours or greater, in increments of 1 mg per day. The effective dose range is 1 mg to 6 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1 mg to 6 mg per day *[see Clinical Studies (14.2, 14.3)]*. RISPERDAL® doses higher than 6 mg per day were not studied.

Pediatrics

The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg per day, as tolerated, to the recommended target dose of 1mg to 2.5 mg per day. Although

efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 mg and 6 mg per day, no additional benefit was observed above 2.5 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with RISPERDAL®. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of RISPERDAL® in such longer-term treatment (i.e., beyond 3 weeks). The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.3 Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)

The dosage of RISPERDAL® should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL® can be administered once daily, or half the total daily dose can be administered twice daily.

For patients with body weight less than 20 kg, initiate dosing at 0.25 mg per day. For patients with body weight greater than or equal to 20 kg, initiate dosing at 0.5 mg per day. After a minimum of four days, the dose may be increased to the recommended dose of 0.5 mg per day for patients less than 20 kg and 1.0 mg per day for patients greater than or equal to 20 kg. Maintain this dose for a minimum of 14 days. In patients not achieving sufficient clinical response, the dose may be increased at intervals of 2 weeks or greater, in increments of 0.25 mg per day for patients less than 20 kg, or increments of 0.5 mg per day for patients greater than or equal to 20 kg. The effective dose range is 0.5 mg to 3 mg per day. No dosing data are available for children who weigh less than 15 kg.

Once sufficient clinical response has been achieved and maintained, consider gradually lowering the dose to achieve the optimal balance of efficacy and safety. The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Patients experiencing persistent somnolence may benefit from a once-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

2.4 Dosing in Patients with Severe Renal or Hepatic Impairment

For patients with severe renal impairment (CLcr < 30 mL/min) or hepatic impairment (10-15 points on Child Pugh System), the initial starting dose is 0.5 mg twice daily. The dose may be increased in increments of 0.5 mg or less, administered twice daily. For doses above 1.5 mg twice daily, increase in intervals of one week or greater *[see Use in Specific Populations (8.6 and 8.7)]*.

2.5 Dose Adjustments for Specific Drug Interactions

When RISPERDAL® is co-administered with enzyme inducers (e.g., carbamazepine), the dose of RISPERDAL® should be increased up to double the patient's usual dose. It may be necessary to decrease the RISPERDAL® dose when enzyme inducers such as carbamazepine are discontinued *[see Drug Interactions (7.1)]*. Similar effect may be expected with co-administration of RISPERDAL® with other enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital).

When fluoxetine or paroxetine is co-administered with RISPERDAL®, the dose of RISPERDAL® should be reduced. The RISPERDAL® dose should not exceed 8 mg per day in adults when co-administered with these drugs. When initiating therapy, RISPERDAL® should be titrated slowly. It may be necessary to increase the RISPERDAL® dose when enzyme inhibitors such as fluoxetine or paroxetine are discontinued *[see Drug Interactions (7.1)]*.

2.6 Administration of RISPERDAL® Oral Solution

RISPERDAL® Oral Solution can be administered directly from the calibrated pipette, or can be mixed with a beverage prior to administration. RISPERDAL® Oral Solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea.

2.7 Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

3 DOSAGE FORMS AND STRENGTHS

RISPERDAL® Tablets are available in the following strengths and colors: 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green). All are capsule shaped, and imprinted with “JANSSEN” on one side and either “Ris 0.25”, “Ris 0.5”, “R1”, “R2”, “R3”, or “R4” on the other side according to their respective strengths.

RISPERDAL® Oral Solution is available in a 1 mg/mL strength.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in the following strengths, colors, and shapes: 0.5 mg (light coral, round), 1 mg (light coral, square), 2 mg (coral, square), 3 mg (coral, round), and 4 mg (coral, round). All are biconvex and etched on one side with “R0.5”, “R1”, “R2”, “R3”, or “R4” according to their respective strengths.

4 CONTRAINDICATIONS

RISPERDAL® is contraindicated in patients with a known hypersensitivity to RISPERDAL®. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated

patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus RISPERDAL® when compared to patients treated with RISPERDAL® alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed.

RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[see Boxed Warning and Warnings and Precautions (5.1)]*

5.3 Neuroleptic Malignant Syndrome

Antipsychotic drugs including RISPERDAL® can cause a potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase (CPK), myoglobinuria, rhabdomyolysis, and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential

diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, prescribe RISPERDAL® in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, consider drug discontinuation. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including RISPERDAL®, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including RISPERDAL®, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of RISPERDAL®.

Pooled data from three double-blind, placebo-controlled schizophrenia studies and four double-blind, placebo-controlled bipolar monotherapy studies are presented in Table 2.

Table 2. Change in Random Glucose from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects with Schizophrenia or Bipolar Mania

		RISPERDAL®	
	Placebo	1-8 mg/day	>8-16 mg/day
		Mean change from baseline (mg/dL)	
	n=555	**n=748**	**n=164**
Serum Glucose	-1.4	0.8	0.6
		Proportion of patients with shifts	
Serum Glucose (<140 mg/dL to ≥200 mg/dL)	0.6% (3/525)	0.4% (3/702)	0% (0/158)

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with a mean change in glucose of +2.8 mg/dL at Week 24 (n=151) and +4.1 mg/dL at Week 48 (n=50).

Data from the placebo-controlled 3- to 6-week study in children and adolescents with schizophrenia (13-17 years of age), bipolar mania (10-17 years of age), or autistic disorder (5 to 17 years of age) are presented in Table 3.

Table 3. Change in Fasting Glucose from Three Placebo-Controlled, 3- to 6-Week, Fixed-Dose Studies in Children and Adolescents with Schizophrenia (13-17 years of age), Bipolar Mania (10-17 years of age), or Autistic Disorder (5 to 17 years of age)

	Placebo	RISPERDAL® 0.5-6 mg/day
	Mean change from baseline (mg/dL)	
	n=76	**n=135**
Serum Glucose	-1.3	2.6
	Proportion of patients with shifts	
Serum Glucose (<100 mg/dL to ≥126 mg/dL)	0% (0/64)	0.8% (1/120)

In longer-term, uncontrolled, open-label extension pediatric studies, RISPERDAL® was associated with a mean change in fasting glucose of +5.2 mg/dL at Week 24 (n=119).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Pooled data from 7 placebo-controlled, 3- to 8- week, fixed- or flexible-dose studies in adult subjects with schizophrenia or bipolar mania are presented in Table 4.

Table 4. Change in Random Lipids from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects with Schizophrenia or Bipolar Mania

	Placebo	RISPERDAL® 1-8 mg/day	RISPERDAL® >8-16 mg/day
		Mean change from baseline (mg/dL)	
Cholesterol	**n=559**	**n=742**	**n=156**
Change from baseline	0.6	6.9	1.8
Triglycerides	**n=183**	**n=307**	**n=123**
Change from baseline	-17.4	-4.9	-8.3
		Proportion of patients With Shifts	
Cholesterol (<200 mg/dL to ≥240 mg/dL)	2.7% (10/368)	4.3% (22/516)	6.3% (6/96)
Triglycerides (<500 mg/dL to ≥500 mg/dL)	1.1% (2/180)	2.7% (8/301)	2.5% (3/121)

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with a mean change in (a) non-fasting cholesterol of +4.4 mg/dL at Week 24 (n=231) and +5.5 mg/dL at Week 48 (n=86); and (b) non-fasting triglycerides of +19.9 mg/dL at Week 24 (n=52).

Pooled data from 3 placebo-controlled, 3- to 6-week, fixed-dose studies in children and adolescents with schizophrenia (13-17 years of age), bipolar mania (10-17 years of age), or autistic disorder (5-17 years of age) are presented in Table 5.

Table 5. Change in Fasting Lipids from Three Placebo-Controlled, 3- to 6-Week, Fixed-Dose Studies in Children and Adolescents with Schizophrenia (13-17 Years of Age), Bipolar Mania (10-17 Years of Age), or Autistic Disorder (5 to 17 Years of Age)

	Placebo	RISPERDAL® 0.5-6 mg/day
	Mean change from baseline (mg/dL)	
Cholesterol	**n=74**	**n=133**
Change from baseline	0.3	-0.3
LDL	**n=22**	**n=22**
Change from baseline	3.7	0.5
HDL	**n=22**	**n=22**
Change from baseline	1.6	-1.9
Triglycerides	**n=77**	**n=138**
Change from baseline	-9.0	-2.6
	Proportion of patients with shifts	
Cholesterol	2.4%	3.8%
(<170 mg/dL to ≥200 mg/dL)	(1/42)	(3/80)
LDL	0%	0%
(<110 mg/dL to ≥130 mg/dL)	(0/16)	(0/16)
HDL	0%	10%
(≥40 mg/dL to <40 mg/dL)	(0/19)	(2/20)
Triglycerides	1.5%	7.1%
(<150 mg/dL to ≥200 mg/dL)	(1/65)	(8/113)

In longer-term, uncontrolled, open-label extension pediatric studies, RISPERDAL® was associated with a mean change in (a) fasting cholesterol of +2.1 mg/dL at Week 24 (n=114); (b) fasting LDL of -0.2 mg/dL at Week 24 (n=103); (c) fasting HDL of +0.4 mg/dL at Week 24 (n=103); and (d) fasting triglycerides of +6.8 mg/dL at Week 24 (n=120).

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of 7% or greater of body weight from 7 placebo-controlled, 3- to 8- week, fixed- or flexible-dose studies in adult subjects with schizophrenia or bipolar mania are presented in Table 6.

Table 6. Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Gain in Body Weight From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects With Schizophrenia or Bipolar Mania

		RISPERDAL®	
	Placebo (n=597)	1-8 mg/day (n=769)	>8-16 mg/day (n=158)
Weight (kg)			
Change from baseline	-0.3	0.7	2.2
Weight Gain			
≥7% increase from baseline	2.9%	8.7%	20.9%

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with a mean change in weight of +4.3 kg at Week 24 (n=395) and +5.3 kg at Week 48 (n=203).

Data on mean changes in body weight and the proportion of subjects meeting the criterion of ≥7% gain in body weight from nine placebo-controlled, 3- to 8-week, fixed-dose studies in children and adolescents with schizophrenia (13-17 years of age), bipolar mania (10-17 years of age), autistic disorder (5-17 years of age), or other psychiatric disorders (5-17 years of age) are presented in Table 7.

Table 7. Mean Change in Body Weight (kg) and the Proportion of Subjects With ≥7% Gain in Body Weight From Nine Placebo-Controlled, 3- to 8-Week, Fixed-Dose Studies in Children and Adolescents With Schizophrenia (13-17 Years of Age), Bipolar Mania (10-17 Years of Age), Autistic Disorder (5 to 17 Years of Age) or Other Psychiatric Disorders (5-17 Years of Age)

	Placebo (n=375)	**RISPERDAL® 0.5-6 mg/day (n=448)**
Weight (kg)		
Change from baseline	0.6	2.0
Weight Gain		
≥7% increase from baseline	6.9%	32.6%

In longer-term, uncontrolled, open-label extension pediatric studies, RISPERDAL® was associated with a mean change in weight of +5.5 kg at Week 24 (n=748) and +8.0 kg at Week 48 (n=242).

In a long-term, open-label extension study in adolescent patients with schizophrenia, weight increase was reported as a treatment-emergent adverse event in 14% of patients. In 103 adolescent patients with schizophrenia, a mean increase of 9.0 kg was observed after 8 months of RISPERDAL® treatment. The majority of that increase was observed within the first 6 months. The average percentiles at baseline and 8 months, respectively, were 56 and 72 for weight, 55 and 58 for height, and 51 and 71 for body mass index.

In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed,

which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index.

In one 3-week, placebo-controlled trial in children and adolescent patients with acute manic or mixed episodes of bipolar I disorder, increases in body weight were higher in the RISPERDAL® groups than the placebo group, but not dose related (1.90 kg in the RISPERDAL® 0.5-2.5 mg group, 1.44 kg in the RISPERDAL® 3-6 mg group, and 0.65 kg in the placebo group). A similar trend was observed in the mean change from baseline in body mass index.

When treating pediatric patients with RISPERDAL® for any indication, weight gain should be assessed against that expected with normal growth.

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, RISPERDAL® elevates prolactin levels and the elevation persists during chronic administration. RISPERDAL® is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.7 Orthostatic Hypotension

RISPERDAL® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment *[see Dosage and Administration (2.1, 2.4)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including RISPERDAL®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue RISPERDAL® and have their WBC followed until recovery.

5.9 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse reaction is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients.

Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse reaction. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

5.10 Seizures

During premarketing testing in adult patients with schizophrenia, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. *[see Boxed Warning and Warnings and Precautions (5.1)]*

5.12 Priapism

Priapism has been reported during postmarketing surveillance. Severe priapism may require surgical intervention.

5.13 Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

5.14 Patients with Phenylketonuria

Inform patients that RISPERDAL® M-TAB® Orally Disintegrating Tablets contain phenylalanine**.** Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes (Hyperglycemia and diabetes mellitus, Dyslipidemia, and Weight Gain) *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension *[see Warnings and Precautions (5.7)]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.8)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*
- Priapism *[see Warnings and Precautions (5.12)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.13)]*
- Patients with Phenylketonuria *[see Warnings and Precautions (5.14)]*.

The most common adverse reactions in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were nausea,

somnolence, sedation, vomiting, dizziness, and akathisia *[see Adverse Reactions,Discontinuations Due to Adverse Reactions (6.1)]*.

The data described in this section are derived from a clinical trial database consisting of 9803 adult and pediatric patients exposed to one or more doses of RISPERDAL® for the treatment of schizophrenia, bipolar mania, autistic disorder, and other psychiatric disorders in pediatrics and elderly patients with dementia. Of these 9803 patients, 2687 were patients who received RISPERDAL® while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with RISPERDAL® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia

Adult Patients with Schizophrenia

Table 8 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with schizophrenia in three 4- to 8-week, double-blind, placebo-controlled trials.

Table 8. Adverse Reactions in ≥2% of RISPERDAL®-Treated Adult Patients (and greater than placebo) with Schizophrenia in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Reaction		
	RISPERDAL®		
System/Organ Class	**2-8 mg per day**	**>8-16 mg per day**	**Placebo**
Adverse Reaction	**(N=366)**	**(N=198)**	**(N=225)**
Cardiac Disorders			
Tachycardia	1	3	0
Eye Disorders			
Vision blurred	3	1	1
Gastrointestinal Disorders			
Nausea	9	4	4
Constipation	8	9	6
Dyspepsia	8	6	5
Dry mouth	4	0	1
Abdominal discomfort	3	1	1
Salivary hypersecretion	2	1	<1
Diarrhea	2	1	1
General Disorders			
Fatigue	3	1	0
Chest pain	2	2	1
Asthenia	2	1	<1
Infections and Infestations			
Nasopharyngitis	3	4	3
Upper respiratory tract infection	2	3	1
Sinusitis	1	2	1
Urinary tract infection	1	3	0
Investigations			
Blood creatine phosphokinase increased	1	2	<1
Heart rate increased	<1	2	0
Musculoskeletal and Connective Tissue Disorders			
Back pain	4	1	1
Arthralgia	2	3	<1
Pain in extremity	2	1	1

System/Organ Class Adverse Reaction	Percentage of Patients Reporting Reaction RISPERDAL® 2-8 mg per day (N=366)	 >8-16 mg per day (N=198)	 Placebo (N=225)
Nervous System Disorders			
Parkinsonism*	14	17	8
Akathisia*	10	10	3
Sedation	10	5	2
Dizziness	7	4	2
Dystonia*	3	4	2
Tremor*	2	3	1
Dizziness postural	2	0	0
Psychiatric Disorders			
Insomnia	32	25	27
Anxiety	16	11	11
Respiratory, Thoracic and Mediastinal Disorders			
Nasal congestion	4	6	2
Dyspnea	1	2	0
Epistaxis	<1	2	0
Skin and Subcutaneous Tissue Disorders			
Rash	1	4	1
Dry skin	1	3	0
Vascular Disorders			
Orthostatic hypotension	2	1	0

* Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson's disease. Akathisia includes akathisia and restlessness. Dystonia includes dystonia, muscle spasms, muscle contractions involuntary, muscle contracture, oculogyration, tongue paralysis. Tremor includes tremor and parkinsonian rest tremor.

Pediatric Patients with Schizophrenia

Table 9 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with schizophrenia in a 6-week double-blind, placebo-controlled trial.

Table 9. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients (and greater than placebo) with Schizophrenia in a Double-Blind Trial

	Percentage of Patients Reporting Reaction RISPERDAL®		
System/Organ Class Adverse Reaction	**1-3 mg per day (N=55)**	**4-6 mg per day (N=51)**	**Placebo (N=54)**
Gastrointestinal Disorders			
Salivary hypersecretion	0	10	2
Nervous System Disorders			
Sedation	24	12	4
Parkinsonism*	16	28	11
Tremor	11	10	6
Akathisia*	9	10	4
Dizziness	7	14	2
Dystonia*	2	6	0
Psychiatric Disorders			
Anxiety	7	6	0

* Parkinsonism includes extrapyramidal disorder, muscle rigidity, musculoskeletal stiffness, and hypokinesia. Akathisia includes akathisia and restlessness. Dystonia includes dystonia and oculogyration.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Mania

Adult Patients with Bipolar Mania

Table 10 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with bipolar mania in four 3-week, double-blind, placebo-controlled monotherapy trials.

Table 10. Adverse Reactions in ≥2% of RISPERDAL®-Treated Adult Patients (and greater than placebo) with Bipolar Mania in Double-Blind, Placebo-Controlled Monotherapy Trials

System/Organ Class Adverse Reaction	Percentage of Patients Reporting Reaction RISPERDAL® 1-6 mg per day (N=448)	Placebo (N=424)
Eye Disorders		
Vision blurred	2	1
Gastrointestinal Disorders		
Nausea	5	2
Diarrhea	3	2
Salivary hypersecretion	3	1
Stomach discomfort	2	<1
General Disorders		
Fatigue	2	1
Nervous System Disorders		
Parkinsonism*	25	9
Sedation	11	4
Akathisia*	9	3
Tremor*	6	3
Dizziness	6	5
Dystonia*	5	1
Lethargy	2	1

* Parkinsonism includes extrapyramidal disorder, parkinsonism, musculoskeletal stiffness, hypokinesia, muscle rigidity, muscle tightness, bradykinesia, cogwheel rigidity. Akathisia includes akathisia and restlessness. Tremor includes tremor and parkinsonian rest tremor. Dystonia includes dystonia, muscle spasms, oculogyration, torticollis.

Table 11 lists the adverse reactions reported in 2% or more of RISPERDAL®-treated adult patients with bipolar mania in two 3-week, double-blind, placebo-controlled adjuvant therapy trials.

Table 11. Adverse Reactions in ≥2% of RISPERDAL®-Treated Adult Patients (and greater than placebo) with Bipolar Mania in Double-Blind, Placebo-Controlled Adjunctive Therapy Trials

	Percentage of Patients Reporting Reaction	
System/Organ Class Adverse Reaction	**RISPERDAL® + Mood Stabilizer (N=127)**	**Placebo + Mood Stabilizer (N=126)**
Cardiac Disorders		
Palpitations	2	0
Gastrointestinal Disorders		
Dyspepsia	9	8
Nausea	6	4
Diarrhea	6	4
Salivary hypersecretion	2	0
General Disorders		
Chest pain	2	1
Infections and Infestations		
Urinary tract infection	2	1
Nervous System Disorders		
Parkinsonism*	14	4
Sedation	9	4
Akathisia*	8	0
Dizziness	7	2
Tremor	6	2
Lethargy	2	1
Psychiatric Disorders		
Anxiety	3	2
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	5	2
Cough	2	0

* Parkinsonism includes extrapyramidal disorder, hypokinesia and bradykinesia. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Bipolar Mania

Table 12 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with bipolar mania in a 3-week double-blind, placebo-controlled trial.

Table 12. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients (and greater than placebo) with Bipolar Mania in Double-Blind, Placebo-Controlled Trials

System/Organ Class Adverse Reaction	Percentage of Patients Reporting Reaction RISPERDAL® 0.5-2.5 mg per day (N=50)	 3-6 mg per day (N=61)	 Placebo (N=58)
Eye Disorders			
Vision blurred	4	7	0
Gastrointestinal Disorders			
Abdominal pain upper	16	13	5
Nausea	16	13	7
Vomiting	10	10	5
Diarrhea	8	7	2
Dyspepsia	10	3	2
Stomach discomfort	6	0	2
General Disorders			
Fatigue	18	30	3
Metabolism and Nutrition Disorders			
Increased appetite	4	7	2
Nervous System Disorders			
Sedation	42	56	19
Dizziness	16	13	5
Parkinsonism*	6	12	3
Dystonia*	6	5	0
Akathisia*	0	8	2
Psychiatric Disorders			
Anxiety	0	8	3
Respiratory, Thoracic and Mediastinal Disorders			
Pharyngolaryngeal pain	10	3	5
Skin and Subcutaneous Tissue Disorders			
Rash	0	7	2

* Parkinsonism includes musculoskeletal stiffness, extrapyramidal disorder, bradykinesia, and nuchal rigidity. Dystonia includes dystonia, laryngospasm, and muscle spasms. Akathisia includes restlessness and akathisia.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Autistic Disorder

Table 13 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients treated for irritability associated with autistic disorder in two 8-week, double-blind, placebo-controlled trials and one 6-week double-blind, placebo-controlled study.

Table 13. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients (and greater than placebo) Treated for Irritability Associated with Autistic Disorder in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Reaction	
System/Organ Class **Adverse Reaction**	**RISPERDAL®** **0.5-4.0 mg/day** **(N=107)**	**Placebo** **(N=115)**
Gastrointestinal Disorders		
Vomiting	20	17
Constipation	17	6
Dry mouth	10	4
Nausea	8	5
Salivary hypersecretion	7	1
General Disorders and Administration Site Conditions		
Fatigue	31	9
Pyrexia	16	13
Thirst	7	4
Infections and Infestations		
Nasopharyngitis	19	9
Rhinitis	9	7
Upper respiratory tract infection	8	3
Investigations		
Weight increased	8	2
Metabolism and Nutrition Disorders		
Increased appetite	44	15
Nervous System Disorders		
Sedation	63	15
Drooling	12	4
Headache	12	10
Tremor	**8**	**1**
Dizziness	8	2
Parkinsonism*	8	1
Renal and Urinary Disorders		
Enuresis	16	10
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17	12
Rhinorrhea	12	10
Nasal congestion	10	4
Skin and Subcutaneous Tissue Disorders		
Rash	8	5

*Parkinsonism includes musculoskeletal stiffness, extrapyramidal disorder, muscle rigidity, cogwheel rigidity, and muscle tightness.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Risperidone

The following additional adverse reactions occurred across all placebo-controlled, active-controlled, and open-label studies of RISPERDAL in adults and pediatric patients.

Blood and Lymphatic System Disorders: anemia, granulocytopenia, neutropenia

Cardiac Disorders: sinus bradycardia, sinus tachycardia, atrioventricular block first degree, bundle branch block left, bundle branch block right, atrioventricular block

Ear and Labyrinth Disorders: ear pain, tinnitus

Endocrine Disorders: hyperprolactinemia

Eye Disorders: ocular hyperemia, eye discharge, conjunctivitis, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, lacrimation increased, photophobia, glaucoma, visual acuity reduced

Gastrointestinal Disorders: dysphagia, fecaloma, fecal incontinence, gastritis, lip swelling, cheilitis, aptyalism

General Disorders: edema peripheral, thirst, gait disturbance, influenza-like illness, pitting edema, edema, chills, sluggishness, malaise, chest discomfort, face edema, discomfort, generalized edema, drug withdrawal syndrome, peripheral coldness, feeling abnormal

Immune System Disorders: drug hypersensitivity

Infections and Infestations: pneumonia, influenza, ear infection, viral infection, pharyngitis, tonsillitis, bronchitis, eye infection, localized infection, cystitis, cellulitis, otitis media, onychomycosis, acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

Investigations: body temperature increased, blood prolactin increased, alanine aminotransferase increased, electrocardiogram abnormal, eosinophil count increased, white blood cell count decreased, blood glucose increased, hemoglobin decreased, hematocrit decreased, body temperature decreased, blood pressure decreased, transaminases increased

Metabolism and Nutrition Disorders: decreased appetite, polydipsia, anorexia

Musculoskeletal and Connective Tissue Disorders: joint stiffness, joint swelling, musculoskeletal chest pain, posture abnormal, myalgia, neck pain, muscular weakness, rhabdomyolysis

Nervous System Disorders: balance disorder, disturbance in attention, dysarthria, unresponsive to stimuli, depressed level of consciousness, movement disorder, transient ischemic attack, coordination abnormal, cerebrovascular accident, speech disorder, syncope, loss of consciousness, hypoesthesia, tardive dyskinesia, dyskinesia, cerebral ischemia, cerebrovascular disorder, neuroleptic malignant syndrome, diabetic coma, head titubation

Psychiatric Disorders: agitation, blunted affect, confusional state, middle insomnia, nervousness, sleep disorder, listlessness, libido decreased, and anorgasmia

Renal and Urinary Disorders: enuresis, dysuria, pollakiuria, urinary incontinence

Reproductive System and Breast Disorders: menstruation irregular, amenorrhea, gynecomastia, galactorrhea, vaginal discharge, menstrual disorder, erectile dysfunction, retrograde ejaculation, ejaculation disorder, sexual dysfunction, breast enlargement

Respiratory, Thoracic, and Mediastinal Disorders: wheezing, pneumonia aspiration, sinus congestion, dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory disorder, hyperventilation, nasal edema

Skin and Subcutaneous Tissue Disorders: erythema, skin discoloration, skin lesion, pruritus, skin disorder, rash erythematous, rash papular, rash generalized, rash maculopapular, acne, hyperkeratosis, seborrheic dermatitis

Vascular Disorders: hypotension, flushing

Additional Adverse Reactions Reported with RISPERDAL® CONSTA®

The following is a list of additional adverse reactions that have been reported during the premarketing evaluation of RISPERDAL® CONSTA®, regardless of frequency of occurrence:

Cardiac Disorders: bradycardia

Ear and Labyrinth Disorders: vertigo

Eye Disorders: blepharospasm

Gastrointestinal Disorders: toothache, tongue spasm

General Disorders and Administration Site Conditions: pain

Infections and Infestations: lower respiratory tract infection, infection, gastroenteritis, subcutaneous abscess

Injury and Poisoning: fall

Investigations: weight decreased, gamma-glutamyltransferase increased, hepatic enzyme increased

Musculoskeletal, Connective Tissue, and Bone Disorders: buttock pain

Nervous System Disorders: convulsion, paresthesia

Psychiatric Disorders: depression

Skin and Subcutaneous Tissue Disorders: eczema

Vascular Disorders: hypertension

Discontinuations Due to Adverse Reactions

Schizophrenia - Adults

Approximately 7% (39/564) of RISPERDAL®-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more RISPERDAL®-treated patients were:

Table 14. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Schizophrenia Trials

	RISPERDAL®		
Adverse Reaction	**2-8 mg/day (N=366)**	**>8-16 mg/day (N=198)**	**Placebo (N=225)**
Dizziness	1.4%	1.0%	0%
Nausea	1.4%	0%	0%
Vomiting	0.8%	0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0%	0%
Dystonia	0.5%	0%	0%
Agitation	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Orthostatic hypotension	0.3%	0.5%	0%
Akathisia	0.3%	2.0%	0%

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Schizophrenia - Pediatrics

Approximately 7% (7/106), of RISPERDAL®-treated patients discontinued treatment due to an adverse reaction in a double-blind, placebo-controlled trial, compared with 4% (2/54) placebo-treated patients. The adverse reactions associated with discontinuation for at least one RISPERDAL®-treated patient were dizziness (2%), somnolence (1%), sedation (1%), lethargy (1%), anxiety (1%), balance disorder (1%), hypotension (1%), and palpitation (1%).

Bipolar Mania - Adults

In double-blind, placebo-controlled trials with RISPERDAL® as monotherapy, approximately 6% (25/448) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 5% (19/424) of placebo-treated patients. The adverse reactions associated with discontinuation in RISPERDAL®-treated patients were:

Table 15. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Bipolar Mania Clinical Trials

Adverse Reaction	RISPERDAL® 1-6 mg/day (N=448)	Placebo (N=424)
Parkinsonism	0.4%	0%
Lethargy	0.2%	0%
Dizziness	0.2%	0%
Alanine aminotransferase increased	0.2%	0.2%
Aspartate aminotransferase increased	0.2%	0.2%

Bipolar Mania - Pediatrics

In a double-blind, placebo-controlled trial 12% (13/111) of RISPERDAL®-treated patients discontinued due to an adverse reaction, compared with 7% (4/58) of placebo-treated patients. The adverse reactions associated with discontinuation in more than one RISPERDAL®-treated pediatric patient were nausea (3%), somnolence (2%), sedation (2%), and vomiting (2%).

Autistic Disorder - Pediatrics

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n = 156), one RISPERDAL®-treated patient discontinued due to an adverse reaction (Parkinsonism), and one placebo-treated patient discontinued due to an adverse event.

Dose Dependency of Adverse Reactions in Clinical Trials

Extrapyramidal Symptoms

Data from two fixed-dose trials in adults with schizophrenia provided evidence of dose-relatedness for extrapyramidal symptoms associated with RISPERDAL® treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day), including (1) a Parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Table 16.

Dose Groups	Placebo	RISPERDAL® 2 mg	RISPERDAL® 6 mg	RISPERDAL® 10 mg	RISPERDAL® 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	17%	21%	21%	35%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day):

Table 17.

Dose Groups	RISPERDAL® 1 mg	RISPERDAL® 4 mg	RISPERDAL® 8 mg	RISPERDAL® 12 mg	RISPERDAL® 16 mg
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	17%	18%	20%

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectile dysfunction, ejaculation disorder, sexual function abnormal, fatigue, and skin discoloration.

Changes in Body Weight

Weight gain was observed in short-term, controlled trials and longer-term uncontrolled studies in adult and pediatric patients *[see Warnings and Precautions (5.5), Adverse Reactions (6), and Use in Specific Populations (8.4)]*.

Changes in ECG Parameters

Between-group comparisons for pooled placebo-controlled trials in adults revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In pooled placebo-controlled acute mania trials in adults, there were small decreases in mean heart rate, similar among all treatment groups.

In the two placebo-controlled trials in children and adolescents with autistic disorder (aged 5 - 16 years) mean changes in heart rate were an increase of 8.4 beats per minute in the RISPERDAL® groups and 6.5 beats per minute in the placebo group. There were no other notable ECG changes.

In a placebo-controlled acute mania trial in children and adolescents (aged 10 – 17 years), there were no significant changes in ECG parameters, other than the effect of RISPERDAL® to transiently increase pulse rate (< 6 beats per minute). In two controlled schizophrenia trials in adolescents (aged 13 – 17 years), there were no clinically meaningful changes in ECG parameters including corrected QT intervals between treatment groups or within treatment groups over time.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of risperidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions include: alopecia, anaphylactic reaction, angioedema, atrial fibrillation, cardiopulmonary arrest, diabetic ketoacidosis in patients with impaired glucose metabolism, dysgeusia, hypoglycemia, hypothermia, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice, mania, pancreatitis, pituitary adenoma, precocious puberty, pulmonary embolism, QT prolongation, sleep apnea syndrome, sudden death, thrombocytopenia, thrombotic thrombocytopenic purpura, urinary retention, and water intoxication.

7 DRUG INTERACTIONS

7.1 Pharmacokinetic-related Interactions

The dose of RISPERDAL® should be adjusted when used in combination with CYP2D6 enzyme inhibitors (e.g., fluoxetine, and paroxetine) and enzyme inducers (e.g., carbamazepine) *[see Table 18 and Dosage and Administration (2.5)]*. Dose adjustment is not recommended for RISPERDAL® when co-administered with ranitidine, cimetidine, amitriptyline, or erythromycin *[see Table 18]*.

Table 18 Summary of Effect of Coadministered Drugs on Exposure to Active Moiety (Risperidone + 9-Hydroxy-Risperidone) in Healthy Subjects or Patients with Schizophrenia

Coadministered Drug	Dosing Schedule		Effect on Active Moiety (Risperidone + 9-Hydroxy-Risperidone (Ratio*)		Risperidone Dose Recommendation
	Coadministered Drug	Risperidone	AUC	Cmax	
Enzyme (CYP2D6) Inhibitors					
Fluoxetine	20 mg/day	2 or 3 mg twice daily	1.4	1.5	Re-evaluate dosing. Do not exceed 8 mg/day
Paroxetine	10 mg/day	4 mg/day	1.3	-	Re-evaluate dosing. Do not exceed 8 mg/day
	20 mg/day	4 mg/day	1.6	-	
	40 mg/day	4 mg/day	1.8	-	
Enzyme (CYP3A/ PgP inducers) Inducers					
Carbamazepine	573 ± 168 mg/day	3 mg twice daily	0.51	0.55	Titrate dose upwards. Do not exceed twice the patient's usual dose
Enzyme (CYP3A) Inhibitors					
Ranitidine	150 mg twice daily	1 mg single dose	1.2	1.4	Dose adjustment not needed
Cimetidine	400 mg twice daily	1 mg single dose	1.1	1.3	Dose adjustment not needed
Erythromycin	500 mg four times daily	1 mg single dose	1.1	0.94	Dose adjustment not needed
Other Drugs					
Amitriptyline	50 mg twice daily	3 mg twice daily	1.2	1.1	Dose adjustment not needed

*Change relative to reference

Effect of Risperidone on other drugs

Lithium

Repeated oral doses of RISPERDAL® (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). Dose adjustment for lithium is not recommended.

Valproate

Repeated oral doses of RISPERDAL® (4 mg once daily) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of RISPERDAL®. Dose adjustment for valproate is not recommended.

Digoxin

RISPERDAL® (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin. Dose adjustment for digoxin is not recommended.

7.2 Pharmacodynamic-related Interactions

Centrally-Acting Drugs and Alcohol

Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally-acting drugs and alcohol.

Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

Levodopa and Dopamine Agonists

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Clozapine

Chronic administration of clozapine with RISPERDAL® may decrease the clearance of risperidone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Adequate and well controlled studies with RISPERDAL have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including RISPERDAL®) during the third

trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There was no increase in the incidence of malformations in embryo-fetal studies in rats and rabbits at 0.4–6 times MHRD. Increased pup mortality was noted at all doses in peri-postnatal studies in rats. RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Data

Human Data

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in neonates following in utero exposure to antipsychotics in the third trimester. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

There was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown

Animal Data

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 body surface area basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 body surface area basis). There were no teratogenic effects in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 body surface area basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 body surface area basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 body surface area basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups

were observed, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 body surface area basis.

Placental transfer of risperidone occurs in rat pups.

8.2 Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Risperidone and 9-hydroxyrisperidone are present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from risperidone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Approved Pediatric Indications

Schizophrenia

The efficacy and safety of RISPERDAL® in the treatment of schizophrenia were demonstrated in 417 adolescents, aged 13 – 17 years, in two short-term (6 and 8 weeks, respectively) double-blind controlled trials *[see Indications and Usage (1.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]*. Additional safety and efficacy information was also assessed in one long-term (6-month) open-label extension study in 284 of these adolescent patients with schizophrenia.

Safety and effectiveness of RISPERDAL® in children less than 13 years of age with schizophrenia have not been established.

Bipolar I Disorder

The efficacy and safety of RISPERDAL® in the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in 169 children and adolescent patients, aged 10 – 17 years, were demonstrated in one double-blind, placebo-controlled, 3-week trial *[see Indications and Usage (1.2), Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

Safety and effectiveness of RISPERDAL® in children less than 10 years of age with bipolar disorder have not been established.

Autistic Disorder

The efficacy and safety of RISPERDAL® in the treatment of irritability associated with autistic disorder were established in two 8-week, double-blind, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years *[see Indications and Usage (1.3), Adverse Reactions (6.1) and Clinical Studies (14.4)]*. Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania who were of similar age and weight, and who received similar dosages of RISPERDAL® as patients treated for irritability associated with autistic disorder.

A third study was a 6-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of a lower than recommended dose of risperidone in subjects 5 to 17 years of age with autistic disorder and associated irritability, and related behavioral symptoms. There were two weight-based, fixed doses of risperidone (high-dose and low-dose). The high dose was 1.25 mg per day for patients weighing 20 to < 45 kg, and it was 1.75 mg per day for patients weighing ≥ 45 kg. The low dose was 0.125 mg per day for patients for patients weighing 20 to < 45 kg, and it was 0.175 mg per day for patients weighing ≥ 45 kg. The study demonstrated the efficacy of high-dose risperidone, but it did not demonstrate efficacy for low-dose risperidone.

Adverse Reactions in Pediatric Patients

Tardive Dyskinesia

In clinical trials in 1885 children and adolescents treated with RISPERDAL®, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of RISPERDAL® treatment *[see also Warnings and Precautions (5.4)]*.

Weight Gain

Weight gain has been observed in children and adolescents during treatment with RISPERDAL®. Clinical monitoring of weight is recommended during treatment.

Data derive from short-term placebo-controlled trials and longer-term uncontrolled studies in pediatric patients (ages 5 to 17 years) with schizophrenia, bipolar disorder, autistic disorder, or other psychiatric disorders. In the short-term trials (3 to 8 weeks), the mean weight gain for RISPERDAL®-treated patients was 2 kg, compared to 0.6 kg for placebo-treated patients. In these trials, approximately 33% of the RISPERDAL® group had weight gain ≥7%, compared to 7% in the placebo group. In longer-term, uncontrolled, open-label pediatric studies, the mean weight gain was 5.5 kg at Week 24 and 8 kg at Week 48 *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

Somnolence

Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. Somnolence was the most commonly observed adverse reaction in the clinical trial of bipolar disorder in children and adolescents, as well as in the schizophrenia trials in adolescents. As was seen in the autistic disorder trials, these adverse reactions were most often of early onset and transient in duration *[see Adverse Reactions (6.1 and 6.2)]*. Patients experiencing persistent somnolence may benefit from a change in dosing regimen *[*see *Dosage and Administration (2.1, 2.2, and 2.3)]*.

Hyperprolactinemia

RISPERDAL® has been shown to elevate prolactin levels in children and adolescents as well as in adults *[see Warnings and Precautions (5.6)]*. In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania, 49% of patients who received RISPERDAL® had elevated prolactin levels compared to 2% of patients who received placebo. Similarly, in placebo-controlled trials in children and adolescents (aged 10 to 17 years) with bipolar disorder, or adolescents (aged 13 to 17 years) with schizophrenia, 82–87% of patients who received RISPERDAL® had elevated levels of prolactin compared to 3-7% of patients on placebo. Increases were dose-dependent and generally greater in females than in males across indications.

In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.

Growth and Sexual Maturation

The long-term effects of RISPERDAL® on growth and sexual maturation have not been fully evaluated in children and adolescents.

Juvenile Animal Studies

Juvenile dogs were treated for 40 weeks with oral risperidone doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen, with a no-effect dose of 0.31 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus its active metabolite paliperidone (9-hydroxy-risperidone) which were similar to those in children and adolescents receiving the maximum recommended human dose (MRHD) of 6 mg/day. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12 week drug-free recovery period.

In a study in which juvenile rats were treated with oral risperidone from days 12 to 50 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus paliperidone about half those observed in humans at the MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest testable dose (1.25 mg/kg/day). This dose produced plasma levels (AUC) of risperidone plus paliperidone which were about two thirds of those observed in humans at the MRHD.

8.5 Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.4, 2.5)]*. While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg twice daily followed by careful titration *[see Warnings and Precautions (5.7)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.4)]*.

8.6 Renal Impairment

In patients with moderate to severe (Clcr 59 to 15 mL/min) renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60%, compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease *[see Dosage and Administration (2.4)]*.

8.7 Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease *[see Dosage and Administration (2.4)]*.

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to RISPERDAL®. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

RISPERDAL® (risperidone) is not a controlled substance.

9.2 Abuse

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

Premarketing experience included eight reports of acute RISPERDAL® overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

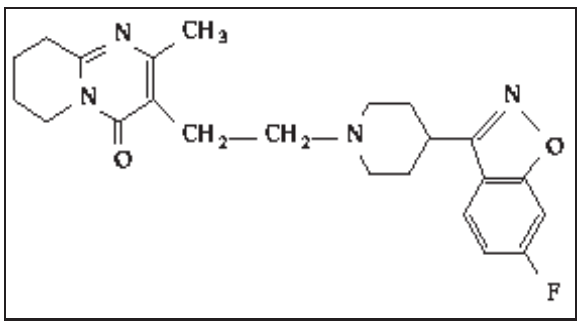
Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of RISPERDAL® and paroxetine.

10.2 Management of Overdosage

For the most up to date information on the management of RISPERDAL® overdosage, contact a certified poison control center (1-800-222-1222 or www.poison.org). Provide supportive care including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. There is no specific antidote to RISPERDAL®.

11 DESCRIPTION

RISPERDAL® contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® Tablets are for oral administration and available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. RISPERDAL® tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). The 0.25 mg, 0.5 mg, 2 mg, 3 mg, and 4 mg tablets also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. RISPERDAL® Oral Solution contains the following inactive ingredients: tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (coral), 3 mg (coral), and 4 mg (coral) strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 2 mg, 3 mg, and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of RISPERDAL®, in schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. The clinical effect from RISPERDAL® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$ *[see Clinical Pharmacology (12.1)]* may explain some of the other effects of RISPERDAL®.

12.2 Pharmacodynamics

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1

histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

12.3 Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, RISPERDAL® can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone *[see Drug Interactions (7)]*. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given RISPERDAL® do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL® may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone *[see Drug Interactions (7)]*. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely *[see Drug Interactions (7)]*.

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, RISPERDAL® did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

In vitro studies demonstrated that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Drug-Drug Interaction Studies

[See Drug Interactions (7)].

Specific Populations

Renal and Hepatic Impairment

[See Use in Specific Populations (8.6 and 8.7)].

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients *[see Use in Specific Populations (8.5)]*.

Pediatric

The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63 mg/kg, 2.5 mg/kg, and 10 mg/kg for 18 months to mice

and for 25 months to rats. These doses are equivalent to approximately 2, 9, and 38 times the maximum recommended human dose (MRHD) for schizophrenia of 16 mg/day on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 body surface basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The table below summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis

No evidence of mutagenic or clastogenic potential for risperidone was found in the Ames gene mutation test, the mouse lymphoma assay, the *in vitro* rat hepatocyte DNA-repair assay, the *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster ovary cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 body surface area basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered orally at doses of 0.31 to 5 mg/kg, sperm motility and

concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m^2 body surface area basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

13.2 Animal Toxicology

Juvenile dogs were treated for 40 weeks with oral risperidone doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were observed with a no-effect dose of 0.31 mg/kg/day. This dose produced plasma AUC levels of risperidone plus its active metabolite paliperidone (9-hydroxy-risperidone) which were similar to those in children and adolescents receiving the maximum recommended human dose (MRHD) of 6 mg/day. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12 week drug-free recovery period.

In a study in which juvenile rats were treated with oral risperidone from days 12 to 50 of age, a reversible impairment of performance in a test of learning and memory was observed in females only with a no-effect dose of 0.63 mg/kg/day. This dose produced plasma AUC levels of risperidone plus paliperidone about half those observed in humans at the MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest testable dose of 1.25 mg/kg/day. This dose produced plasma AUC levels of risperidone plus paliperidone which were about two thirds of those observed in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the

Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (twice-daily schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2 mg/day, 6 mg/day, 10 mg/day, and 16 mg/day, on a twice-daily schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1 mg/day, 4 mg/day, 8 mg/day, 12 mg/day, and 16 mg/day, on a twice-daily schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a once-daily schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Pediatrics

The efficacy of RISPERDAL® in the treatment of schizophrenia in adolescents aged 13–17 years was demonstrated in two short-term (6 and 8 weeks), double-blind controlled trials. All patients met DSM-IV diagnostic criteria for schizophrenia and were experiencing an acute episode at time of enrollment. In the first trial (study #1), patients were randomized into one of three treatment groups: RISPERDAL® 1-3 mg/day (n = 55, mean modal dose = 2.6 mg), RISPERDAL® 4-6 mg/day (n = 51, mean modal dose = 5.3 mg), or placebo (n = 54). In the second trial (study #2), patients were randomized to either RISPERDAL® 0.15-0.6 mg/day (n = 132, mean modal dose = 0.5 mg) or RISPERDAL® 1.5–6 mg/day (n = 125, mean modal dose = 4 mg). In all cases, study medication was initiated at 0.5 mg/day (with the exception of the 0.15-0.6 mg/day group in study #2, where the initial dose was 0.05 mg/day) and titrated to the target dosage range by approximately Day 7. Subsequently, dosage was increased to the maximum tolerated dose within the target dose range by Day 14. The primary efficacy variable in all studies was the mean change from baseline in total PANSS score.

Results of the studies demonstrated efficacy of RISPERDAL® in all dose groups from 1-6 mg/day compared to placebo, as measured by significant reduction of total PANSS score. The efficacy on the primary parameter in the 1-3 mg/day group was comparable to the 4-6 mg/day group in study #1, and similar to the efficacy demonstrated in the 1.5–6 mg/day group in study #2. In study #2, the efficacy in the 1.5-6 mg/day group was statistically significantly greater than that in the 0.15-0.6 mg/day group. Doses higher than 3 mg/day did not reveal any trend towards greater efficacy.

14.2 Bipolar Mania - Monotherapy

Adults

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in two short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the YMRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

Pediatrics

The efficacy of RISPERDAL® in the treatment of mania in children or adolescents with Bipolar I disorder was demonstrated in a 3-week, randomized, double-blind, placebo-controlled, multicenter trial including patients ranging in ages from 10 to 17 years who were experiencing a manic or mixed episode of bipolar I disorder. Patients were randomized into one of three treatment groups: RISPERDAL® 0.5-2.5 mg/day (n = 50, mean modal dose = 1.9 mg), RISPERDAL® 3-6 mg/day (n = 61, mean modal dose = 4.7 mg), or placebo (n = 58). In all cases, study medication was initiated at 0.5 mg/day and titrated to the target dosage range by Day 7, with further increases in dosage to the maximum tolerated dose within the targeted dose range by Day 10. The primary rating instrument used for assessing efficacy in this study was the mean change from baseline in the total YMRS score.

Results of this study demonstrated efficacy of RISPERDAL® in both dose groups compared with placebo, as measured by significant reduction of total YMRS score. The efficacy on the primary parameter in the 3-6 mg/day dose group was comparable to the 0.5-2.5 mg/day dose group. Doses higher than 2.5 mg/day did not reveal any trend towards greater efficacy.

14.3 Bipolar Mania – Adjunctive Therapy with Lithium or Valproate

The efficacy of RISPERDAL® with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in adult patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of YMRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

14.4 Irritability Associated with Autistic Disorder

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of these subjects were under 12 years of age and most weighed over 20 kg (16-104.3 kg).

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

The results of these trials are as follows:

(1) In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=101), aged 5 to 16 years, received twice daily doses of placebo or RISPERDAL® 0.5-3.5 mg/day on a weight-adjusted basis. RISPERDAL®, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day), significantly improved scores on the ABC-I subscale and on the CGI-C scale compared with placebo.

(2) In the other 8-week, placebo-controlled trial in children with autistic disorder (n=55), aged 5 to 12 years, RISPERDAL® 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day,

equivalent to 1.4 mg/day), significantly improved scores on the ABC-I subscale compared with placebo.

A third trial was a 6-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of a lower than recommended dose of risperidone in subjects (N=96) 5 to 17 years of age with autistic disorder (defined by DSM-IV criteria) and associated irritability and related behavioral symptoms. Approximately 77% of patients were younger than 12 years of age (mean age = 9), and 88% were male. Most patients (73%) weighed less than 45 kg (mean weight = 40 kg). Approximately 90% of patients were antipsychotic-naïve before entering the study.

There were two weight-based, fixed doses of risperidone (high-dose and low-dose). The high dose was 1.25 mg per day for patients weighing 20 to < 45 kg, and it was 1.75 mg per day for patients weighing ≥ 45 kg. The low dose was 0.125 mg per day for patients weighing 20 to < 45 kg, and it was 0.175 mg per day for patients weighing ≥ 45 kg. The dose was administered once daily in the morning, or in the evening if sedation occurred.

The primary efficacy endpoint was the mean change in the Aberrant Behavior Checklist – Irritability subscale (ABC-I) score from baseline to the end of Week 6. The study demonstrated the efficacy of high-dose risperidone, as measured by the mean change in ABC-I score. It did not demonstrate efficacy for low-dose risperidone. The mean baseline ABC-I scores were 29 in the placebo group (n = 35), 27 in the risperidone low-dose group (n = 30), and 28 in the risperidone high-dose group (n = 31). The mean changes in ABC-I scores were -3.5, -7.4, and -12.4 in the placebo, low-dose, and high-dose group respectively. The results in the high-dose group were statistically significant (p< 0.001) but not in the low-dose group (p=0.164).

Long-Term Efficacy

Following completion of the first 8-week double-blind study, 63 patients entered an open-label study extension where they were treated with RISPERDAL® for 4 or 6 months (depending on whether they received RISPERDAL® or placebo in the double-blind study). During this open-label treatment period, patients were maintained on a mean modal dose of RISPERDAL® of 1.8-2.1 mg/day (equivalent to 0.05 - 0.07 mg/kg/day).

Patients who maintained their positive response to RISPERDAL® (response was defined as ≥ 25% improvement on the ABC-I subscale and a CGI-C rating of ‘much improved’ or ‘very much improved’) during the 4-6 month open-label treatment phase for about 140 days, on average, were randomized to receive RISPERDAL® or placebo during an 8-week, double-blind withdrawal study (n=39 of the 63 patients). A pre-planned interim analysis of data from patients who completed the withdrawal study (n=32), undertaken by an independent Data Safety

Monitoring Board, demonstrated a significantly lower relapse rate in the RISPERDAL® group compared with the placebo group. Based on the interim analysis results, the study was terminated due to demonstration of a statistically significant effect on relapse prevention. Relapse was defined as ≥ 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline of the randomized withdrawal phase).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RISPERDAL® (risperidone) Tablets

RISPERDAL® (risperidone) Tablets are imprinted "JANSSEN" on one side and either "Ris 0.25", "Ris 0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

0.25 mg dark yellow, capsule-shaped tablets: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, and hospital unit dose blister packs of 100 NDC 50458-301-01.

0.5 mg red-brown, capsule-shaped tablets: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, and hospital unit dose blister packs of 100 NDC 50458-302-01.

1 mg white, capsule-shaped tablets: bottles of 60 NDC 50458-300-06, bottles of 500 NDC 50458-300-50, and hospital unit dose blister packs of 100 NDC 50458-300-01.

2 mg orange, capsule-shaped tablets: bottles of 60 NDC 50458-320-06, bottles of 500 NDC 50458-320-50, and hospital unit dose blister packs of 100 NDC 50458-320-01.

3 mg yellow, capsule-shaped tablets: bottles of 60 NDC 50458-330-06, bottles of 500 NDC 50458-330-50, and hospital unit dose blister packs of 100 NDC 50458-330-01.

4 mg green, capsule-shaped tablets: bottles of 60 NDC 50458-350-06 and hospital unit dose blister packs of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) Oral Solution

RISPERDAL® (risperidone) 1 mg/mL Oral Solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of

4 (2 X 2) tablets. Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-395-28, and long-term care blister packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-315-28, and long-term care blister packaging of 30 tablets NDC 50458-315-30.

2 mg coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

16.2 Storage and Handling

RISPERDAL® Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

RISPERDAL® 1 mg/mL Oral Solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL® and their caregivers:

17.1 Orthostatic Hypotension

Advise patients and caregivers about the risk of orthostatic hypotension, especially during the period of initial dose titration *[see Warnings and Precautions (5.7)]*.

17.2 Interference with Cognitive and Motor Performance

Inform patients and caregivers that RISPERDAL® has the potential to impair judgment, thinking, or motor skills. Advise caution about operating hazardous machinery, including automobiles, until patients are reasonably certain that RISPERDAL® therapy does not affect them adversely *[see Warnings and Precautions (5.9)]*.

17.3 Pregnancy

Advise patients and caregivers to notify their physician if the patient becomes pregnant or intends to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

17.4 Nursing

Inform patients and caregivers that risperidone and its active metabolite are present in human breast milk; there is a potential for serious adverse reactions from RISPERDAL in nursing infants. Advise patients that the decision whether to discontinue nursing or to discontinue the RISPERDAL® should take into account the importance of the drug to the patient *[see Use in Specific Populations (8.3)]*.

17.5 Concomitant Medication

Advise patients and caregivers to inform their physicians if the patient is taking, or plans to take, any prescription or over-the-counter drugs, because there is a potential for interactions *[see Drug Interactions (7)]*.

17.6 Alcohol

Advise patients to avoid alcohol while taking RISPERDAL® *[see Drug Interactions (7.2)]*.

17.7 Phenylketonurics

Inform patients with Phenylketonuria and caregivers that RISPERDAL® M-TAB® Orally Disintegrating Tablets contain phenylalanine. Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine *[see Warnings and Precautions (5.14)]*.

17.8 Metabolic Changes

Inform patients and caregivers that treatment with RISPERDAL® can be associated with hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain*[see Warnings and Precautions (5.5)]*.

17.9 Tardive Dyskinesia

Inform patients and caregivers about the risk of tardive dyskinesia *[see Warnings and Precautions (5.4)]*.

RISPERDAL® Tablets
Active ingredient is made in Ireland
Finished product is manufactured by:
Janssen Ortho, LLC
Gurabo, Puerto Rico 00778

RISPERDAL® Oral Solution
Active ingredient is made in Belgium
Finished product is manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets
Active ingredient is made in Ireland
Finished product is manufactured by:
Janssen Ortho, LLC
Gurabo, Puerto Rico 00778

RISPERDAL® Tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and RISPERDAL® Oral Solution are manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Revised July 2012

DRUGDEX-EV 1530

MICROMEDEX
DRUGDEX® Evaluations

Database updated March 2010

RISPERIDONE

0.0 Overview

1) Class
a) This drug is a member of the following class(es):
Antipsychotic
Benzisoxazole
2) Dosing Information
a) Adult
1) if overlapping of antipsychotics is necessary, in all cases, the period of overlapping should be minimized; if switching patients from depot antipsychotics and if medically appropriate, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)
2) previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone long-acting injection to ensure that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
a) Bipolar I disorder
1) (oral, monotherapy or in combination with lithium or valproate) initial, 2 to 3 mg ORALLY once a day (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) (oral, monotherapy or in combination with lithium or valproate) maintenance, dosage adjustments should be made in increments of 1 mg/day at intervals of at least 24 hours; doses higher than 6 mg/day have not been evaluated in clinical trials (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
3) (intramuscular, monotherapy or in combination with lithium or valproate) initiation of therapy, recommended to establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
4) initial, 25 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
5) (intramuscular, monotherapy or in combination with lithium or valproate) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
b) Schizophrenia
1) (oral) initial, 1 mg ORALLY twice daily, with increases in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dose of 3 mg twice daily on the third day OR 1 mg ORALLY once daily, with increases to 2 mg daily on the second day to a target dose of 4 mg once daily on the third day (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)
2) (oral) maintenance, small, ORAL dose increments/decrements of 1 to 2 mg are recommended at intervals of not less than 1 week. Maximal effect is usually seen within a range of 4 to 8 mg/day. Doses above 6 mg/day for twice-daily dosing were not shown to be more efficacious than lower doses; the safety of doses above 16 mg/day has not been evaluated in clinical trials (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)
3) (intramuscular) initiation of therapy, recommended to establish tolerability to oral risperidone prior to initiation of

treatment with the risperidone long-acting IM injection; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

4) initial, 25 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

5) (intramuscular) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

b) Pediatric

1) safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients under 18 years of age (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) safety and effectiveness of oral risperidone in pediatric patients less than 13 years of age with schizophrenia or less than 10 years with bipolar mania have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) safety and effectiveness or oral risperidone in pediatric patients less than 5 years of age with autistic disorder have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

a) Autistic disorder - Irritability

1) dosing individualized according to the response and tolerability (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

2) (weight less than 20 kg) initial, 0.25 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 0.5 mg/day (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

3) (weight less than 20 kg) maintenance, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days and may increase doses at 2-week intervals or longer, in increments of 0.25 mg per day to achieved sufficient clinical response; use with caution in children weighing less than 15 kg (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

4) (weight 20 kg or greater) initial, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 1 mg/day (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

5) (weight 20 kg or greater) maintenance, 1 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days; may increase doses at 2-week intervals or longer, in increments of 0.5 mg per day to achieved sufficient clinical response (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

6) in patients with persistent somnolence, a once-daily dose at bedtime or half the daily dose twice daily, or a reduction of the dose may be considered (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

b) Bipolar I disorder

1) (10 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a maximum recommended dose of 2.5 mg/day (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

c) Schizophrenia

1) (13 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 3 mg/day (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Contraindications

a) hypersensitivity to risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009), paliperidone (an active metabolite of risperidone) or to any product component

4) Serious Adverse Effects

a) Agranulocytosis
b) Death
c) Diabetic ketoacidosis
d) Hypothermia
e) Leukopenia
f) Neuroleptic malignant syndrome
g) Neutropenia
h) Pancreatitis
i) Priapism

j) Purpura
k) Seizure
l) Sudden cardiac death
m) Syncope
n) Tardive dyskinesia
o) Thrombocytopenia
p) Thrombotic thrombocytopenic purpura
5) Clinical Applications
a) FDA Approved Indications
1) Autistic disorder - Irritability
2) Bipolar I disorder
3) Schizophrenia

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Risperidone
C) Physicochemical Properties
1) Molecular Weight
a) 410.49 (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008)
2) Solubility
a) Risperidone is practically freely soluble in methylene chloride, soluble in methanol and 0.1 N hydrochloride, and insoluble in water (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008).

1.2 Storage and Stability

A) Preparation
1) Intramuscular route
a) Preparation
1) Risperidone long-acting injection must only be suspended in the diluent supplied by the manufacturer in the dose pack. Allow the drug and diluent to come to room temperature prior to reconstitution. After injecting the diluent into the vial, shake the vial vigorously for a minimum of 10 seconds. The suspension should appear uniform, thick, and milky in color. The particles will be visible in liquid, but no dry particle should remain. It should be used immediately after suspension and must be used within 6 hours of reconstitution. If two minutes pass before injection, resuspend by shaking vigorously, as settling will occur over time once the product is in suspension (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) Administration
1) Do NOT inject intravenously. Administer by deep intramuscular injection into the deltoid or gluteal muscles, alternating between the 2 arms or two buttocks. Use a 1-inch 21 gauge needle for deltoid injection and a 2-inch 20 gauge needle for gluteal injection. Do not combine different dosage strengths in a single administration (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) Oral route
a) Orally Disintegrating Tablets
1) Oral disintegrating tablets are supplied in blister packs and should not be opened until ready for use. Peel back foil to expose tablet; do NOT push the tablet through the foil backing because this could damage the tablet. Use dry hands to remove the tablet from the blister unit and immediately place the entire tablet on the tongue. The tablet should be consumed immediately once it is removed form the blister unit. Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Do not split or chew the tablet (Prod Info RISPERDAL(R), RISPER-

DAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

b) Oral Solution

1) Calibrated dispensing-pipettes are provided with risperidone oral solution. The oral solution is compatible with water, coffee, orange juice, and low-fat milk. However, it is not compatible with cola or tea (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

B) Intramuscular route

1) The long-acting injection should be stored in the refrigerator between 36 and 46 degrees Fahrenheit (F) (2 and 8 degrees Celsius); or if refrigeration is not available, it may be stored at temperatures not exceeding 77 degrees F (25 degrees C) for no more than 7 days prior to administration; protect from light (Prod Info Risperdal(R) Consta(TM), 2003h).

C) Oral route

1) Solution

a) Store the oral solution at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); protect from light and freezing (Prod Info Risperdal(R), 2004).

2) Tablet

a) Tablets should be stored at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); protect from light and moisture (Prod Info Risperdal(R), 2004).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Intramuscular route

1.3.1.A.1 Bipolar I disorder

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be established with oral risperidone prior to initiation of treatment with the long-acting risperidoneintramuscular injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly every 2 weeks. For patients not responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 weeks. Clinical effects from a dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher dose. The maximum dose should not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and should be reassessed periodically to determine the necessity of continued treatment. Risperidone long-acting injection should be administered by deep intramuscular injection into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administered by a health care professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection of long-acting risperidone and should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administration (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treatment in patients previously discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.1.A.2 Schizophrenia

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be established with oral risperidone prior to initiation of treatment with the long-acting risperidoneintramuscular injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly every 2 weeks. For patients not responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 weeks. Clinical effects from a dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher dose. The maximum dose should not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and should be reassessed periodically to determine the necessity of continued treatment. Risperidone long-acting injection should be administered by deep intramuscular injection into the deltoid or gluteal muscles, alternating

between the two arms or two buttocks; should be administered by a health care professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
c) Oral risperidone or another antipsychotic medication should be administered with the initial injection of long-acting risperidone and should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administration (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treatment in patients previously discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.1.B Intramuscular route/Oral route

1) Switching Antipsychotics
a) If overlapping of antipsychotics is necessary, in all cases, the period of overlapping should be minimized. Immediate discontinuation of previous antipsychotic treatment may be acceptable for some patients while gradual discontinuation may be appropriate for others. If switching patients from depot antipsychotics and if medically appropriate, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005).
b) Previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone long-acting injection to ensure that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.1.C Oral route

1.3.1.C.1 Bipolar I disorder

a) Risperidone is approved for use as monotherapy or in combination with lithium or valproate in the treatment of bipolar mania. Risperidone should be administered once daily at an initial dose of 2 to 3 milligrams (mg) per day. If needed, dosage adjustments should be made at intervals of at least 24 hours in increments/decrements of 1 mg/day. In clinical trials, doses ranging from 1 to 6 mg/day were used; doses higher than 6 mg/day have not been studied (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
b) The effectiveness of risperidone for maintenance therapy beyond 3 weeks has not been evaluated. While, the continuation of treatment in a responding patient is generally desirable for maintenance of the initial response and for prevention of new manic episodes, there are no data from clinical trials to support the use of risperidone in long-term treatment (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

1.3.1.C.2 Schizophrenia

a) Low doses, 1 milligram (mg) twice daily, should be generally used initially to avoid the typical first-dose effects of alpha-adrenoreceptor antagonists. Doses may be increased by 1 mg twice daily until a target dose of 6 mg per day (3 mg twice daily) is reached on day 3. Controlled trials have demonstrated that total daily doses of up to 8 mg on a once-daily regimen are also safe and effective. In some patients, slower titration may be indicated. Further increases/decreases in dose, if indicated, should be limited to 1 to 2 mg at weekly intervals since steady state for the active metabolite would not be attained for one week in the typical patient. In clinical trials, maximal antipsychotic efficacy was seen with doses between 4 and 8 mg/day while effective oral doses ranged from 4 to 16 mg/day. However, doses above 6 mg/day at a twice-daily dosing regimen are not generally recommended as they were associated with more extrapyramidal and other adverse effects, with no additional treatment benefit than lower doses (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005; Borison et al, 1992b; Anon, 1991a; Mesotten et al, 1989).
b) If risperidone is discontinued, reinitiate with the initial titration schedule (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005).
c) In a controlled, clinical trial, risperidone given at once-daily doses of 2 to 8 milligrams was effective in delaying relapse in patients who had been clinically stable for 4 weeks or longer. However, patients should be periodically reas-

sessed to determine the need for maintenance treatment (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005).

d) The Consensus Study Group on Risperidone Dosing reports their empiric clinical experience has resulted in a lower-dose and slower-titration strategy for many patients. They target a goal of 2 to 4 milligrams (mg) daily during the first week of treatment. If no initial response occurs, the dose is increased to 6 to 8 mg/day during the second week of treatment. If there is no response at this dose during the next 2 weeks, then a higher dose may be warranted, usually increases of 2 mg/week up to a maximum daily dose of 16 mg/day are attempted. Any further dosage adjustments, if indicated, should be made at intervals of no less than 1 week (Borison et al, 1992b).

e) In a small study (n=11) rapid oral-loading risperidone was well tolerated within 24 hours. Seven patients achieved the target dose of 3 milligrams (mg) twice daily in 16 hours; 3 patients achieved the maintenance dose in 24 hours and 1 patient tolerated a regimen of 2 mg three times daily (Feifel et al, 2000).

f) In dose comparison studies chiefly utilizing chronic schizophrenic patients, the most consistently positive responses on all measures were seen for the 6 milligram (mg) dose group (Marder & Meibach, 1994a; Chouinard et al, 1993b; Marder, 1992) and for the 4 mg group in one study (Muller-Spahn, 1992a). In a review of 12 double-blind studies (n=2099), symptom improvement was maximal at 4 to 8 mg/day (Lemmens et al, 1999). There was no suggestion of increased benefit from larger doses. Another study utilizing only neuroleptic naive patients found a superior outcome in the 2 to 4 mg group versus a 5 to 8 mg dose group (Kopala et al, 1997).

1.3.1.C.3) Bioequivalence

a) Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005; van Schaick et al, 2003).

1.3.1.D First episode psychosis

1) In randomized clinical studies, low doses of risperidone (2 mg/day to 6 mg/day) were effective in treating initial symptoms of first-episode psychosis and were associated with a lower prevalence of extrapyramidal symptoms (Moller et al, 2008; Schooler et al, 2005; Merlo et al, 2002; Emsley, 1999).

1.3.2 Dosage in Renal Failure

A) Oral

1) The recommended initial dosage in patients with severe renal impairment is 0.5 milligrams twice daily. Doses may be increased by 0.5 milligrams twice daily until a dose of 3 milligrams per day (1.5 milligrams twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 milligrams twice daily at weekly intervals. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is recommended for patients in renal failure and caution is advised for overall use in this patient population until further research is available (Fachinfo Risperdal(R), 1997).

B) Intramuscular

1) Patients with renal impairment should receive titrated doses of oral risperidone prior to initiating treatment with the risperidone long-acting intramuscular injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral risperidone twice daily for one week; then the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dose of 2 mg is well tolerated, 25 mg of risperidone long-acting injection can be given intramuscularly every 2 weeks. Although the efficacy has not been confirmed in clinical trials, 12.5 mg of risperidone long-acting injection may be given to patients with renal impairment. Continue oral supplementation for 3 weeks following the first injection until the main release of risperidone from the injection site has begun. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) Oral

1) The recommended initial dosage in patients with severe hepatic impairment is 0.5 milligrams (mg) twice a day. Doses may be increased by 0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice daily at weekly intervals. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is recommended for patients with hepatic insufficiency and caution is advised for overall use in this patient population until further research is available (Fachinfo Risperdal(R), 2000).

B) Intramuscular

1) Patients with hepatic impairment should receive titrated doses of oral risperidone prior to initiating treatment with the

risperidone long-acting intramuscular (IM) injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral risperidone twice daily for one week; then the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dose of 2 mg is well tolerated, 25 mg of risperidone long-acting injection can be given IM every 2 weeks. Although the efficacy has not been confirmed in clinical trials, 12.5 mg of risperidone long-acting injection may be given to patients with hepatic impairment. Continue oral supplementation for 3 weeks following the first injection until the main release of risperidone from the injection site has begun. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.4 Dosage in Geriatric Patients

A) Oral

1) The initial dosage should be 0.5 milligrams (mg) orally twice a day. Doses may be increased by 0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice daily at weekly intervals. Slower titration may be necessary in some patients. If once-daily dosing is desired, initiate and titrate patient on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is recommended for geriatric patients and caution is advised for overall use in this patient population until further research is available (Fachinfo Risperdal(R), 2000).

B) Intramuscular

1) The recommended dosage of risperidone long-acting injection for elderly patients is 25 milligrams intramuscularly every 2 weeks. Oral risperidone or another antipsychotic medication should be administered with the initial injection of long-acting risperidone and should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.6 Dosage in Other Disease States

A) Debilitated Patients

1) Debilitated patients may have less ability to eliminate risperidone than normal patients. The initial dosage should be 0.5 milligrams (mg) twice daily. Doses may be increased by 0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice daily at weekly intervals. Slower titration may be necessary in some patients. If once-daily dosing is desired, initiate and titrate patient on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005).

B) Hypotension Predisposition

1) Patients with a predisposition to hypotension or for whom hypotension may pose a risk should receive a reduced dosage. The initial dosage should be 0.5 milligrams (mg) twice a day. Doses may be increased by 0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice daily at weekly intervals. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005).

C) Concomitant Medications

1) For patients on CYP2D6 inhibitors (eg, fluoxetine, paroxetine), risperidone long-acting intramuscular injection may be initiated at doses of 12.5 milligrams (mg) or 25 mg. For patients already on 25 mg of long-acting risperidone injection and initiating fluoxetine or paroxetine, continue the 25 mg dose. However, if clinical judgement warrants, the dose of risperidone may be decreased to 12.5 mg or risperidone long-acting intramuscular injection may be discontinued. Although, the efficacy of 12.5 mg has not been confirmed in clinical trials (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) For patients on CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital), the dose of risperidone long-acting intramuscular injection will need to be titrated accordingly, especially during initiation or discontinuation of the CYP3A4 inducers. When CYP3A4 inducers are discontinued, continue with the 25 milligram (mg) dose. However, if clinical judgement warrants, the dose of risperidone may be decreased to 12.5 mg or risperidone long-acting intramuscular injection may be discontinued. Although, the efficacy of 12.5 mg has not been confirmed in clinical trials (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

D) Poor Tolerability to Psychotropic Medications

1) Although the efficacy has not been confirmed in clinical trials, 12.5 milligrams intramuscularly may be given to patients with a history of poor tolerability to psychotropic medications (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Intramuscular route

1) The safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients under 18 years of age (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.4.1.B Oral route

1.4.1.B.1 Autistic disorder - Irritability

a) Dosing should be individualized according to the response and tolerability. Doses are administered once daily or half the total daily dose twice daily. In patients with persistent somnolence, a once-daily dose at bedtime or half the daily dose twice daily, or a reduction of the dose may be considered (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
b) For children weighing less than 20 kilograms (kg), the recommended initial dose is 0.25 milligram (mg) ORALLY daily. Doses may be increased after a minimum of 4 days to 0.5 mg per day. Doses should be maintained for at least 14 days. They may be increased at 2-week intervals or longer, in increments of 0.25 mg per day if the patient has not achieved sufficient clinical response. Once adequate clinical response has been achieved and maintained, doses may be lowered gradually to obtain the optimal balance of efficacy and safety. Risperidone should be used with caution in children weighing less than 15 kg (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
c) For children weighing 20 kilograms (kg) or greater, the recommended initial dose is 0.5 milligram (mg) ORALLY daily. Doses may be increased after at least 4 days to 1 mg per day. Doses should be maintained for at least 14 days. They may be increased at 2-week intervals or longer, in increments of 0.5 mg per day if the patient has not achieved sufficient clinical response. Once adequate clinical response has been achieved and maintained, doses may be lowered gradually to obtain the optimal balance of efficacy and safety (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
d) In clinical trials, a response (based on at least 25% improvement on ABC-I) was achieved in 90% of patients following doses of risperidone between 0.5 mg and 2.5 mg per day. In one of the pivotal trials, the maximum daily dose of risperidone was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or greater, or 3 mg in patients weighing greater than 45 kg, when the therapeutic effect reached plateau (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

1.4.1.B.2 Bipolar I disorder

a) For the short-term treatment of bipolar mania, initiate treatment at 0.5 milligrams (mg) orally once daily, given as a single daily dose either in the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day, as indicated and tolerated. The maximum recommended daily dose is 2.5 mg/day. If somnolence occurs, the daily dose may be divided into 2 equal doses. Data are unavailable to support use of risperidone beyond 3 weeks for the treatment of bipolar mania. Therefore, if therapy is required for extended periods, periodically reevaluate the long-term usefulness for the individual patient (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

1.4.1.B.3 Schizophrenia

a) In children 13 years of age and older, initiate treatment at 0.5 milligrams (mg) orally once daily, given as a single daily dose either in the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day, as indicated and tolerated. The maximum recommended daily dose is 3 mg/day. If somnolence occurs, the daily dose may be divided into 2 equal doses. Data are unavailable to support use of risperidone beyond 8 weeks in adolescents with schizophrenia. Therefore, if therapy is required for extended periods, periodically reevaluate the long-term usefulness for the individual patient. If risperidone is discontinued, reinitiate with the initial titration schedule. When switching schizophrenic patients from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) The safety and effectiveness in children less than 13 years of age with schizophrenia or less than 10 years of age with acute mania associated with bipolar I disorder have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
5) The safety and effectiveness in pediatric patients with autistic disorder less than 5 years of age have not been established (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
6) Risperidone was beneficial in children and adolescents with pervasive developmental disorder. Starting doses of 0.25 milligrams (mg) twice daily and increased in 0.25 mg/day increments every 5 to 7 days have been used (Fisman & Steele, 1996). Optimal doses ranged from 0.75 to 6 mg daily (Perry et al, 1997; Fisman & Steele, 1996).

2.0 Pharmacokinetics

2.1 Onset and Duration

A) Onset
1) Initial Response
a) Psychotic symptoms, oral: 1 to 2 weeks (Vanden Borre et al, 1993; Borison et al, 1992a; Mesotten et al, 1989a).
b) Psychotic symptoms, intramuscular: 3 weeks (Prod Info Risperdal(R) Consta(TM), 2003i).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug occurs (less than approximately 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003i).
B) Duration
1) Single Dose
a) Psychotic symptoms, intramuscular: 7 weeks (Prod Info Risperdal(R) Consta(TM), 2003i).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug occurs (less than approximately 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003i).
2) Multiple Dose
a) Psychotic symptoms, oral: 1 year (Addington et al, 1993; Carman & Wyatt-Knowles, 1993; Bressa et al, 1991; De Wilde & Dierick, 1991); (Mertens, 1991).
1) Clinical improvement in positive and negative symptoms has been observed for up to 7 months (Addington et al, 1993; Carman & Wyatt-Knowles, 1993; Bressa et al, 1991; De Wilde & Dierick, 1991); (Mertens, 1991).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration
1) Oral
a) A therapeutic range has not been established. A dose of 6 mg/day produces a risperidone serum level of 50 to 150 nmol/L in 90% of patients (Olesen et al, 1998).
b) Plasma concentrations are dose proportional over the dosing range of 1 to 16 mg daily (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).
B) Time to Peak Concentration
1) Oral, solution: 1 hour (Prod Info Risperdal(R), 2004).

2.3 ADME

2.3.1 Absorption

A) Bioavailability
1) Oral: 70% (CV=25%) (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a; Anon, 1991; Vanden Bussche et al, 1988).
a) The relative oral bioavailability from a tablet was 94% (CV=10%) when compared to a solution (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a; Anon, 1991; Vanden Bussche et al, 1988).

B) Effects of Food
1) None (Prod Info Risperdal(R), 2004)(Anon, 1991; Vanden Bussche et al, 1988).

2.3.2 Distribution

A) Distribution Sites
1) Protein Binding
a) Risperidone: approximately 90% (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i).
b) 9-hydroxyrisperidone: 77% (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i).
B) Distribution Kinetics
1) Volume of Distribution
a) 1 to 2 liters/kilogram (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Liver, extensive (Prod Info Risperdal(R) Consta(TM), 2003i); (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).
a) Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP2D6 (debrisoquin hydroxylase) with a second minor pathway of N-dealkylation (Prod Info Risperdal(R) Consta(TM), 2003i); (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).
b) Metabolism is sensitive to the debrisoquine hydroxylation type genetic polymorphism (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).
B) Metabolites
1) 9-hydroxyrisperidone, active (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).
a) Metabolite is approximately equi-effective to the parent compound in terms of receptor binding activity (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).

2.3.4 Excretion

A) Total Body Clearance
1) 3.2 to 13.7 liters/hour (L/hr) (Prod Info Risperdal(R) Consta(TM), 2003i).
a) The clearance of risperidone and risperidone plus 9-hydroxyrisperidone is 13.7 L/h and 5 L/h in extensive CYP2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor metabolizers, respectively (Prod Info Risperdal(R) Consta(TM), 2003i).

2.3.5 Elimination Half-life

A) Parent Compound
1) ELIMINATION HALF-LIFE
a) oral: 20 to 30 hours (Prod Info Risperdal(R), 2004)(Anon, 1991; Vanden Bussche et al, 1988).
1) The apparent half-life of risperidone was 3 hours in extensive metabolizers and 20 hours in poor metabolizers (Prod Info Risperdal(R), 2004).
2) ELIMINATION HALF-LIFE
a) intramuscular: 3 to 6 days (Prod Info Risperdal(R) Consta(TM), 2003i).
1) The half-life of intramuscular risperidone is related to the erosion of the microspheres and subsequent absorption of risperidone (Prod Info Risperdal(R) Consta(TM), 2003i).
B) Metabolites
1) 9-hydroxyrisperidone, 21 to 30 hours (Prod Info Risperdal(R), 2004).
a) The apparent half-life of 9-hydroxyrisperidone was 21 hours in extensive metabolizers and 30 hours in poor metabolizers (Prod Info Risperdal(R), 2004).

3.0 Cautions

3.0.A) Black Box WARNING

1) Intramuscular (Powder for Suspension, Extended Release)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Risperidone is not approved for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral (Tablet; Tablet, Disintegrating; Solution)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Risperidone is not approved for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

3.1 Contraindications

A) hypersensitivity to risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009), paliperidone (an active metabolite of risperidone) or to any product component

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

B) agranulocytosis, leukopenia and neutropenia have been reported; risk factors include history of low WBC, leukopenia or neutropenia; monitoring recommended (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

C) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

D) cerebrovascular adverse events (stroke, transient ischemic attack), including fatalities, have been reported in elderly patients with dementia-related psychosis (unapproved use) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

E) conditions that may contribute to elevated body temperature; may disrupt body temperature regulation (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

F) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

G) diseases or conditions that could affect metabolism or hemodynamic responses (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

H) elderly patients; increased risk of tardive dyskinesia, especially among elderly women (Prod Info RISPERDAL(R) CON-

STA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
I) elderly patients; increased risk of orthostatic hypotension, especially during the initial dose-titration period (oral) (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
J) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
K) hepatic impairment, severe; increased risperidone exposure and side effects have been reported; dosage adjustment necessary (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
L) hyperglycemia has been reported, some may lead to ketoacidosis, hyperosmolar coma, or death (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
M) hyperprolactinemia; may result in galactorrhea, amenorrhea, gynecomastia, impotence, hypogonadism and decreased bone density; incidence of hyperprolactinemia appears to be higher with risperidone relative to other antipsychotic agents (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
N) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
O) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; immediately discontinue drug (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
P) Parkinson's disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
Q) priapism has been reported; severe cases may require surgical intervention (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
R) renal impairment, severe; increase in free fraction of risperidone and side effects have been reported; dosage adjustment necessary (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
S) seizure disorder, history, or conditions which lower seizure threshold (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
T) suicide risk; close monitoring of high-risk patients recommended (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
U) tardive dyskinesia, potentially irreversible; discontinue treatment if appropriate (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

3.3 Adverse Reactions

3.3.1 Cardiovascular Effects

3.3.1.A Cardiac dysrhythmia

1) During clinical trials of schizophrenic and bipolar I disorder patients, there was no significant difference in the QTc intervals between patients receiving risperidone long-acting injection at recommended doses and patients receiving placebo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) The manufacturer reports that intergroup comparisons for pooled, placebo-controlled studies did not reveal statistically significant differences between oral risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. There was a mean increase in heart rate of 1 beat per minute when all risperidone doses were pooled from randomized, controlled studies in several indications, as compared with no change for patients who received placebo. In short-term studies of patients with schizophrenia, higher doses of risperidone (8 to 16 milligrams/day) were associated with a higher mean increase in heart rate (4 to 6 beats per minute) as compared with placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007;

Prod Info RISPERDAL(R) oral solution, 2007).
3) QRS prolongation and QTc prolongation, sometimes resulting in death, have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ak; Ravin & Levenson, 1997p; Gesell & Stephen, 1997h; Lo Vecchio et al, 1996h; Brown et al, 1993i).
4) A 40-year-old man experienced symptomatic bradyarrhythmia 1 day following an increase in his risperidone dose from 2 milligrams (mg)/day to 6 mg/day. The patient developed sinus bradycardia (38 beats per minute) and had several episodes of sinus pauses lasting 2 to 3 seconds. During this time, the QTc interval was 410 milliseconds. Risperidone was discontinued and the symptoms resolved over the following 48 hours (Goyal & Goyal, 2003).
5) A 7-year-old boy developed sinus dysrhythmia and a QTc interval of 0.46 seconds after a single dose of risperidone 1 milligram (mg) for attention deficit hyperactivity disorder (Gesell & Stephen, 1997h).
6) A 34-year-old woman with no history of cardiac disease developed fatal pulseless electrical activity following treatment with risperidone. On day 3, she developed postural hypotension and was then maintained on 2 milligrams (mg) twice daily. On day 5, she developed cardiac arrest and was treated for pulseless electrical activity with a prolonged QRS interval and an abnormal QTc interval of 480 milliseconds (msec). Despite resuscitative efforts, the patient expired (Ravin & Levenson, 1997p).

3.3.1.B Hypertension

1) Incidence: 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, hypertension was reported in 3% of patients receiving risperidone intramuscular (n=154) as monotherapy compared with 1% in placebo (n=149) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.1.C Orthostatic hypotension

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Orthostatic hypotension was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope (0.2% of patients in phase 2 and 3 studies receiving oral risperidone, and 0.8% of patients receiving intramuscular risperidone in multiple-dose studies) has been reported. A large clinical trial revealed a positive dose-related trend for orthostatic dizziness. A dose reduction should be considered if hypotension occurs. Use risperidone cautiously in patients with known cardiovascular or cerebrovascular disease and conditions which may predispose patients to hypotension (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.1.D Palpitations

1) Incidence: oral, adults, 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Palpitations were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) In two 3-week, double-blind, placebo-controlled studies of adjuvant oral risperidone therapy in adults, palpitations were reported by 2% of patients receiving risperidone (n=127) compared to 0% for placebo (n=126) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) During premarketing (n=2607) evaluation of oral risperidone, palpitations were reported. Data from a large study comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day) revealed a positive dose-related trend (p less than 0.05) for palpitations (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.1.E Peripheral edema

1) Incidence: adults, up to 3%; children, less than 5% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) In a 12-week placebo-controlled trial of adult schizophrenic patients , peripheral edema was reported in 2% and 3% of patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 1% in placebo (n=98)(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During premarketing risperidone studies of various design types, peripheral edema was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) In a study of 110 elderly Chinese patients (age 65 or greater), 16% experienced peripheral edema. Leg-pitting edema was the primary complaint leading to discontinuation of treatment (Hwang et al, 2001).
5) A 27-year-old woman developed pitting edema in the legs and moderate periorbital and facial edema during the third week of risperidone (4 milligrams per day (mg/day)) treatment for schizophrenia. She experienced a 5 kilogram (kg) weight gain during this period. The patient had received diphenhydramine during the first 3 weeks for the management of mild dystonia and restlessness; this treatment was not continued after week 3. Resolution of edema occurred within 1 week when the dose of risperidone was reduced to 3 mg/day. No recurrence of edema was reported during an 8-month follow-up period (Tamam et al, 2002).
6) A 35-year-old male experienced edema with a 15 pound weight gain after 2 1/2 weeks of risperidone therapy. His other medications included divalproex sodium and clorazepate. Diuretic therapy with hydrochlorothiazide 25 milligrams (mg)/day and triamterene 50 mg/day resolved the edema within 1 week. The authors note that although edema is associated with divalproex, it did not occur until the risperidone was added. They suggest that both of these medications when used together may be more likely to cause edema by some unknown mechanism (Baldassano & Ghaemi, 1996).

3.3.1.F Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drugs and 186,600 nonusers of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using risperidone compared to those who were not using antipsychotic drugs (incidence-rate ratio, 2.91; 95% confidence interval (CI), 2.26 to 3.76; p less than 0.001). In participants being treated with atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) (Ray et al, 2009).

3.3.1.G Summary

1) AV block, myocardial infarction, palpitations, hypertension, hypotension, pulmonary embolism, T-wave inversions, angina pectoris, prolonged QRS interval, abnormal QTc interval, tachycardia, bradyarrhythmia, and edema have all been reported with risperidone administration. Stroke and transient ischemic attack have been reported in the elderly (mean age 85 years old) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.1.H Syncope

1) Incidence: adults, up to 2%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Syncope was reported in 0.2% (6/2607) of patients receiving oral risperidone in Phase 2 and 3 clinical trials (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) During a 12-week clinical trial, syncope was observed in 2% of patients receiving risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98). In multidose studies, syncope occurred in 0.8% (12/1499) of patients receiving long-acting injections (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.1.I Tachycardia

1) Incidence: oral, adults, up to 5%; children, up to 7% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Tachycardia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009), and in up to 5% of adult patients receiving oral therapy, and in 0% to 7% of pediatric patients receiving oral therapy. Tachycardia was responsible for 0.3% and 0.5% of discontinuation of therapy in schizophrenic adult trials in patients receiving 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respectively, compared with 0% in placebo (n=225) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) A compensatory increased heart rate (7 to 8 beats/minute) may develop at therapeutic doses of risperidone (Keegan, 1994).

3.3.2 Dermatologic Effects

3.3.2.A Acne

1) Incidence: adults, 1% to 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) During risperidone clinical trials, acne was reported in 2% of adult patients receiving intramuscular therapy and in 1% of bipolar adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.2.B Discoloration of skin

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) During risperidone clinical trials, skin discoloration was reported in less than 1% of adult patients receiving oral therapy and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.2.C Dry skin

1) Incidence: intramuscular, adults, up to 2% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) In a 12-week placebo-controlled trial of adult schizophrenic patients, dry skin was reported in 2% and 0% of patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 0% in placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.2.D Injection site reaction

1) Incidence: intramuscular, 1% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During the 10th week of a 12-week clinical trial, injection site reaction (including redness, swelling, or induration) was observed in 1% of patients receiving risperidone 25 mg or 50 mg long-acting injection (n=202). Between the first and last injections, there was a decrease in the mean injection pain intensity scores (0=no pain to 100=unbearable pain) in the placebo group (16.7 to 12.6) and risperidone long-acting injection groups (25 mg: 12 to 9; 50 mg: 18.2 to 11.8). In a separate study in which long-acting risperidone injection was given into the deltoid muscle every 2 weeks over 8 weeks period, only mild injection site events were observed in patients receiving doses of 37.5 mg or 50 mg at 2 hours after the injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.2.E Peeling of skin

1) A 37-year-old male with DSM-IV bipolar I disorder experienced rash and desquamation following oral risperidone treatment. The patient presented to an inpatient clinic as euphoric and irritable with rapid speech, sleep and appetite distur-

bances. The patient's medical history consisted of several manic episodes since the age of 23. Treatment with oral risperidone solution 2 mg at bedtime was initiated, along with lithium (900 mg/day), diazepam (15 mg/day), zolpidem (10 mg at bedtime), and procyclidine hydrochloride (5 mg at bedtime). Facial flushing and rash under the patient's eyes were seen on day 3 of treatment. Risperidone and lithium were both increased to 4 mg/day and 1200 mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the entire face and neck, with desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to quetiapine 150 mg/day. Quetiapine was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two days following risperidone discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.F Rash

1) Incidence: oral, adults, 2% to 4%; children, up to 11% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Rash was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, rash was reported in 2% to 4% of adult patients receiving oral therapy, and in 0% to 11% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) A 37-year-old male with DSM-IV bipolar I disorder experienced rash and desquamation following oral risperidone treatment. The patient presented to an inpatient clinic as euphoric and irritable with rapid speech, sleep and appetite disturbances. The patient's medical history consisted of several manic episodes since the age of 23. Treatment with oral risperidone solution 2 mg at bedtime was initiated, along with lithium (900 mg/day), diazepam (15 mg/day), zolpidem (10 mg at bedtime), and procyclidine hydrochloride (5 mg at bedtime). Facial flushing and rash under the patient's eyes were seen on day 3 of treatment. Risperidone and lithium were both increased to 4 mg/day and 1200 mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the entire face and neck, with desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to quetiapine 150 mg/day. Quetiapine was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two days following risperidone discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.G Summary

1) Rash, dry skin, seborrhea, skin discoloration, injection site reaction, photosensitivity, skin exfoliation, pruritus, alopecia, acne, increased sweating, skin ulceration, and dermatitis were reported with risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Body temperature above normal

1) Hyperthermia has been associated with the use of antipsychotic agents, including oral risperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.3.B Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF DIABETES

3.3.3.C Diabetic ketoacidosis

1) Incidence: rare (Lu & Yan, 2009)
2) Diabetic ketoacidosis in patients with impaired glucose metabolism has been reported during the risperidone postmarketing period (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) A 27-year-old schizophrenic male was hospitalized with fever and severe diabetic ketoacidosis (DKA) resulting in death following 2 months of risperidone treatment. The patient had no history of diabetes. On admission his serum glucose was 1297 mg/dL, ketone body and metabolic acidosis were positive, and his glycosylated hemoglobin was 13%. Risperidone was immediately discontinued. However, despite insulin treatment and fluid replacement, the patient died within 12 hours due to the rapid progression of DKA. The authors suggest risperidone-induced hyperglycemia resulting in fatal diabetic ketoacidosis (Lu & Yan, 2009).

3.3.3.D Excessive thirst

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) During the double-blind, placebo-controlled trials for oral risperidone, less than 1% of adults and less than 5% of pediatric patients reported experiencing thirst (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Risperidone was suspected of causing polydipsia in a 28-year-old male receiving the drug for treatment of schizophrenia (undifferentiated type). His schizophrenia had been refractory to various oral and injectable antipsychotics and electroconvulsive therapy. He was started on risperidone 8 mg/day (which improved his psychotic symptoms). Within 2 weeks, he started drinking water excessively, 4 to 5 liters within a variable period of a few minutes to 8 hours. His polydipsia episodes initially occurred intermittently at 10- to 15-day intervals, but over time, became more frequent (ie, every 3 to 4 days, sometimes twice daily), especially after his risperidone was increased to 16 mg/day. In addition to polydipsia, the patient experienced polyuria and, occasionally, nausea, vomiting, marked lassitude, slurring of speech, and drowsiness after an episode. Staring and unresponsiveness would sometimes precede an episode. Later risperidone was decreased to 8 mg/day; however, no decrease in frequency of polydipsia episodes occurred. Then risperidone was withdrawn. Polydipsia disappeared during the 2-week drug-free period. The patient was started on clozapine, and had no return of polydipsia. The authors noted that during the time the patient was drinking excessive amounts of water, he never developed hyponatremia or water intoxication. Diabetes mellitus or insipidus, as well as syndrome of inappropriate secretion of antidiuretic hormone (SIADH), had been ruled out, and he was taking no other medication linked to polydipsia (Kar et al, 2002).

3.3.3.E Hyperglycemia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Hyperglycemia, including cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving atypical antipsychotics, including risperidone. Hyperglycemia has resolved in some cases after discontinuation of the drug, while in other cases, continuation of antidiabetic treatment was required after drug discontinuation (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Hyperglycemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Hyperglycemia was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.3.F Hyperprolactinemia

1) Summary
a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-generation antipsychotics or risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantly elevated (p less than 0.05) following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several clinical trials of patients with schizophrenia. Younger patients and women of

childbearing potential have a greater risk for hyperprolactinemia following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbances, sexual dysfunction, decreased bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al, 2009).

c) Elevated prolactin levels associated with risperidone use appear to be dose-dependent and greater in females than males. Prolactin elevations are higher with risperidone use compared to elevations associated with other antipsychotic agents (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

d) Adverse events associated with hyperprolactinemia include inhibited reproductive function, galactorrhea, amenorrhea, gynecomastia and impotence. Hypogonadism associated with chronic hyperprolactinemia may lead to reduced bone density in both males and females (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

2) Incidence: oral, adults, less than 1%; children, 49% to 87% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3) Adult

a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Hyperprolactinemia was reported in less than 1% of patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Risperidone is associated with increased prolactin which persists with chronic therapy (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Hellings et al, 2005; Kleinberg et al, 1999; Caracci & Ananthamoorthy, 1999). Male patients with primary hypothyroidism may be particularly sensitive to a neuroleptic-induced elevation of prolactin levels and close monitoring is suggested within the first 3 months of initiating risperidone therapy (Mabini et al, 2000).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females on risperidone with females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prolactin was measured once each during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with mental retardation and pervasive developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and maintenance doses of risperidone were 0.92 milligrams/day (mg/day) (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day), respectively. For adults (mean age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/day (1 to 1.5 mg/day), respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 nanograms/mL for females. In children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/milliliter (ng/mL) increased to 31 +/- 11.6 nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 26 weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increased to 93.3 +/- 54.2 nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 33 weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanograms/mL versus 11.5 nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult males in the acute phase (128.1 versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/mL versus 26.8 nanograms/mL) (Hellings et al, 2005).

d) In a small study of 20 women, risperidone produced prolactin levels twice as high as in women receiving typical neuroleptic agents (Caracci & Ananthamoorthy, 1999). Another author reviewed the results of 4 clinical trials and found significant increases in prolactin levels with risperidone versus haloperidol. In women, risperidone increased prolactin levels significantly higher at all doses than in women receiving haloperidol 10 milligrams/day (mg/day) (p less than 0.001). Women receiving haloperidol 20 mg/day had similar prolactin levels to women receiving risperidone. In men, risperidone 4 to 6 mg/day produced significantly higher prolactin levels than haloperidol 10 mg/day (p=0.01) but not 20 mg/day. With doses of risperidone 6 mg/day and greater, prolactin levels were significantly greater than all haloperidol doses (p less than 0.01). Elevated prolactin levels are associated with amenorrhea, galactorrhea, hypogonadism, and osteoporosis. Amenorrhea or galactorrhea has been reported in 10% of female patients receiving risperidone (Kleinberg et al, 1999).

4) Pediatric

a) In double-blind clinical trials lasting 8 weeks in children and adolescents (5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, bipolar mania, or schizophrenia, elevated prolactin levels were reported in 49% patients receiving risperidone compared to 2% of patients receiving placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In placebo-controlled clinical trials in adolescents (13 to 17 years) with schizophrenia and children and adolescents

(10 to 17 years) with bipolar disorder, elevated prolactin levels were reported in 82% to 87% of patients receiving risperidone versus 3% to 7% receiving placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females on risperidone with females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prolactin was measured once each during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with mental retardation and pervasive developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and maintenance doses of risperidone were 0.92 milligrams/day (mg/day) (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day), respectively. For adults (mean age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/day (1 to 1.5 mg/day), respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 nanograms/mL for females. In children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/milliliter (ng/mL) increased to 31 +/- 11.6 nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 26 weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increased to 93.3 +/- 54.2 nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 33 weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanograms/mL versus 11.5 nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult males in the acute phase (128.1 versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/mL versus 26.8 nanograms/mL) (Hellings et al, 2005).

5) Management

a) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotics that have the potential for inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding changes in libido or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejaculatory dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be considered (Bostwick et al, 2009).

3.3.3.G Hypothermia

1) Hypothermia has been associated with the use of antipsychotic agents, including oral risperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) A 37-year-old woman with psychosis in association with Prader-Willi syndrome suffered hypothermia with cellulitis and confusion while on risperidone therapy. Her rectal temperature was 30 degrees Celsius. She had experienced 2 previous episodes of hypothermia beginning 1 month after starting risperidone treatment. Withdrawal of risperidone resulted in normalization of temperature. She later had the same problem with olanzapine therapy. Hypothyroidism was excluded. The authors hypothesized that hypothermia may result from antipsychotic blockade of the serotonin 5-HT(2) receptor (Phan et al, 1998).

3.3.3.H Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.I Weight gain

1) Summary

a) In adult clinical trials, up to 18% of patients receiving oral risperidone reported weight gains of at least 7% of body weight compared to 9% reported for placebo. (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Weight gain was reported in up to 14% of adolescent and pediatric patients (5 to 16 years) receiving oral risperidone in clinical trials (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

c) During clinical trial of schizophrenic patients, weight gain was reported in 5% and 4% of patients receiving risperidone 25 mg long-acting injection and risperidone 50 mg long-acting injection, respectively. In 2 clinical trials of adult bipolar I disorder patients, weight gain was reported in 5% to 7% of patients receiving long-acting risperidone injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

d) An adverse event analysis from a large study comparing five fixed doses of oral risperidone (1, 4, 8, 12 and 16 milligrams/day) demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

2) Incidence: oral, adults, up to 18%; children, up to 14%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 4% to 5%; bipolar I disorder, 5% to 7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3) Adult

a) Statistically significant weight gains of at least 7% of body weight were reported in 18% of patients receiving oral risperidone versus 9% reported for placebo in a pooled analysis of 6- to 8-week placebo-controlled trials of adults with schizophrenia (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, weight gain was reported in 5% of patients receiving risperidone 25 mg long-acting injection (n=99) and 4% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 2% of patients receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, weight gain was reported in 5% of patients receiving long-acting risperidone injection (n=154) as monotherapy compared with 1% in placebo (n=149). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, weight gain was reported in 7% of patients receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67)(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

c) An adverse event analysis from a large study comparing five fixed doses of oral risperidone (1, 4, 8, 12 and 16 milligrams/day) demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

d) Mean weight gain in patients treated with atypical neuroleptics included zotepine 4.3 kilograms (kg), clozapine 3.1 kg, sulpiride 1.9 kg, and risperidone 1.5 kg, according to a retrospective chart review. The weight gain was significantly more for those using atypical neuroleptics compared with patients receiving classic neuroleptics, such as haloperidol, flupenthixol, or pimozide (p=0.01). The highest risk of weight gain was seen in patients who were young and had not been previously treated with neuroleptics (Wetterling & Mussigbrodt, 1999).

e) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardation and autism showed significant weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a mean of 8.2 kg; adolescents (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

4) Pediatric

a) In two pooled 8-week, double-blind, placebo-controlled trials of adolescent and pediatric patients (5 to 16 years) with irritability associated with autistic disorder, increases in weight were reported in 5% of patients receiving oral risperidone (n=76) compared to 0% for placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Treatment-emergent weight gain (mean increases of 9 kg) was reported in 14% of adolescents (n=103) in a long-term, open-label extension study of oral risperidone. Most increases were observed within the first months of the study (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

c) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardation and autism showed significant weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a mean of 8.2 kg; adolescents (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

d) Risperidone-treated adolescents had significantly higher weight gains and increases in body mass index (BMI) than adolescents treated with conventional neuroleptic agents (p=0.0141 and p=0.0011, respectively). Adolescent inpatients living at a residential treatment center being treated with risperidone (n=18), conventional antipsychotics (n=23), or no antipsychotic medication (n=19) had their weight and BMI followed for 6 months. In the risperidone group mean changes were a gain of 8.64 kilograms (kg) and 3.67 kg/square meter (m(2)), for conventional antipsychotics changes were a gain of 3.03 kg and 0.31 kg/m(2), and for the no antipsychotic group changes were a loss of 1.04 kg and 1.01 kg/m(2). The average daily dose of risperidone was 2.83 milligrams (mg) and gains did not correlate with dose (Kelly et al, 1998).

3.3.3.J Weight loss

1) Incidence: adults, 1% to 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, placebo-controlled trial of intramuscular risperidone, weight decreases were reported in 4% of adults receiving risperidone 25 mg (n=99), and 1% receiving risperidone 50 mg (n=103), compared to 1% receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.4 Gastrointestinal Effects

3.3.4.A Abdominal pain

1) Incidence: oral, adults, 2% to 4%; children, 15% to 18% (Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Abdominal pain was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, abdominal pain was reported in 2% to 4% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, abdominal pain occurred in 18% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 15% in patients treated with 3 to 6 mg daily (n=61), compared with 5% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.B Constipation

1) Incidence: oral, adults, 5% to 9%; children, 21% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 5% to 7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, constipation was reported in 5% and 7% of patients receiving 25 mg (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with 1% in placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, constipation was reported in 8% to 9% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of constipation was 21% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 8% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.C Decrease in appetite

1) Incidence: adult, bipolar disorder, 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, decreased appetite was reported in 6% of patients receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.4.D Diarrhea

1) Incidence: oral, adults, up to 6%; children, 7% to 8% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Diarrhea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Diarrhea was reported up to 6% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, diarrhea occurred in 8% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared with 2% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.E Excessive salivation

1) Incidence: oral, adults, 1% to 4%; children, up to 22% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 1% to 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, salivary hypersecretion was reported in 4% of patients receiving risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During risperidone clinical trials, increased salivation was reported in 1% to 4% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, increased salivation occurred in 0% of patients treated with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 4% in placebo (n=54) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of increased salivation was 22% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 6% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.F Increased appetite

1) Incidence: oral, children, 4 to 49% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar I disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, increased appetite was reported in 4% of patients receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, increased appetite occurred in 4% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared with 2% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of increased appetite was 49% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 19% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.G Indigestion

1) Incidence: oral, adults, 4% to 10%; children, 5% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, dyspepsia was reported in 6% and 6% of patients receiving 25 mg (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with 0% in placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During risperidone clinical trials, dyspepsia was reported in 4% to 10% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, dyspepsia occurred in 16% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 5% in patients treated with 3 to 6 mg daily (n=61), compared with 3% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.H Nausea

1) Incidence: oral, adults, 4% to 9%; children, 8% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 3% to 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, nausea was reported in 3% and 4% of patients receiving 25 mg (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with 5% in placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, nausea was reported in 4% to 9% of adult patients receiving oral therapy. Nausea was responsible for 1.4% of discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/day (n=366) compared with 0% in patients receiving risperidone 8 to 16 mg/day (n=198), or in placebo (n=225) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, nausea occurred in 16% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 13% in patients treated with 3 to 6 mg daily (n=61), compared with 7% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.I Pancreatitis

1) During postmarketing risperidone use, pancreatitis has been reported (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Neuroleptic malignant syndrome and probable acute pancreatitis was described in a 45-year-old female with disorganized schizophrenia treated with risperidone for 2 years. A month prior to transferring to a clinic within the hospital, the patient presented with muscular stiffness, increase in nonspeaking , oppositivity, food phobia, decreased voluntary bowel or urinary function, and a rise in body temperature. Laboratory findings showed hyperamylasemia, hyperlipasemia, myoglobinuria, and an increase in CPK plasma levels, suggesting rhabdomyolysis and probable acute pancreatitis. However, an abdominal computed tomography scan revealed nothing significant. In the following days, the patient's myoglobinuria and CPK slowly normalized , but both amylasemia 636 units/L (normal range, 5 units/L to 53 units/L) and lipasemia 1293 units/L (normal range 114 units/L to 286 units/L) levels increased to maximum despite any clinical or radiological evidence. Neurological exam revealed extrapyramidal stiffness, and the patient was laconic, negative, uncooperative and seemed confused toward time and space. Risperidone was discontinued and lorazepam therapy was initiated, which produced a slow resolution to her muscular stiffness. Amylasemia and lipasemia levels gradually decreased and returned to normal within 20 days. Clozapine 12.5 mg/day (titrated over more than 30 days to 300 mg/day) was introduced resulting in significant improvement in the patients psychopathological outcome. At her 18-month follow-up the patient maintained good clinical balance with no issues (Ghio et al, 2009).

3) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 16% of the cases were associated with the use of risperidone at a mean daily dose of 4 milligrams. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003c).

4) A 32-year-old, male, chronic, paranoid schizophrenic, patient developed cholestatic hepatitis and pancreatitis 1 week after beginning risperidone 2 milligrams (mg) daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, jaundice, dark urine and clay-colored stools. He had no history of abdominal trauma, alcohol, or drug abuse and tests for autoimmune diseases, cytomegalovirus , hepatitis A, B, and C were all negative. Initial laboratory results were: amylase,

1,617 international units/L; AST, 179 international units/L; ALT, 366 international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; CB, 1.9 mg/dL. One week after discontinuing risperidone, the patient improved clinically and his laboratory results were: amylase, 113 international units/L; AST, 26 international units/L; ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units/L; TB, 0.7 international units/L; CB, 0.5 international units/L (Cordeiro & lkis, 2001).
5) A 32-year-old male was diagnosed with pancreatitis after he complained of diffuse abdominal pain, nausea, and constipation, 3 weeks after starting risperidone therapy. His initial amylase level was 1087 international units (international units)/liter(L). He had a mild leukocytosis, slight glycemic elevation, but no other changes in liver function tests. His risperidone was tapered off over 2 weeks. His amylase declined to 147 international units/L (Berent et al, 1997).

3.3.4.J Summary

1) Hypersalivation, pancreatitis, constipation, diarrhea, nausea, dyspepsia, vomiting, abdominal pain, toothache, anorexia, stomatitis, dysphagia, melena, flatulence, fecal incontinence, rectal hemorrhage, gingivitis, and gastroesophageal reflux have been reported with risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.4.K Toothache

1) Incidence: intramuscular, 1% to 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) In a 12-week placebo-controlled trial of adult schizophrenic patients, toothache was reported in 1% and 3% of patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 0% in placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.4.L Vomiting

1) Incidence: oral, children, 10% to 12% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) Vomiting was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Pediatric
a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, vomiting occurred in 12% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 10% in patients treated with 3 to 6 mg daily (n=61), compared with 7% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.4.M Xerostomia

1) Incidence: oral, adults, up to 4%; children, up to 13% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% to 7%(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, dry mouth was reported in 0% of patients receiving risperidone 25 mg long-acting injection (n=99) and 7% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During risperidone clinical trials, dry mouth was reported up to 4% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of dry mouth was 13% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 6% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.5 Hematologic Effects

3.3.5.A Agranulocytosis

1) Agranulocytosis has been reported during clinical and postmarketing use of risperidone. The potential risk factors include a history of low WBC and drug-induced leukopenia or neutropenia. These patients should have frequent monitoring of CBC during the first few months of treatment. Consider discontinuing therapy at the first sign of clinically significant decline in WBC if there is no other causative factors (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).
2) Agranulocytosis, including fatal cases, has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) A case report described agranulocytosis in a 40-year-old woman after 2 weeks of risperidone treatment. She had previously experienced agranulocytosis with other antipsychotic therapies: chlorpromazine with carbamazepine (WBC count, 2500/mm(3); neutrophil rate, 30%), haloperidol (WBC count, 2200/mm(3); neutrophil rate, 52%), and zuclopenthixol (WBC count, 2700/mm(3); neutrophil rate, 29%). With risperidone 4 mg/day, her WBC count was 2400/mm(3) and her neutrophil count was 32% (Finkel et al, 1998).

3.3.5.B Anemia

1) Incidence: oral, adults, up to 1% (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Anemia was reported in less than 1% of adult patients treated with oral risperidone 2 to 8 mg per day (n=366), 1% of those treated with risperidone greater than 8 to 16 mg/day (n=198), and 0% of those treated with placebo in three double-blind, placebo-controlled trials 4 to 8 weeks duration including adult patients being treated for schizophrenia (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).
3) Anemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.C Leukopenia

1) Leukopenia has been reported during clinical and postmarketing use of risperidone. The potential risk factors include a history of low WBC, and drug induced leukopenia and neutropenia. These patients should have frequent monitoring of CBC during the first few months of treatment. Consider discontinuing therapy at the first sign of clinically significant decline in WBC if there is no other causative factors (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) A case report described leukopenia in a 32-year-old man following treatment with risperidone and aripiprazole. The patient, who had a long history of paranoid schizophrenia, had been initiated on risperidone 2 mg/day a few years earlier. Although he reported no side effects and the results of his annual physical exam were normal, laboratory assessment showed a WBC and absolute neutrophil count (ANC) of 2.8 x 10(9) and 1.27 x 10(9), respectively. Risperidone-induced leukopenia was suspected and the patient agreed to reduce the risperidone dose to 1 mg/day. A few weeks later, a lab workup showed WBC count and ANC at 2.7 x 10(9) and 1.22 x 10(9), respectively. Subsequently, risperidone was discontinued and the patient was initiated on aripiprazole 10 mg daily. He was evaluated every 4 weeks and reported no adverse effects. Six months later, his WBC count and ANC were 2.4 x 10(9) and 0.85 x 10(9), respectively, and aripiprazole was discontinued. Two weeks later, he experienced paranoid delusions, irritable mood, and auditory hallucinations for which he was hospitalized. Upon admission, his WBC count and ANC were 6.4 x 10(9) and 1.29 x 10(9), respectively. He was discharged after being reinitiated on aripiprazole 10 mg/day. At a follow-up appointment, his WBC count and ANC were again low (2.9 x 10(9) and 1.29 x 10(9), respectively). It was decided to discontinue aripiprazole and treat the patient with paliperidone 6 mg and lithium 300 mg. Subsequent to the medication change, his WBC count and ANC increased to 3.3 x 10(9) and 1.42 x 10(9). A full hematologic workup was pending at the time of this publication (Qureshi & Rubin, 2008).
3) A 63-year-old man developed leukopenia and neutropenia 1 week after beginning risperidone 2 mg twice daily for schizophrenia. The reaction was confirmed upon rechallenge. He had experienced a similar reaction with clozapine (Dernovsek & Tavcar, 1997).
4) A case of leukopenia, possibly related to risperidone, was reported following 7 days of therapy (2 to 6 mg/day) for schizophrenia. The white count decreased from 5100/mm(3) to 3500/mm(3) over 7 days, and the neutrophil count decreased from 3430/mm(3) to 1820/mm(3). On day 9, the neutrophil count had further decreased to 980/mm(3). The patient

also had influenza during this same time period which may have confounded the circumstances (Meylan et al, 1995).

3.3.5.D Neutropenia

1) Neutropenia has been reported during clinical and postmarketing use of risperidone. The potential risk factors include a history of low WBC, and drug induced leukopenia and neutropenia. These patients should be evaluated for signs of infection, and frequent monitoring of CBC during the first few months of treatment is recommended. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm(3)) should discontinue risperidone and have their WBC followed at discontinuation of treatment until recovery (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.E Purpura

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
2) During premarketing risperidone studies of various design types, purpura was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).
3) During premarketing trials of approximately 1300 patients receiving oral risperidone, a 28-year-old female was reported to have developed thrombotic thrombocytopenic purpura, which included fever, jaundice and bruising. The patient recovered following plasmapheresis (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.F Thrombocytopenia

1) Thrombocytopenia has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) A case report described thrombocytopenia in a 48-year-old man following risperidone use. The patient, who had no history of hematological disorders, presented to the emergency room with sudden right hemiplegia, aphasia, and disorientation. He had a history of hypertension but was not receiving medication for it. According to a brain CT scan, there was hemorrhaging in the left temporoparietal region. Upon admission, his platelet count was 160,000/microliter and he was treated fairly conservatively. On day 3, he went into a coma due to brain edema and underwent emergency surgery. His postoperative regimen included carbamazepine 600 mg/day to prevent convulsions, nizatidine 300 mg/day to prevent gastric ulcer, and nifedipine 40 mg/day for hypertension. At 2 days post-operation, he experienced marked agitation, emotional lability, and sensory aphasia and would not remain on bedrest. A diagnosis of postoperative delirium was made for which the patient was initiated on risperidone 1 mg twice daily resulting in an improvement in symptoms. Two weeks later, his platelet count was 38,000/microliter. Because thrombocytopenia was suspected and his delirium had improved, risperidone was discontinued. Four days after risperidone discontinuation, platelet count increased to 112,000/microliter. He continued to receive carbamazepine and nifedipine until discharge, but nizatidine was discontinued 3 days after risperidone was discontinued. Upon discharge on post-surgery day 32, his platelet count was 158,000/microliter with WBC and RBC counts within normal limits. Two months later, his platelet count was 176,000/microliter (Semba & Okui, 2009).

3.3.5.G Thrombotic thrombocytopenic purpura

1) In a large open-marketing trial of approximately 1300 patients receiving oral risperidone therapy, a 28-year-old female developed thrombotic thrombocytopenic purpura (TTP), which included fever, jaundice and bruising. The patient recovered following plasmapheresis. The relationship of the TTP to risperidone is not known (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.6 Hepatic Effects

3.3.6.A gamma-Glutamyltransferase deficiency

1) Reductions in plasma gamma-glutamyl transferase have been reported with risperidone therapy (Anon, 1991a; Mesotten et al, 1989).

3.3.6.B Increased liver function test

1) Incidence: oral, adults, up to 1%; children, up to 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Increased hepatic enzymes were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, increased hepatic enzymes were reported in up to 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) A 32-year-old male patient with chronic paranoid schizophrenia developed cholestatic hepatitis and pancreatitis 1 week after beginning risperidone 2 milligrams (mg) daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, jaundice, dark urine, and clay-colored stools. He had no history of abdominal trauma, alcohol, or drug abuse, and tests for autoimmune diseases, cytomegalovirus , hepatitis A, B, and C were all negative. Initial laboratory results were: amylase, 1,617 international units/L; AST, 179 international units/L; ALT, 366 international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; and CB, 1.9 mg/dL. One week after discontinuing risperidone, the patient improved clinically and his laboratory results were: amylase, 113 international units/L; AST, 26 international units/L; ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units/L; TB, 0.7 international units/L; and CB, 0.5 international units/L (Cordeiro & lkis, 2001).
5) Two patients developed moderate increases of liver function tests within the first 1 or 2 weeks of risperidone therapy. The levels nearly normalized spontaneously with only a slight decrease of 1 milligram in one patient and an unchanged dose in the other. It has been suggested to check liver function tests in the early phase of risperidone treatment (Whitworth et al, 1999).
6) An 81-year-old man with paranoid delusions, Parkinson's disease, dementia, and depression developed hepatotoxicity after only 2 doses of risperidone 0.5 milligrams (mg). Other medications included aspirin, diltiazem, sublingual nitroglycerin, levothyroxine, and doxepin. Baseline liver functions tests had been normal before beginning risperidone. After 2 doses, he was noted to be jaundiced with aspartate aminotransferase (AST) 434 units/liter (L), alanine aminotransferase (ALT) 101 units/L, total bilirubin 3.6 milligrams/deciliter (mg/dL), and alkaline phosphatase 244 units/L. Ultrasound showed mild splenomegaly and small gallstones. Two weeks after discontinuation of risperidone, liver function tests were normal (Phillips et al, 1998).

3.3.6.C Pancreatitis

1) Neuroleptic malignant syndrome with probable acute pancreatitis was described in a 45-year-old female after receiving risperidone. A month prior to transferring to a clinic within the hospital, the patient presented with muscular stiffness, nonspeaking increased, oppositivity, food phobia, decreased voluntary bowel or urinary function, and a rise in body temperature. Laboratory findings at that time showed hyperamylasemia, hyperlipasemia, myoglobinuria, and an increase in CPK plasma levels. A diagnosis of rhabdomyolysis and probable acute pancreatitis was made. An abdominal computed tomography scan revealed nothing significant, but suggested an edematous form of pancreatitis. In the following days, the patient's myoglobinuria and CPK slowly returned to normal levels, however, both amylasemia (636 units/L, normal range, 5 units/L to 53 units/L) and lipasemia (1293 units/L, normal range 114 units/L to 286 units/L) levels increased to maximum despite any evidence. Neurological exam showed the patient to have extrapyramidal stiffness, however, her blood pressure, myoglobinuria, and CPK levels were all normal and within range. The patient was laconic, negative, uncooperative and seemed confused toward time and space. The decision to discontinue risperidone was made even though the patient had been taking it for the past 2 years. Lorazepam therapy was initiated, which produced a slow solution to her muscular stiffness. Amylasemia and lipasemia levels gradually decreased and returned to normal within 20 days. Clozapine 12.5 mg/day titrating up to a dose of 300 mg/day was introduced resulting in significant improvement in the patients psychopathological outcome. At her 18-month follow-up the patient has maintained good clinical balance with no issues (Ghio et al, 2009).

3.3.8 Musculoskeletal Effects

3.3.8.A Abnormal gait

1) Incidence: intramuscular, bipolar disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, gait abnormality was reported in 4% of patients receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.8.B Arthralgia

1) Incidence: oral, schizophrenia, 2% to 3% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar I disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, arthralgia was reported in 4% of patients receiving long-acting risperidone injection (n=72) compared with 3% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, arthralgia was reported in 2% to 3% of adult schizophrenic patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.8.C Decreased bone mineral density

1) In a small study, decreased bone mineral density was observed in female, premenopausal schizophrenia patients receiving risperidone (n=12; 3 to 6 milligrams (mg)/day for at least 24 months), but not in those receiving olanzapine (n=14; 15 to 20 mg/day for at least 24 months). Age-adjusted bone speed of sound was significantly lower in women treated with risperidone as compared with patients taking olanzapine when determined at the radius and phalanx (p less than 0.05), but not the tibia. This effect is most likely due to persistent risperidone-induced hyperprolactinemia (Becker et al, 2003).

3.3.8.D Myalgia

1) Incidence: oral, adults, 0% to 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Myalgia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, myalgia was reported in 0% to 2% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.8.E Pain, in Extremity

1) Incidence: intramuscular, schizophrenia, 2% to 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, pain in extremity was reported in 6% of patients receiving risperidone 25 mg long-acting injection (n=99) and 2% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.8.F Summary

1) Arthralgia, myalgia, arthrosis, synostosis, skeletal pain, abnormal gait, and decreases in bone mineral density have been reported with risperidone therapy (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9 Neurologic Effects

3.3.9.A Akathisia

1) Incidence: oral, adults, 5% to 9%; children, up to 10% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenic adults, 4% to 11% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, akathisia, including restlessness, was reported in 4% and 11% of patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 6% in placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During premarketing risperidone studies of various design types, akathisia, which includes akathisia and hyperkinesia, was reported in 5% to 9% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) A 69-year-old woman suffered protracted akathisia after risperidone withdrawal. The akathisia and parkinsonism had originally started with haloperidol therapy, but due to lack of efficacy she was switched to risperidone 1.5 milligrams (mg) twice daily. The akathisia persisted for 4 months and risperidone was discontinued. Her restlessness became worse during the first week and did not respond to lorazepam. Five weeks later, propranolol therapy resulted in a gradual resolution of the akathisia (Rosebush et al, 1997).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, akathisia occurred in 7% of patients treated with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 6% in placebo (n=54) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, akathisia occurred in 0% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared with 2% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.B Cerebrovascular accident

1) Incidence: adults, less than 1%, children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) In premarketing oral risperidone clinical trials, cerebrovascular disorder was reported in less than 1% of adults and in less than 5% of pediatric patients receiving risperidone therapy. During postmarketing period, cerebrovascular accidents have also been reported with the use of long-acting risperidone injection (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) Cerebrovascular adverse events (stroke, transient ischemic attack) occurred at a significantly higher rate in elderly individuals (mean age 85 years of age) who received risperidone compared to those given placebo. Individuals in these 4 placebo-controlled trials ranged from 73 to 97 years of age and were being treated for dementia-related psychosis (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.C Chorea

1) In a case report, chorea and tardive dyskinesia were reported in a 13 1/2 year-old female receiving risperidone. Nine months after the initiation of risperidone and dose decrease, chorea-like movements were evident. Risperidone was discontinued. At month 12, movements were decreased and at month 16, the movement disorder was resolved (Carroll et al, 1999).

3.3.9.D Confusion

1) Incidence: children, 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of confusion was 5% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 0% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.E Disturbance of attention

1) Incidence: adults, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, disturbance in attention was reported

in 4% of patients receiving long-acting risperidone intramuscular (n=72) compared with 0% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.F Dizziness

1) Incidence: oral, adults, 4% to 11%; children, 7% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 7% to 11%; bipolar I disorder, 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week clinical trial in schizophrenic patients, dizziness was observed in 7% of patients receiving risperidone 25 mg long-acting injection (n=99) and 11% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 6% of patients receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, dizziness was reported in 3% of patients receiving risperidone intramuscular (n=154) as monotherapy compared with 1% in placebo (n=149) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Dizziness was responsible for 1.4% and 1% of discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respectively, compared with 0% in placebo (n=225).

b) During premarketing risperidone studies of various design types, dizziness was reported in 4% to 10% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, dizziness occurred in 7% of patients treated with risperidone 1 to 3 mg daily (n=55), 14% treated with 4 to 6 mg daily (n=51), compared with 2% in placebo (n=54). Dizziness was responsible for 2% of discontinuation of therapy in schizophrenic trials including pediatric patients treated with risperidone (n=106) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, dizziness occurred in 16% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 13% in patients treated with 3 to 6 mg daily (n=61), compared with 5% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of dizziness was 9% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 3% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.G Dystonia

1) Incidence: oral, adults, less than 5% to 11%; children, 8% to 18% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Dystonia, which includes spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty breathing, and/or protrusion of the tongue, was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Dystonia was reported in 5% to 11% of adult patients receiving oral therapy, and in 8% to 18% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.H EEG abnormality

1) In a case report, fifteen days after initiation of risperidone 2 milligrams (mg) per day, a 55-year-old man developed extrapyramidal symptoms, with EEG (electroencephalogram) revealing bifrontal slow-wave abnormalities (De Leon et al, 1997).

3.3.9.I Extrapyramidal disease

1) Summary

a) Extrapyramidal symptoms were reported in 7% to 31% of adult patients receiving oral risperidone therapy. In clinical trials of risperidone, extrapyramidal symptoms were found to be dose-related (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007). The overall incidence of extrapyramidal symptoms in patients treated with 25 mg long-acting risperidone injection was comparable to that of placebo but was higher in patients receiving 50 mg long-acting risperidone injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Incidence: adults, 7% to 31% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult

a) In a 12-week, double-blind, placebo-controlled trial comparing 3 doses of long-acting risperidone (25 mg, 50 mg and 75 mg) with placebo in patients with schizophrenia, the overall incidence of extrapyramidal symptoms in patients treated with 25 mg long-acting risperidone injection was comparable to that of placebo but was higher in patients receiving 50 mg long-acting risperidone injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) In two 8-week, fixed-dose trials of adult schizophrenia patients, extrapyramidal symptoms increased in frequency as the oral risperidone dose increased 7% to 31% in 1 mg to 16 mg treatment groups (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

c) A 43-year-old male treated with risperidone 6 milligrams per day presented with episodic blepharospasms (Meige's disease) that occurred spontaneously or were brought on by stress requiring him to discontinue driving. The more he tried to open his eyes the more tightly they closed (Ananth et al, 2000).

d) In a review of risperidone studies, factors associated with the development of extrapyramidal symptoms included a dose-dependent increase in severity with higher doses, especially above 8 milligrams (mg)/day (p less than 0.001). Also, a higher baseline score on the extrapyramidal symptom rating scale (ESRS) was associated with a reduction in the severity of EPS (p less than 0.001). It has also been noted that worse scores on the ESRS scale correspond with an increased time since diagnosis, especially in the elderly (Lemmens et al, 1999).

e) A 79-year-old woman treated with risperidone 1 milligram (mg) twice daily for behavior problems associated with dementia, developed severe extrapyramidal symptoms when donepezil 10 mg daily was added to her regimen. Risperidone was discontinued and donepezil decreased to 5 mg. There was a complete resolution of symptoms. The authors hypothesize that extrapyramidal symptoms occurred due to an excess in central acetylcholine while dopamine receptors were blocked (Magnuson et al, 1998).

f) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidone caused few or no extrapyramidal symptoms. Mean changes in Extrapyramidal Symptom Rating Scale (ESRS) scores from baseline to worst score were significantly lower in each risperidone group than the haloperidol group (P less than 0.001). At 6 milligrams (mg)/day, the mean (ESRS) change score was not significantly different from that of the placebo group (Simpson & Lindenmayer, 1997a).

g) A 26-year-old man developed extrapyramidal symptoms the day after starting risperidone 4 milligrams (mg). He described difficulty breathing which his physician characterized as possible laryngospasm. This resolved after the medication was discontinued. Three weeks later, the patient requested that the risperidone be restarted. Risperidone 2 mg was restarted and after 2 days the patient reported painful and very distressing tongue movements. The risperidone was decreased to 1 mg and these symptoms subsided after 2 days (Brown, 1997).

h) A 55-year-old man with a left acoustic neurinoma (a manifestation of his neurofibromatosis) developed a severe extrapyramidal reaction to risperidone. Over a period of 10 years, he had experienced a gradual deterioration with periods of violence and paranoid ideation. He was started on risperidone 2 milligrams daily. Fifteen days later, he experienced multiple symptoms including rigidity, cogwheeling, and slowness. Risperidone was discontinued and he returned to baseline (De Leon et al, 1997).

i) Acute dystonia with an oculogyric crisis occurred in a 33-year-old male with paranoid schizophrenia during reinitiation of risperidone treatment after a period of noncompliance. Following a 2-month period of noncompliance, he restarted risperidone and was taking 3 milligrams (mg) twice daily by the third day of treatment; the next day he experienced intermittent retrocollis and tonic upward deviation of both eyes for 2 hours. The only other medication at the time of this dystonic reaction was clonazepam 3 mg at bedtime. He was treated with benztropine 2 mg IM (intramuscular) and all signs resolved; a second dose was given when he complained of muscle tightening which resolved 30 minutes after treatment. He continued risperidone, clonazepam, and benztropine 1 mg twice daily for a week, after which he discontinued the benztropine. At a 1-month follow-up, there was no further indication of dystonia (Faulk et al, 1996). A similar reaction occurred in a 34-year-old schizophrenic male who was titrated in 3 days up to risperidone 3 milligrams (mg) twice daily after a noncompliant period in which he used crack cocaine. He experienced rigid extremities, mild torticollis, tongue protrusion, and laryngospasm and was cyanotic. He was treated with diphenhydramine 50 milligrams intravenously with complete resolution of all symptoms within 10 minutes. Risperidone dose was decreased to 1 mg twice daily

and titrated more slowly without further side effects (Brody, 1996).

j) Acute dystonia occurred in a 17-year-old male with new onset schizophrenia who had been administered risperidone 2 milligrams (mg) twice daily. After 3 doses, he experienced throat restriction, thickening of the tongue, increased salivation, shortness of breath for 10 to 15 minutes, mild cogwheel rigidity, and stiffness. Risperidone was reduced to 2 mg at bedtime and benztropine 2 mg twice daily added. Benztropine 2 mg IM was given. Risperidone 2 mg at bedtime and benztropine 2 mg twice daily were given for the next 2 days. By day 5, he showed increased mental and autonomic instability; risperidone was reduced to 2 mg at bedtime, benztropine was reduced to 1 mg, and two doses of lorazepam 1 mg were given. All medications were then discontinued and all symptoms resolved on day 7 (Takhar & Manchanda, 1996).

4) Pediatric

a) A 12-year-old boy, with attention-deficit hyperactivity disorder and psychotic symptoms, developed extrapyramidal reactions following treatment with risperidone and several other drugs. On the day before a laser treatment to remove a birth mark, the boy had begun taking risperidone 1 milligram (mg) twice daily in addition to sertraline 25 mg per day and methylphenidate 10 mg in the morning. His premedications for the procedure included morphine, ketorolac, and tropisetron. Eight hours after the procedure, he developed shortness of breath, stiffness, difficulty talking and moving, had slurred speech, and was unable to close his mouth. Twitching began in his hands, shoulders, neck, and head and progressed to jerking movements of his jaw and arms. He was treated with benztropine 0.02 mg/kilogram for these acute dystonic reactions and his symptoms gradually improved. His risperidone dose was decreased to 0.5 mg per day and ketorolac and tropisetron were eliminated from the premedication regimen (due to potential synergism for causing the extrapyramidal reactions). There was no recurrence of dystonic symptoms during the remaining five laser procedures (Teoh et al, 2002).

b) A 7-year-old boy developed hypertonicity of the extremities, confusion, lethargy, and limited tongue movement after a single dose of risperidone 1 milligram (mg) for attention deficit hyperactivity disorder. Two doses of diphenhydramine did not improve the dystonia; the child recovered the following day (Gesell & Stephen, 1997h).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.J Headache

1) Incidence: intramuscular, 15% to 21% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, headache was reported in 15% of patients receiving risperidone 25 mg long-acting injection (n=99) and 21% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 12% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.K Insomnia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Insomnia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Insomnia was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.L Paresthesia

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Paresthesia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) Six patients (aged 37 to 65 years old) developed burning paresthesias while on risperidone therapy. The locations affected included the feet, lower body, back, face, arms, throat, and chest. The burning resolved with continued therapy in two cases, and the risperidone was discontinued in the other 4 cases (Heimberg & Yearian, 1996).

3.3.9.M Parkinsonism

1) Incidence: oral, adults, 0.6% to 20%; children, 2% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 8% to 15%; bipolar I disorder, 15% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During risperidone clinical trials, parkinsonism, which includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia, was reported in 8% to 15% of adult patients receiving intramuscular therapy for schizophrenia. Parkinsonism, which includes muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia, was reported in 15% of patients receiving intramuscular therapy for bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Adult patients receiving oral therapy reported 0.6% to 20%, and in 2% to 16% of pediatric patients receiving oral therapy. Parkinsonism was responsible for 0.4% of discontinuation of therapy in bipolar mania adult trials in patients receiving oral therapy with 1 to 6 mg/day (n=448) compared with 0% in placebo (n=424) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007) .
3) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patients who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.N Reduced sensation of skin

1) Incidence: intramuscular, schizophrenia, 2% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, hypoesthesia was reported in 2% of patients receiving risperidone 25 mg long-acting injection (n=99) and 0% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.O Seizure

1) Incidence: 0.3% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During premarketing trials, seizures occurred in 0.3% of patients receiving oral risperidone (9/2607) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007) and in 0.3% of patients receiving intramuscular risperidone (5/1499) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Two cases reported with oral therapy were associated with hyponatremia. Risperidone should be used cautiously in patients with a history of seizures (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Diaz, 1996).
3) A 64-year-old woman experienced a seizure 2 days after beginning risperidone therapy. She received two 1 milligram (mg) doses and two 2 mg doses before having a 1-minute generalized tonic-clonic seizure with a 5-minute postictal confusion period. At the time of beginning risperidone therapy, she also received trimethoprim-sulfamethoxazole for a urinary tract infection and astemizole for scalp itch. Therapy with risperidone was restarted at 0.5 mg/day and increased to 0.5 mg twice daily with control of her psychotic symptoms and no further seizures (Lane et al, 1998).

3.3.9.P Somnolence

1) Incidence: oral, adults, 5% to 14%; children, 12% to 67% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 5% to 6%; bipolar I disorder, 7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) During risperidone clinical trials of various design types, somnolence was reported in 5% to 6% of adult patients receiving intramuscular therapy for schizophrenia and 7% in patients with bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009), and in 5% to 14% of adult patients receiving oral therapy. Somnolence was responsible for 0.8% and 0.5% of discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respectively, compared with 0% in placebo (n=225) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, somnolence occurred in 24% of patients treated with risperidone 1 to 3 mg daily (n=55), 12% treated with 4 to 6 mg daily (n=51), compared with 4% in placebo (n=54). Somnolence was responsible for 2% of discontinuation of therapy in schizophrenic trials including pediatric patients treated with risperidone (n=106) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, somnolence occurred in 42% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 56% in patients treated with 3 to 6 mg daily (n=61), compared with 19% in placebo (n=58). Somnolence was responsible for 5% of discontinuation of therapy in bipolar mania trials including pediatric patients treated with risperidone (n=111) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of somnolence was 67% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 23% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.Q Stuttering

1) A 32-year-old Korean patient with a prior history of stuttering demonstrated a recurrence of stuttering with risperidone 1 milligram (mg) on day 5 of hospitalization. The dosage was increased to 8 milligrams daily on day 25 and the stuttering was more pronounced. Due to his auditory hallucinations and idea of reference, the dosage was maintained. On day 48, the stuttering was lessened (Lee et al, 2001).

3.3.9.R Summary

1) Stutter, chorea, EEG (electroencephalogram) abnormalities, extrapyramidal symptoms, catatonia, tardive dyskinesia, paresthesias, seizures, somnolence, dizziness, insomnia, headache, amnesia, vertigo, stupor, confusion, impaired concentration, hypoesthesia, tongue paralysis, torticollis, coma, migraine, withdrawal syndrome, sleep-related eating disorder, and yawning have been reported with risperidone administration (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.S Tardive dyskinesia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, up to 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Tardive dyskinsia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During premarketing risperidone studies of various design types, tardive dyskinesia was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info

RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) In a 52-week, double-blind, placebo-controlled trial in patients with bipolar disorder, dyskinesia was reported in 6% of patients receiving long-acting risperidone injection (n=72) compared with 3% receiving placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

5) A potentially irreversible tardive dyskinesia may develop in patients receiving antipsychotic drugs; this may be related to the duration of treatment and the cumulative dose. Less commonly, the syndrome can develop after brief treatment periods at low doses. Antipsychotics may mask the underlying process by suppressing the signs and symptoms of the syndrome. The prevalence of the syndrome appears to be highest among the elderly, especially elderly women; however, it is impossible to rely upon prevalence to estimate which patients are likely to develop the syndrome. The syndrome may remit partially or completely upon discontinuation of the antipsychotic medication (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006; Carroll et al, 1999; Saran, 1998; Sakkas et al, 1998; Campbell, 1999; Gwinn & Caviness, 1997; Meco et al, 1997).

6) The use of long-acting risperidone in schizophrenic patients has been associated with a low incidence of emergent tardive dyskinesia, as well as improvement in existing dyskinesia. In an open label trial (n=725), patients with stable schizophrenia or schizoaffective disorder received long-acting risperidone in 25 mg, 50 mg, or 75 mg intramuscular doses every 2 weeks for up to 50 weeks. Dyskinesia was assessed via the Extrapyramidal Symptom Rating Scale (ESRS) at months 1, 2, 3, 6, 9, and 12; tardive dyskinesia was defined as either 2 or more "mild" scores or 1 or more "moderate" scores on the ESRS dyskinesia 7-item subscale over at least a 4-week period. Of the 662 patients for whom ESRS data were available, 530 (80.1%) had no dyskinesia and 132 (19.2%) has existing dyskinesia at study enrollment. Emergent tardive dyskinesia was observed in 0.94% (5/530) of patients without dyskinesia at baseline. This represents an annualized rate of 1.19% when adjusted for study drug exposure or when assessed by Kaplan-Meier survival analysis (95% confidence interval (CI), 0.15 to 2.24). The incidence of tardive dyskinesia was similar among all doses, with no observation of a dose-dependent effect. For patients with dyskinesia existing at baseline, mean ESRS scores were significantly improved from baseline to endpoint (6.9 vs 4.6, respectively; p less than 0.001) (Gharabawi et al, 2005).

7) Case Reports

a) Tardive dyskinesia (TD) has been reported in a 24-year-old male following risperidone treatment for Tourette's syndrome (TS). At age 15, the patient developed repetitive twisting movements of his head and neck. Nine years following the onset of symptoms, he was diagnosed with TS. He experienced motor and phonic tics, along with obsessional thoughts. Sertraline (50 mg/day) and haloperidol (0.5 mg/day) was initiated. No follow-up was available. The patient returned for treatment with identical symptoms, so risperidone (1 mg/day) and fluoxetine (40 mg/day) were initiated and maintained. His tics were mild, but the patient developed oromandibular dyskinetic movements of the lower jaw after 4 months of treatment. Treatment with risperidone was discontinued and vitamin E with clonazepam was initiated. The patient experienced a significant improvement in dyskinetic symptoms within about 45 days, yet the patient's TS significantly worsened causing severe distress (Thomas et al, 2009).

b) Tardive dyskinesia (TD) has been reported in a 44-year-old female following risperidone treatment for undifferentiated schizophrenia. The patient suffered for 4 years with delusions, hallucinations, alogia, and had minimal contact with reality. Following her first psychotic episode, she was hospitalized and risperidone 4 mg/day was initiated. Symptoms improved, but without complete resolution. Upon discharge, the patient maintained her risperidone dose without issue for approximately 4 years. Her risperidone dose was increased to 6 mg/day following a worsening of positive psychotic symptoms. Within 2 weeks, she experienced partial remission of delusions and significant reduction of aggression, hostility and auditory hallucinations. However, the patient reported abnormal movements of the jaw, lips, mouth, tongue, and lower extremities 4 months following the increased risperidone dose. With no family history of movement disorders and testing results were normal, the patient was diagnosed with neuroleptic-induced TD. Risperidone was switched to aripiprazole 15 mg/day, and was gradually discontinued. Her severity of TD started to subside within 2 weeks, and he remained on aripiprazole with no reoccurrence of TD or other involuntary movements or psychotic symptoms (Caykoylu et al, 2009).

c) In a substudy (n=21) of a randomized double-blind, placebo-controlled trial, a 51-year-old female developed tardive dyskinesia, manifested by involuntary tongue movements during maintenance. For the substudy, the mean risperidone dose was 2 mg per day for the first 10 weeks (acute) and 1.36 mg per day (maintenance). During the acute phase, prolactin level was 239.5 nanograms/mL and during maintenance after 41 weeks from initial risperidone dose, prolactin was 199.6 nanograms/mL. Prolactin remained elevated at 85.3 nanograms/mL after 5.1 years (Hellings et al, 2005).

d) In case reports, risperidone has caused tardive dyskinesias with doses as low as 1 milligrams (mg) daily (Saran, 1998) and with a course of therapy as short as 8 months (Sakkas et al, 1998). In patients with a history of tardive dyskinesias, risperidone has worsened their dyskinesia or made it reappear within 1 week of therapy (Sherr & Thaker, 1998). Several more cases of tardive dyskinesia due to risperidone have been reported in the literature (Campbell, 1999).

e) A 69-year-old man with a long history of bipolar disorder developed involuntary oral-buccal-lingual dyskinesias and parkinsonism while treated with risperidone. A few months after being treated with valproic acid, lorazepam, bupropion, trihexyphenidyl, and risperidone 3 milligrams (mg) twice daily, he developed involuntary mouth movements, tremor,

slowness, and difficulty with gait. At 10 months, the risperidone and trihexyphenidyl were discontinued. Three weeks later the movements and parkinsonism persisted. At seven weeks, there was no rigidity present but the dyskinesia persisted. The patient was then lost to follow-up. The authors believe that the tardive dyskinesia and parkinsonism was induced by risperidone and that the bupropion may have contributed. However, since the parkinsonism improved after discontinuation of risperidone, they believe that the risperidone was mostly responsible for these extrapyramidal effects (Gwinn & Caviness, 1997).

3.3.9.T Transient ischemic attack

1) Cerebrovascular adverse events (eg, stroke, transient ischemic attack) occurred at a significantly higher rate in elderly individuals (mean age 85 years of age) who received oral risperidone compared to those given placebo. Individuals in these 4 placebo-controlled trials ranged from 73 to 97 years of age and were being treated for dementia-related psychosis, which is not an approved use of risperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.U Tremor

1) Incidence: oral, adults, up to 5% to 6%; children, 10% to 12% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% to 3%; bipolar I disorder, 24% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, tremor was reported in 0% of patients receiving risperidone 25 mg long-acting injection (n=99) and 3% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, tremor was reported in 24% of patients receiving long-acting risperidone intramuscular (n=72) compared with 16% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Adult patients receiving oral therapy reported tremor 5% to 6% in adult patients (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, tremor occurred in 11% of patients treated with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 6% in placebo (n=54) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of tremor was 12% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 1% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.10 Ophthalmic Effects

3.3.10.A Abnormal vision

1) Incidence: oral, adults, 1% to 3%; children, 4% to 7% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 2% to 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, blurred vision was reported in 2% of patients receiving risperidone 25 mg long-acting injection (n=99) and 3% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, abnormal vision was reported in 1% to 3% of adult patients receiving oral therapy, and in 4% to 7% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.12 Psychiatric Effects

3.3.12.A Agitation

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Agitation was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, agitation was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy. Agitation was responsible for 1.1% and 1% of discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respectively, compared with 0% in placebo (n=225) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) Agitation and aggressive reaction occurred in 1% or more (and were at least as frequent among) risperidone-treated patients (dosage: 10 mg/day or less) than among placebo-treated patients (Diaz, 1996).

3.3.12.B Anxiety

1) Incidence: oral, adults, 2% to 16%; children, up to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) Anxiety was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) During risperidone clinical trials, anxiety was reported in 2% to 16% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, anxiety occurred in 7% of patients treated with risperidone 1 to 3 mg daily (n=55), 6% treated with 4 to 6 mg daily (n=51), compared with 0% in placebo (n=54). Anxiety was responsible for 1% of discontinuation of therapy in schizophrenic trials including pediatric patients treated with risperidone (n=106) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, anxiety occurred in 0% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 8% in patients treated with 3 to 6 mg daily (n=61), compared with 3% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of anxiety was 16% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 15% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.12.C Catatonia

1) A 61-year-old schizophrenic woman developed catatonia after beginning risperidone 2 milligrams (mg) daily. The woman had a history of frontal lobotomy 36 years previously. She had been receiving fluphenazine decanoate 25 mg intramuscularly every 2 weeks. Two weeks after her last dose, she began risperidone which was increased to 5 mg. Catatonic symptoms worsened and she was taken off risperidone and placed on clozapine. Her catatonia subsided within 5 days (Bahro et al, 1999).

3.3.12.D Delirium

1) Three cases of possible risperidone-induced delirium were reported in patients aged 71, 83, and 83 years. All were hospitalized patients being treated for major depression with psychotic features. In each case, the mania abated after

risperidone was discontinued. The authors acknowledge that the delirium may have been multifactorial in etiology, however, risperidone use appeared to be a risk factor (Ravona-Springer et al, 1998).
2) An 85-year-old woman with schizophreniform disorder was treated with risperidone 1 milligrams (mg) daily and then increased to 1 mg twice daily after 4 days with resultant delirium. The woman was restless, disoriented, and hallucinating. Risperidone was discontinued and she recovered after 18 hours (Tavcar & Dernovsek, 1998).

3.3.12.E Fatigue

1) Incidence: oral, adults, 1% to 3%; children, 18% to 42% .(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 3% to 9% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adults
a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, fatigue, which includes asthenia, was reported in 3% of patients receiving risperidone 25 mg long-acting injection (n=99) and 9% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) During risperidone clinical trials, fatigue was reported in 1% to 3% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatrics
a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, fatigue occurred in 18% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 30% in patients treated with 3 to 6 mg daily (n=61), compared with 3% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of fatigue was 42% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 13% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.12.F Mania

1) Mania has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) A review of the literature identified 16 cases of mania related to risperidone therapy. Patients were treated with 2.5 to 9 milligrams daily for schizoaffective, bipolar type, mixed (n=2); schizoaffective, bipolar type, depressed (n=4); schizophrenia (n=5); schizoaffective, depressed (n=2); recurrent depression, psychotic (n=1); and bipolar type I, manic (n=2). The onset of development of manic symptoms ranged from 2 to 40 days. Five of 16 patients were receiving no other medications and in 6 cases it wasn't determined if there were concomitant medications. Two patients received valproate, 1 lithium, and 1 haloperidol concomitantly, which makes causality difficult to assess. In 2 cases, risperidone was continued and manic symptoms resolved without treatment. On 7 occasions, risperidone was discontinued and in the remaining 6 instances, risperidone was either continued with antimanic medications or reduced in dosage, or both. Remission of symptoms generally occurred within 2 to 14 days, although there was one case where it took 60 days for manic symptoms to resolve (Aubrey et al, 2000).
3) Four cases of mania developing after beginning risperidone therapy were presented. Two patients were treated for schizophrenia with risperidone 5 and 6 milligrams (mg) while 1 patient was treated for schizoaffective disorder with risperidone 2 mg. Sexual disinhibition was one of the most predominant symptoms. In 1 patient, only risperidone discontinuation was needed to resolve the mania. In another schizophrenic patient, carbamazepine, benzodiazepines, and neuroleptics were required for control. In the schizoaffective patient, valproic acid was needed (Zolezzi & Badr, 1999).
4) Mania occurred in a 50-year-old male with chronic schizophrenia and mild mental retardation. He had been tapered off of haloperidol and risperidone was started and titrated to 9 milligrams/day (mg/day) within 12 days. Forty days later he exhibited manic behavior. Risperidone was reduced to 6 mg/day and clonazepam 2 mg was initiated. A week later the patient was hospitalized and, over a 32-day period, he was treated with lithium, valproic acid, and haloperidol until the mania resolved (Diaz, 1996).
5) Three cases of mania developing within days of starting risperidone therapy were reported. The patient's diagnoses included one with schizoaffective disorder, one with schizophrenia, and one with bipolar I disorder. Risperidone was discontinued in the first patient and decreased in the last 2 patients with resolution of symptoms (Schnierow & Graeber, 1996).

3.3.12.G Nocturnal sleep-related eating disorder

1) Risperidone-induced sleep-related eating disorder was observed in a 68-year-old man following the administration of risperidone for the treatment of vascular dementia. The patient's psychotic symptoms resolved after his daily dose of risperidone was increased from 1 milligram (mg) to 2 mg; however, he began experiencing sleep disturbances almost nightly, including episodes during which he would consume large quantities of food while asleep. These episodes persisted for 2 months and then quickly resolved when the dosage was reduced to 1 mg/day (Lu & Shen, 2004).

3.3.12.H Obsessive-compulsive disorder

1) A schizophrenic man developed obsessive imagery after being treated with risperidone 4 milligrams/day (mg/day) for 18 months. He was also receiving valproate, trihexyphenidyl, and zuclopenthixol. He repeatedly saw the image of a person's face as he went about his activities. This disappeared after the dosage of risperidone was decreased to 3 mg/day (Mahendran, 1999).
2) A 26-year-old woman with schizophrenia developed obsessive-compulsive symptoms after 2 weeks of risperidone therapy. She was receiving risperidone 4 milligrams (mg) daily when she experienced excessive thoughts about playing mahjong. Risperidone was reduced to 2 mg without success. Clomipramine 25 mg was added and the ruminations disappeared. The clomipramine was eventually withdrawn after 4 weeks and she was maintained on risperidone 1 mg daily (Mahendran, 1998).

3.3.12.I Summary

1) Nervousness, depression, psychosis, apathy, delusion, euphoria, emotional lability, and delirium have been reported in patients receiving risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.13 Renal Effects

3.3.13.A Hemorrhagic cystitis

1) An 11-year-old boy with significant behavioral problems developed hemorrhagic cystitis 1 week after beginning risperidone therapy. Other medications included fluoxetine, valproic acid, benztropine, haloperidol, clonidine, trazodone, and nasal desmopressin. He presented with acute onset of dysuria and increased frequency with gross hematuria. There were no signs of viral illness and urine cultures were negative. Ultrasonography showed a thickened bladder wall and mild hydronephrosis. Symptoms were not relieved with oxybutynin and trimethoprim-sulfamethoxazole. Risperidone was withdrawn and symptoms resolved within a week. At a 1-month follow-up, the patient was asymptomatic and ultrasonography showed a normal thin-walled bladder (Hudson & Cain, 1998).

3.3.13.B Urinary incontinence

1) Incidence: oral, adults, 2%; children, up to 22% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) Urinary incontinence was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) During risperidone clinical trials, urinary incontinence was reported in 2% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
c) There was a temporal correlation with risperidone therapy and urinary incontinence in 2 case reports. Both patients developed urinary incontinence with risperidone 4 milligrams daily. Upon discontinuation of risperidone, urinary incontinence resolved (Agarwal, 2000).
3) Pediatric
a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, urinary incontinence oc-

curred in 0% of patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 5% in patients treated with 3 to 6 mg daily (n=61), compared with 0% in placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of urinary incontinence was 22% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 20% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.14 Reproductive Effects

3.3.14.A Abnormal ejaculation

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Ejaculation disorder was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, ejaculation disorder was reported in less than 1% of adult patients receiving oral therapy and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less than 0.05) for ejaculatory dysfunction among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
5) Two cases of probable retrograde ejaculation were attributed to risperidone treatment. A 36-year-old African American man and a 30-year-old Caucasian man, being treated with risperidone 6 milligrams (mg) and 3 mg per day, respectively, were poorly compliant with treatment. It was later determined that their poor compliance was due to concern over an absence of semen with ejaculation (Compton, 2002).
6) The absence of ejaculation was reported in 2 male patients treated with risperidone. In one patient, ejaculation dysfunction disappeared spontaneously after 4 weeks of risperidone treatment. In the other patient, absence of ejaculation was still present 8 weeks after the initiation of risperidone (Raga, 1999).
7) A 38-year-old man experienced ejaculatory dysfunction and dysuria one week after starting risperidone. He had no past history of genitourinary problems. On day 12 of treatment, risperidone was discontinued with symptoms resolving 2 days later. The patient underwent rechallenge with risperidone and symptoms recurred in 2 days. (Madhusoodanan & Brenner, 1996).

3.3.14.B Absence of ejaculation

1) Incidence: adults, 0.1% to 1% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) During risperidone clinical trials, ejaculation failure was reported in up to 1% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.14.C Amenorrhea

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, amenorrhea was reported in 4% of patients receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During risperidone clinical trials, amenorrhea was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Five psychiatric patients developed amenorrhea with elevated serum prolactin levels on risperidone 1 to 8 milligrams/day. In 4 cases, menstruation resumed upon discontinuation; menstruation resumed in case 5 after tapering

risperidone (Kim et al, 1999).

3.3.14.D Erectile dysfunction

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Erectile dysfunction was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less than 0.05) for erectile dysfunction among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.14.E Priapism

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) During risperidone clinical trials, priapism was reported in less than 1% of adult patients receiving oral therapy and in less than 5% of pediatric patients receiving oral therapy. Also, there have been reports of priapism with the use of risperidoneintramuscular injection during postmarketing period (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) A 31-year-old male developed priapism following therapy with risperidone for the treatment of chronic, paranoid-type schizophrenia (10 years). His medical history included obesity, hypercholesterolemia, keloid on neck, and tonsillectomy (age 6 years). His only medication consisted of risperidone 2 mg in the morning and 3 mg at bedtime. The patient presented to the emergency room following 10 days of persistent and painful penile erection. He was not sexually active and had no history of penile, genital, or pelvic trauma. Since laboratory tests returned within normal limits, a diagnosis of priapism was made, and an irrigation of normal saline and an injection of phenylephrine was initiated. However, on day 2, his symptoms worsened and he was admitted to the operating room to have a shunt placed between the corpora cavernosa and corpora spongiosa. The priapism completely resolved within hours of shunt placement. Even though risperidone was an effective treatment for this patient, it was discontinued and replaced with aripiprazole with no further incidence at his 2-month follow-up (Sharma & Fleisher, 2009).
4) An African American male developed priapism on two occasions after receiving risperidone and again after receiving ziprasidone for the treatment of schizophrenia. Following risperidone treatment (4 milligrams (mg) twice daily), the man developed an erection lasting 13 hours, which resolved upon irrigation of the corpora with phenylephrine 200 micrograms. Following discontinuation of risperidone, the patient developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 mg twice daily. This erection lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the ziprasidone was discontinued and the priapism quickly resolved (Reeves & Mack, 2002).
5) A 47-year-old African American man developed priapism after taking risperidone 2 milligrams twice daily for 2 years. He had experienced prolonged painful erections multiple times in the past few weeks. Physical and laboratory examinations revealed no abnormalities apart from the erect penis. Penile irrigation with normal saline and phenylephrine injection caused detumescence. Risperidone was discontinued. No other antipsychotic treatment was started. One month later, he reported spontaneous, partial rigid erection (Ankem et al, 2002).
6) A 26-year-old Hispanic man had a 5-day episode of persistent erection, dysuria, and urinary incontinence. His medications, which he had been receiving for one year, included risperidone, 3 milligrams (mg)/day and divalproex sodium 1500 mg/day for the treatment of intermittent mood and psychotic symptoms. His erection persisted despite two corpora cavernosa irrigations with phenylephrine. Corpora cavernosa venous blood gas analysis was consistent with a diagnosis of low-flow priapism. A cavernosal glandular shunt and a corpora cavernosum/corpus spongiosum shunt were performed. As there have not been any previously reported instances of priapism associated with divalproex use, the authors assumed that risperidone was the likely cause of the condition (Bourgeois and Mundh, 2003).

3.3.14.F Summary

1) Amenorrhea, dysmenorrhea, erectile dysfunction, priapism, and ejaculation failure have been reported in patients receiving risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.15 Respiratory Effects

3.3.15.A Cough

1) Incidence: oral, adults, 3%; children, 24% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 2% to 4%; bipolar I disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, cough was reported in 4% of patients receiving risperidone 25 mg long-acting injection (n=99) and 2% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 3% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, cough was reported in 4% of patients receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, coughing was reported in 3% of adult patients receiving oral therapy, and in 24% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.15.B Dyspnea

1) Incidence: oral, adults, 2%; children, 2% to 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Dyspnea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, dyspnea was reported in 2% of adult patients receiving oral therapy, and in 2% to 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.15.C Pharyngitis

1) Incidence: oral, adults, 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Pharyngitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During clinical trials, pharyngitis was reported in 5% of adult patients receiving risperidone oral therapy compared to 2% receiving placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.15.D Pulmonary embolism

1) A case report described 3 episodes of pulmonary embolism in a 25-year-old man after treatment with olanzapine and with risperidone for early-onset schizoaffective disorder. His physical health was generally good and there was no personal or family history of VTE. He was not overweight nor had his weight or physical activity level changed under neuroleptic medication. Smoking a pack of cigarettes per day was his only known cardiovascular risk factor. His antipsychotic therapy included olanzapine 20 mg/day, paroxetine 20 mg/day and oral valproate 2000 mg/day for his psychotic symptoms. After 12 weeks of treatment, the patient presented with a complaint of sudden back pain radiating to the left front part of his thorax. Over the next few hours, he became short of breath and experienced an episode of hemoptysis. CT scan revealed bilateral pulmonary embolism. Ultrasound of the lower extremities showed no signs of DVT. His coagulopathy workup did not demonstrate any abnormalities. Olanzapine was discontinued and oral warfarin treatment with a target INR of 2.5 (range of 2 to 3) was initiated and maintained for 6 months. Twelve weeks after olanzapine was discontinued, he was initiated on risperidone 3 mg/day for a recurrence of psychotic symptoms. After 3 weeks of risperidone treatment, the patient presented with chest pain, cough, dyspnea, and hemoptysis. Multiple peripheral pulmonary emboli were observed on a chest spiral CT scan. Concomitant DVT in lower extremities was ruled out. Nonadherence to warfarin treatment (evidenced by low

INR) appeared to be the cause of this second episode of pulmonary embolism. Therefore, warfarin was reinitiated under close supervision to confirm adherence. Sixteen weeks later, the patient presented with thoracic pain and dyspnea. Spiral chest CT scan and Doppler ultrasound of the lower limbs indicated bilateral pulmonary embolism with no DVT in the lower limbs. Because antipsychotic agents appeared to be the causal factor of the pulmonary emboli, the patient was administered anticoagulant therapy and amisulpride 400 mg/day which resulted in improvement in his condition. Paroxetine 20 mg/day and valproate 2000 mg/day therapy was continued after being maintained throughout the 3 episodes of pulmonary embolism (Borras et al, 2008).

3.3.15.E Rhinitis

1) Incidence: oral, adults, 2% to 11%; children, 13% to 36% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Rhinitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, rhinitis was reported in 2% to 11% of adult patients receiving oral therapy, and 13% to 36% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.15.F Sinusitis

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Sinusitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.15.G Summary

1) Rhinitis, coughing, sinusitis, pharyngitis, dyspnea, stridor, pneumonia, and aspiration have been reported with risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). A case report described two episodes of pulmonary embolism in a 25-year-old man following oral risperidone therapy. The patient experienced improvement after risperidone was discontinued and anticoagulation therapy was initiated (Borras et al, 2008).

3.3.15.H Upper respiratory infection

1) Incidence: oral, adults, 2% to 3%; children, 34% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% to 2%; bipolar I disorder, 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, upper respiratory tract infection was reported in 2% of patients receiving risperidone 25 mg long-acting injection (n=99) and 0% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 1% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, upper respiratory tract infection was reported in 6% of patients receiving long-acting risperidone injection (n=72) compared with 3% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Upper respiratory tract infection was reported in 2% to 3% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of upper respiratory tract infection was 34% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 15% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.16 Other

3.3.16.A Angioedema

1) Angioedema has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) A 63-year-old woman, who had been hospitalized for 36 years with paranoid schizophrenia, developed periorbital and orbital edema on 3 occasions when risperidone was added to her continuing therapy. In all instances, the edema disappeared within a few days of discontinuation of risperidone. The first time, risperidone 2 milligrams (mg) daily, titrated to 6 mg/day over 2 weeks, was added to her stable regimen of fluphenazine, biperiden, and bromazepam. Periorbital edema occurred after 1 month and faded 1 week after discontinuation of risperidone, with all other medications maintained. A year later, risperidone 6 mg/day was again introduced, along with her current therapy of promethazine, biperiden, clonazepam, and nitrazepam; after 45 days moderate periorbital and orbital edema appeared. Discontinuation of promethazine did not alter the edema. Discontinuation of risperidone resulted in disappearance of the edema within 3 days. Five months later, risperidone was reintroduced at 3 mg/day. After 3 weeks, angioedema occurred, affecting the lips, face, neck, and tongue, making breathing difficult. She was given intensive anti-allergenic therapy and risperidone was discontinued. The edema diminished in a few hours and resolved completely in 4 days (Plesnicar et al, 2001).

3.3.16.B Death

1) Sudden death has been reported in postmarketing use of oral risperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
2) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).
3) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).
4) The findings of one meta-analysis suggest that there may be a small increased risk of death associated with the use of

atypical antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly patients (weighted mean age, 81.2 years) with dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy as compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving atypical antipsychotics as compared with placebo was 1.54 (95% confidence interval (CI), 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dropout rate was observed between antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found by meta-analysis (Schneider et al, 2005).
5) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: relative risk (RR), 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.C Drug withdrawal

1) A 38-year-old man with long-standing schizophrenia unresponsive to conventional therapy received an unsuccessful trial of risperidone which resulted in mania when the drug was withdrawn. He had been increased to risperidone 2 milligrams (mg) twice daily which resulted in tachycardia, tremor, and akathisia. After a taper, his hallucinations and delusions reoccurred but with manic symptoms for the first time. Risperidone 1 mg twice daily was reinitiated with resolution of his psychotic symptoms and his mania (Lane & Chang, 1998a).

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Fever

1) Incidence: oral, adults, 1% to 2%; children, 20% .(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, pyrexia was reported in 2% of patients receiving risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) During risperidone clinical trials, fever was reported in 1% to 2% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, the incidence of fever was 20% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared with 19% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.16.F Neuroleptic malignant syndrome

1) Incidence: adults, less than 1%; children, less than 5%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) Neuroleptic malignant syndrome has been reported in patients receiving long-acting risperidone injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
3) During premarketing risperidone studies of various design types, neuroleptic malignant syndrome was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) Neuroleptic malignant syndrome (NMS), with hyperpyrexia, muscle rigidity, autonomic instability, altered mental status, and elevated CPK levels, myoglobinuria, and acute renal failure cannot be excluded as a side effect of risperidone therapy. If neuroleptic malignant syndrome does occur, all antipsychotic medications and other drugs not essential to concurrent therapy should be discontinued, intensive symptomatic and medical monitoring should be initiated, and treatment of any concomitant serious medical problems should occur. Careful consideration of reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences have been reported (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
5) Adult
a) Neuroleptic malignant syndrome and probable acute pancreatitis was described in a 45-year-old female with disorganized schizophrenia treated with risperidone for 2 years. A month prior to transferring to a clinic within the hospital, the patient presented with muscular stiffness, increase in nonspeaking , oppositivity, food phobia, decreased voluntary bowel or urinary function, and a rise in body temperature. Laboratory findings showed hyperamylasemia, hyperlipasemia, myoglobinuria, and an increase in CPK plasma levels, suggesting rhabdomyolysis and probable acute pancreatitis. However, an abdominal computed tomography scan revealed nothing significant. In the following days, the patient's myoglobinuria and CPK slowly normalized , but both amylasemia 636 units/L (normal range, 5 units/L to 53 units/L) and lipasemia 1293 units/L (normal range 114 units/L to 286 units/L) levels increased to maximum despite any clinical or radiological evidence. Neurological exam revealed extrapyramidal stiffness, and the patient was laconic, negative, uncooperative and seemed confused toward time and space. Risperidone was discontinued and lorazepam therapy was initiated, which produced a slow resolution to her muscular stiffness. Amylasemia and lipasemia levels gradually decreased and returned to normal within 20 days. Clozapine 12.5 mg/day (titrated over more than 30 days to 300 mg/day) was introduced resulting in significant improvement in the patients psychopathological outcome. At her 18-month follow-up the patient maintained good clinical balance with no issues (Ghio et al, 2009).
b) A 27-year-old male developed neuromuscular malignant syndrome 21 months after being treated with risperidone 6 to 8 milligrams daily (Lee et al, 2000).
c) A 47-year-old man developed neuroleptic malignant syndrome after the administration of risperidone during a benzodiazepine (diazepam) withdrawal period. Symptoms abated over the next 9 days after discontinuation of risperidone and treatment with dantrolene, bromocriptine, and diazepam (Bobolakis, 2000).
d) A 73-year-old woman developed neuroleptic malignant syndrome while on monotherapy with risperidone 0.5 milligrams (mg) twice daily for multiinfarct dementia. Symptoms resolved after discontinuation (Gleason & Conigliaro, 1997).
e) Two cases of neuroleptic malignant syndrome (NMS) were reported in which each patient developed NMS symptoms 4 days after beginning risperidone 6 milligrams/day (mg/day). The drug was discontinued and both patients were treated with medical support; the symptoms resolved in 7 and 10 days, respectively. One of these patients was restarted on risperidone 1 mg/day; NMS symptoms returned within 24 to 36 hours. The drug was again discontinued and the symptoms resolved within 72 hours (Tarsy, 1996; Meterissian, 1996). Five previously reported cases of risperidone-associated NMS had histories of extrapyramidal side effects related to the use of various antipsychotic drugs; two of the patients had experienced a previous episode of NMS (Meterissian, 1996).
6) Pediatric
a) Neuroleptic malignant syndrome (NMS) has been reported in a 13-year-old male following risperidone treatment for Joubert syndrome (JS). The patient was admitted for agitation, fever, diaphoresis, and extremity spasms, including his neck. His medication consisted of risperidone 0.5 mg/day and clonazepam 0.1 mg/kg/day for subsequent dystonia. Due to fever, rigidity, and autonomic instability, and elevated CPK levels (1200 units/L), he was diagnosed with risperidone-associated NMS. Risperidone was discontinued with institution of intravenous hydration, biperidene lactate, cold compresses, and paracetamol treatment. His agitation, sweating, dystonia, rigidity and CPK (390 units/L) improved, and he was discharged normalized biochemical results on the fourth day (Vurucu et al, 2009).

3.3.16.G Opioid withdrawal

1) Two patients receiving stable doses of opioids experienced withdrawal symptoms 3 days after beginning risperidone. Symptoms subsided over 2 days following discontinuation of risperidone (Wines & Weiss, 1999d).

3.3.16.H Pain, General

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 1% to 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, generalized pain was reported in 4% of patients receiving risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, generalized pain was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008) (All Trimesters)
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)
a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
3) Crosses Placenta: Yes
4) Clinical Management
a) Risperidone should be used during pregnancy only after consideration is given to the potential benefit to the mother and the potential risk to the fetus. It is recommended that patients notify their physician if they become pregnant or intend to become pregnant during risperidone treatment (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008).
5) Literature Reports
a) A prospective, observational study of 54 women (mean age, 30.7 years) recruited from the Emory Women's Mental Health program exposed to antipsychotic medication during pregnant showed permeability of the placental barrier. Outcomes were determined by maternal and umbilical cord blood samples taken at delivery and through data collected from maternal reports and medical records. Placental passage showed a significant difference between antipsychotic medications, olanzapine 72.1% (95% CI, 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%), and quetiapine 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage. In the risperidone group, there were no reports of preterm labor or infants requiring neonatal intensive care admission. Of the 6 infants with maternal risperidone exposure, one infant weighed less than 2500 g (Newport et al, 2007).
b) A review of pooled data from the Benefit Risk Management Worldwide Safety database found no increase in risk of spontaneous abortions, structural malformations, or fetal teratogenic risk from in utero exposure to risperidone. The voluntary reports (516 prospective and 197 retrospective) of drug exposure during pregnancy identified 713 pregnancies in women with psychiatric illnesses who received risperidone during pregnancy. Of the 68 prospective pregnancies reported with known outcome, organ malformations (3.8%) and spontaneous abortions (16.9%) were documented (non-medically induced abortions excluded). Third-trimester exposure to risperidone was associated with drug withdrawal, or possible withdrawal-emergent syndrome (WES) in 13 retrospectively reported cases. The study lacked information on long-term neurodevelopmental outcomes in the neonate and developing child. In addition, many of the reports were confounded by concomitant medications, several of which are known teratogens (Coppola et al, 2007).
c) A case report described two successive, normal pregnancies in a 23-year-old woman receiving risperidone therapy. The woman had an unplanned yet uneventful pregnancy 6 months after starting risperidone 3 mg/day for treatment of

schizophrenia. She had spontaneous labor at 39 weeks gestation and delivered a healthy baby girl weighing 3.2 kg. There were no postnatal complications. Subsequently, her risperidone dose was decreased to 2 mg/day due to mental stability. Nine months later, she became pregnant again and was maintained on the 2 mg/day dose of risperidone without prenatal complications. Following spontaneous labor at 39 weeks, she delivered a healthy baby boy weighing 3 kg. Both of the infants were breastfed for 6 months. The children did not show any signs of neurodevelopmental delays or behavioral problems at 36 and 18 months of age, respectively (Mendhekar & Lohia, 2008).

d) A case report described a normal pregnancy and healthy baby born to a middle-aged woman with schizophrenia who was treated with risperidone prior to and throughout her pregnancy. Successfully maintained for 7 years on risperidone, her dose was gradually decreased from 3 mg/day to 1 mg/day at 6 months' gestation, then to 0.5 mg/day a few days prior to delivery. The baby was delivered at term and remained healthy over the first 3 months of life (Rodriguez-Salgado, 2008).

e) One case report of agenesis of the corpus callosum in an infant exposed in utero to risperidone has been reported; a causal relationship to risperidone has not been established. In postmarketing surveillance, following use of risperidone in the last trimester of pregnancy, reversible extrapyramidal symptoms have been observed in the neonate (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) In animal and human lactation studies, risperidone and its active 9-hydroxy metabolite are excreted into breast milk (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). It is estimated that a nursing infant would receive 0.84% of the maternal dose as risperidone and an additional 3.46% from 9-hydroxyrisperidone (as risperidone equivalents). Although this amount is not likely to result in sedation or extrapyramidal side effects in a full-term or older infant, the possibility of more serious adverse effects, such as neuroleptic malignant syndrome, should not be overlooked (Hill et al, 2000). Because risperidone is excreted in breast milk, women should not breastfeed during treatment with risperidone (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008).

3) Literature Reports

a) One case report described a 21-year-old woman who was treated postpartum with risperidone. She was advised not to breast feed her infant. After a gradual increase in maternal dose to 6 mg/day, she agreed to provide serial samples (over 24 hours) of plasma and breast milk so that risperidone and 9-hydroxyrisperidone could be measured. The milk to plasma ratios calculated from the AUCs were 0.42 and 0.24 for risperidone and the active metabolite, respectively (Hill et al, 2000).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.42 (Hill et al, 2000)

b) Active Metabolites

1) 9-hydroxyrisperidone (Prod Info Risperdal(R), 1999)

a) Milk to Maternal Plasma Ratio

1) 0.24 (Hill et al, 2000)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of acecainide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of acecainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as acecainide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.C Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of amiodarone and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as amiodarone and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D Amisulpride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of amisulpride with other drugs that potentiallly prolong the QTc interval, such as risperidone, should be approached with caution (Prod Info Solian(R), 1999q; Prod Info Risperdal(R), 2002b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as amisulpride and risperidone, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999y; Ravin & Levenson, 1997i; Gesell & Stephen, 1997d; Lo Vecchio et al, 1996d; Brown et al, 1993d).

3.5.1.E Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.F Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.G Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as aprindine, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H Arsenic Trioxide

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999ab), haloperidol (O'Brien et al, 1999r), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999aj), sertindole (Agelink et al, 2001z), quetiapine (Owens, 2001af), sultopride (Lande et al, 1992ac), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.I Asenapine

1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with antipsychotic drugs known for QT prolongation (eg, haloperidol, risperidone, or quetiapine) should be avoided . In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient (Prod Info SAPHRIS(R) sublingual tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as antipsychotic agents (haloperidol, risperidone, or quetiapine), should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info SAPHRIS(R) sublingual tablets, 2009). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.J Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R),

1999g), haloperidol (O'Brien et al, 1999f), quetiapine (Owens, 2001j), risperidone (Duenas-Laita et al, 1999m; Prod Info Risperdal(R) risperidone, 2002), sertindole (Agelink et al, 2001h), sultopride (Lande et al, 1992g), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993b; Wilt et al, 1993a). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

3.5.1.K Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as azimilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.L Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002; Agelink et al, 2001; Owens, 2001; Prod Info Orap(R), 1999a; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias

(Prod Info Orap(R), 1999).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997).

3.5.1.M Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of bretylium and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bretylium and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as bretylium and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.N Bupropion

1) Interaction Effect: increased plasma levels of risperidone
2) Summary: It is recommended that risperidone, an antipsychotic metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and risperidone should be approached with caution and should be initiated at the lower end of the dose range of risperidone. If bupropion is added to the treatment regimen of a patient already receiving risperidone, consider decreasing the dose of risperidone.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated risperidone metabolism

3.5.1.O Carbamazepine

1) Interaction Effect: increased risperidone clearance
2) Summary: The manufacturer reports that carbamazepine may increase risperidone clearance with chronic combined use. Patients should be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. Eleven subjects received risperidone titrated to 6 mg/day orally for 3 weeks, followed by coadministration of carbamazepine for an additional 3 weeks. Plasma concentrations of risperidone and 9-hydroxyrisperidone were decreased by 50%. The plasma concentrations of carbamazepine were unaffected (Prod Info Risperdal(R) Consta(TM), 2003a). One published case report describes a patient who had risperidone levels which were less than expected during carbamazepine therapy, along with decreased risperidone efficacy. The risperidone level dramatically increased when carbamazepine was discontinued (de Leon & Bork, 1997a). Carbamazepine is an inducer of cytochrome P450 3A (CYP3A) enzymes, while risperidone is primarily metabolized by CYP2D6. Whether carbamazepine is also inducing CYP2D6 or whether risperidone may be partly metabolized by CYP3A is uncertain (Lane & Chang, 1998; de Leon & Bork, 1998). The marked decrease in risperidone levels caused by carbamazepine may result in decreased therapeutic efficacy. When risperidone is used in combination with carbamazepine larger doses of risperidone may be required to achieve or maintain a desired antipsychotic effect (Spina et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of carbamazepine during the

first 4-8 weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by carbamazepine
8) Literature Reports
a) Carbamazepine was reported to induce the metabolism of risperidone in a 22-year-old male with chronic schizophrenia, resulting in low risperidone levels and lack of effectiveness. The patient was started on carbamazepine 600 mg daily and risperidone 4 mg daily. The plasma concentration of 9-hydroxyrisperidone was less than half the expected concentration when the dose of risperidone was doubled to 8 mg daily. After achieving a therapeutic plasma concentration of 9-hydroxyrisperidone (19 mcg/L), the dose of carbamazepine was tapered and stopped. Plasma levels of 9-hydroxyrisperidone increased to 49 mcg/L, necessitating a decrease in the dose of risperidone (de Leon & Bork, 1997).
b) Plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was added or increased when it was discontinued. One study evaluated the pharmacokinetic interactions between risperidone and carbamazepine. Thirty-four patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder participated in the study. All patients were stabilized on risperidone alone or in combination with carbamazepine for at least four weeks. Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in patients treated with risperidone alone and patients comedicated with carbamazepine. The plasma concentrations of both 9-OH risperidone and the sum of risperidone and 9-OH risperidone (active moiety) differed significantly among groups. In five patients evaluated with and without comedication, the plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was added or increased when it was discontinued. The results demonstrate that in patients receiving risperidone alone, the concentration of the active moiety (risperidone plus its active metabolite 9-OH risperidone) was reduced by approximately 70% when carbamazepine was given concomitantly (Spina et al, 2000).
c) The concomitant use of carbamazepine and risperidone leads to a marked decrease in the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone through stimulation of an inducible cytochrome as well as the influence of the cytochrome P450 2D6 genotype. A 50-year-old male with chronic schizophrenia and deficient CYP2D6 activity was given carbamazepine with his existing risperidone therapy. Carbamazepine 800 mg/day for 5 days was added to his medication regimens as a mood stabilizer. After 4 weeks of carbamazepine treatment, the patient exhibited psychotic symptoms including hallucinations, paranoid delusions, ideas of reference, and mild excitement. Plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone, had decreased from 22 and 30 ng/mL, respectively. Carbamazepine concentration was 8.2 mcg/mL. The risperidone dose was increased to 9 mg/day, carbamazepine was discontinued, and lorazepam 5 mg/day was added. Psychotic symptoms improved over the following 3 weeks and concentrations of risperidone and 9-hydroxyrisperidone increased to 40 and 57 ng/mL, respectively. A resultant decrease in the plasma concentrations of risperidone and 9-hydroxyrisperidone suggest that the CYP2D6 genotype may influence susceptibility to a clinically important interaction with risperidone and carbamazepine (Spina et al, 2001).
d) Eleven schizophrenic patients in a drug interaction study received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. The plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. At the initiation of therapy with carbamazepine, patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone may need to be adjusted. A dose increase or additional risperidone may need to be considered. If carbamazepine is discontinued, the dosage of risperidone should be re-evaluated and, if necessary, decreased. A lower dose of risperidone may be required between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003).

3.5.1.P Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic dose (Young et al, 1986). Even though no formal drug interaction studies have been done, the administration of drugs known to prolong the QTc interval, such as antipsychotics and chloral hydrate is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999i), quetiapine (Owens, 2001n), risperidone (Duenas-Laita et al, 1999s), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992k), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998d). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997a).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993c; Wilt et al, 1993b). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol.

3.5.1.Q Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999e), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as chloroquine is not recommended.
7) Probable Mechanism: additive effect on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999j; Ravin & Levenson, 1997d).

3.5.1.R Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999v), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992n), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.S Cimetidine

1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and cimetidine resulted in a 64% increase in the bioavailability of risperidone. The AUC of the active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007). Use caution if these agents are used concomitantly. Monitor patients for increased risperidone adverse events (sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with cimetidine and risperidone has resulted in a 64% increased bioavailability of risperidone. The AUC of the active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info

RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007). Caution is advised if these agents are used concomitantly. Consider monitoring for increased risperidone adverse events, including sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth.
7) Probable Mechanism: unknown

3.5.1.T Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Owens, 2001b; Prod Info Orap(R), 1999c). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999b).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999d; Ravin & Levenson, 1997b).

3.5.1.U Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999t), haloperidol (O'Brien et al, 1999o), quetiapine (Owens, 2001v), risperidone (Duenas-Laita et al, 1999ab), sertindole (Agelink et al, 2001r), sultopride (Lande et al, 1992s), and zotepine (Sweetman, 2004). Even though no formal drug interaction studies have been done, concomitant use of clarithromycin and antipsychotic agents may cause additive effects on the QT interval and is not recommended (Prod Info Biaxin(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) A 32-year-old male with schizoaffective disorder and metabolic syndrome experienced a significant increase in plasma concentration following administration of quetiapine. The patient, hospitalized for acute psychotic symptoms was treated with 50 mg quetiapine daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg clarithromycin along with his evening dose of quetiapine 400 mg. The following morning, 750 mg sultamicillin, 500 mg clarithromycin, and the morning 300-mg quetiapine dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 microgram/L (normal range, 70 to 170 microgram/L). The patient developed severe impaired consciousness and respiratory depression. Quetiapine overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved (Schulz-Du Bois et al, 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993e; Wilt et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(R) risperidone, 2002a).

3.5.1.V Clozapine

1) Interaction Effect: decreased risperidone clearance
2) Summary: The manufacturer reports that clozapine may decrease risperidone clearance with chronic combined use (Prod Info Risperdal(R) Consta(TM), 2003b).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects of risperidone when these drugs are given concurrently.
7) Probable Mechanism: unknown

3.5.1.W Darunavir

1) Interaction Effect: increased risperidone plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir, a CYP2D6 inhibitor, and risperidone, a CYP2D6 substrate, may result in increased plasma concentrations of risperidone, possibly due to inhibition of CYP2D6-mediated risperidone metabolism by darunavir/ritonavir. As this may result in risperidone adverse effects, a lower dose of risperidone should be considered with concomitant use is necessary (Prod Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted darunavir and risperidone may increase risperidone plasma concentrations. Consider using a lower risperidone dose when these agents are coadministered (Prod Info PREZISTA(R) film coated oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated risperidone metabolism by darunavir/ritonavir

3.5.1.X Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of risperidone
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with risperidone should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and risperidone. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to risperidone
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine

1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.Y Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.Z Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.AA Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong

the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AB Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of dofetilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dofetilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as dofetilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AC Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001a), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of dolasetron and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Anzemet(R), 1997a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, and QTc intervals compared to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. Increases

in PR and QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron to fast sodium channels. The cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in heart rate, or both (Prod Info Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993; Wilt et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(R) risperidone, 1999).

3.5.1.AD Doxepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.AE Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999w), haloperidol (O'Brien et al, 1999p), quetiapine (Owens, 2001y), risperidone (Duenas-Laita et al, 1999ad), sertindole (Agelink et al, 2001u), sultopride (Lande et al, 1992v), and zotepine (Sweetman, 2003). Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including antipsychotics is not recommended (Prod Info Inapsine(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AF Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as encainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and risperidone is not recommended due to the poten-

tial for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AG Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001v; Owens, 2001z; Prod Info Haldol(R), 1998f; Lande et al, 1992y). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including enflurane (Owens, 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval, such as antispychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999af; Ravin & Levenson, 1997m).

3.5.1.AH Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999l), haloperidol (O'Brien et al, 1999j), risperidone (Duenas-Laita et al, 1999t), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992l), and zotepine (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if erythromycin and antipsychotics are used concomitantly. Monitor QT interval at baseline and periodically during treatment.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AI Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as flecainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Prod Info Tambocor(R), 1998; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of flecainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitor-

ing is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AJ Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999). Haloperidol (Prod Info Haldol(R), 1998b), risperidone (Prod Info Risperdal(R) risperidone, 2000), amisulpride (Prod Info Solian(R), 1999j), sertindole (Brown & Levin, 1998c); sultopride (Lande et al, 1992j), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AK Fluoxetine

1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by fluoxetine. One study demonstrated increased risperidone levels in patients treated concurrently with fluoxetine and risperidone (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2002). Monitoring the patient for increased risperidone plasma levels side effects may be necessary (Spina et al, 2002). The risperidone dose should be reevaluated if fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008) (Spina et al, 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when fluoxetine is coadministered with risperidone (Spina et al, 2002). Reevaluate the dose of risperidone when concomitant fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) 2.5- to 2.8-fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosage of risperidone should be reevaluated when fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).
b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In an open, 4-week, pharmacokinetic study including 9 patients with schizophrenia or schizoaffective disorder, depressive type, risperidone concentrations increased when fluoxetine was coadministered with risperidone. Patients were stabilized on a fixed dose of risperidone 4 to 6 mg/day for at least four weeks and received adjunctive fluoxetine therapy 20 mg/day for the management of concomitant depression. Mean plasma risperidone concentrations increased from 12 ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0.01) at week 2, and 56 ng/mL (p less than 0.01) at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant increase at 4 weeks compared with baseline. After 4 weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75% (range: 9% to 204%, p less than 0.01) compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increased significantly. Two patients experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The authors suggest that monitoring plasma risperidone levels may be warranted in patients receiving concomitant fluoxetine and risperidone treatment (Spina et al, 2002).

3.5.1.AL Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999m), haloperidol (O'Brien et al, 1999k), quetiapine (Owens, 2001o), risperidone (Duenas-Laita et al, 1999u), sertindole (Agelink et al, 2001m), sultopride (Lande et al, 1992m), and zotepine (Sweetman, 2003). Because antipsychotics may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and antipsychotics is not recommended (Prod Info Foscavir(R), 1998; Ravin & Levenson, 1997h).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AM Gemifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interval, such as antipsychotics, have not been performed, gemifloxacin should be used cautiously in patients receiving antipsychotic medications (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AN Ginkgo Biloba

1) Interaction Effect: increased risk of risperidone adverse effects
2) Summary: Concomitant use of risperidone and ginkgo biloba may have precipitated priapism in one case report. Ginkgo biloba inhibits the cytochrome P450 isoforms 3A4 and 2C9, both of which are responsible for risperidone metabolism. Increased serum concentrations of risperidone may lead to an increased risk of side effects, including priapism, as in this case report (Lin et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution patients taking risperidone to discuss the use of nonprescription medicines, herbs, and dietary supplements with their doctor or pharmacist. If a patient presents with symptoms consistent with excessive risperidone, inquire about the use of nonprescription medicines, herbs, and dietary supplements. It is recommended to avoid ginkgo in patients taking risperidone (Lin et al, 2007).
7) Probable Mechanism: unknown
8) Literature Reports
a) Priapism occurred in a 26-year-old patient treated with risperidone 3 mg/day for 3 years who began ginkgo biloba 2 weeks prior to emergency department admission. He reported no other recent trauma, illness, or use of drugs or medications, and had not had any other adverse effects related to risperidone therapy. He was treating occasional tinnitus with ginkgo biloba 160 mg/day (Lin et al, 2007).

3.5.1.AO Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001w; Owens, 2001ae; Prod Info Solian(R), 1999aa; Prod Info Haldol(R), 1998i; Lande et al, 1992ab). The concurrent administration of

halofantrine with antipsychotics is not recommended (Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AP Haloperidol

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999q; Ravin & Levenson, 1997g; Gesell & Stephen, 1997c) and in overdose situations (Lo Vecchio et al, 1996c; Brown et al, 1993c). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and risperidone are used concomitantly. Screen patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999p; Ravin & Levenson, 1997f; Gesell & Stephen, 1997b) and in overdose situations (Lo Vecchio et al, 1996b; Brown et al, 1993b).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).

3.5.1.AQ Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001t; Owens, 2001x; Prod Info Solian(R), 1999v; Prod Info Haldol(R), 1998e; Lande et al, 1992u). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001x).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval, such as antispychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ac; Ravin & Levenson, 1997k).

3.5.1.AR Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AS Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as ibutilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AT Imipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recom-

mended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.AU Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001y; Owens, 2001ac; Prod Info Solian(R), 1999z; Prod Info Haldol(R), 1998h; Lande et al, 1992aa). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (Owens, 2001ac).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ah; Ravin & Levenson, 1997n).

3.5.1.AV Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes, and its use with other drugs known to cause QT prolongation is not recommended (Prod Info DynaCirc(R), 2000). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999x), haloperidol (O'Brien et al, 1999q), quetiapine (Owens, 2001aa), risperidone (Duenas-Laita et al, 1999ag), sertindole (Agelink et al, 2001w), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AW Itraconazole

1) Interaction Effect: increased risperidone concentrations
2) Summary: In an open-label study, coadministration of itraconazole and risperidone in 19 schizophrenic patients resulted in increased serum concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone. It has been postulated that in addition to cytochrome P450 2D6 enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. Inhibition of risperidone's CYP3A-mediated metabolism by itraconazole, a potent CYP3A inhibitor, may result in increased serum risperidone concentrations and may potentially affect clinical symptoms and side effects of risperidone (Jung et al, 2005). If these two agents are coadministered, consider monitoring patients for clinical symptoms of risperidone efficacy and potentially, increased risperidone side effects (hypotension, sedation, extrapyramidal side effects, arrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of itraconazole and risperidone can result in increased serum concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone. If these two agents are coadministered, consider monitoring patients for clinical symptoms of risperidone efficacy and potentially, increased risperidone side effects (hypotension,

sedation, extrapyramidal side effects, arrhythmias).
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated risperidone metabolism
8) Literature Reports
a) Concurrent administration of itraconazole with risperidone resulted in increased serum risperidone concentrations. Schizophrenic patients (n=19, mean age 41.4 years) who were being treated with 2 to 8 milligrams (mg) of risperidone per day (dosed at 8 am and 8 pm) for at least 2 months were administered itraconazole 200 mg per day (dosed at 8 pm) for 1 week and then withdrawn. Results of this open-label study indicated that the dose-normalized, steady-state plasma concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone, were significantly increased by 82% and 70%, respectively (p less than 0.01). Upon itraconazole discontinuation, both concentrations returned to the levels prior to itraconazole administration. Scores on the Brief Psychiatric Rating scale, signifying improvement in clinical symptoms, decreased by 6% (p=0.017). However, there was no increase in adverse effects as evaluated by the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating scale. It has been postulated that in addition to cytochrome P450 2D6 enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. The proposed mechanism for this interaction is inhibition of risperidone's CYP3A-mediated metabolism by itraconazole, a potent CYP3A inhibitor (Jung et al, 2005).

3.5.1.AX Lamotrigine

1) Interaction Effect: increased risperidone plasma concentrations and risk of adverse effects
2) Summary: Increased risperidone plasma concentrations, with signs of toxicity, developed in a patient administered lamotrigine in addition to a stable dose-regimen of risperidone and clozapine (Bienentreu & Kronmuller, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware of the increased risk of risperidone adverse effects in patients receiving lamotrigine together with risperidone. When concomitant lamotrigine is initiated, discontinued, or the dose of lamotrigine is changed, re-evaluate the dose of risperidone.
7) Probable Mechanism: unknown
8) Literature Reports
a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient receiving lamotrigine in addition to a stable dose-regimen of risperidone and clozapine. The patient, a 26-year-old woman diagnosed with schizophrenia, had sustained only a partial response to her established regimen of clozapine 550 milligrams (mg) daily and risperidone 8 mg daily. Baseline plasma concentrations of risperidone and clozapine were 55-70 nanograms/milliliter (ng/mL) and 800-1100 ng/mL, respectively. Lamotrigine was initiated, with the dose incrementally titrated up to 200 mg daily. Clozapine and risperidone plasma concentrations increased to 1300 ng/mL and 263 ng/mL, respectively; no symptoms of intoxication were observed. Lamotrigine was further titrated up to a dose of 225 mg daily, after which risperidone plasma concentration increased to 412 ng/mL, accompanied by symptoms of dizziness and tiredness. The risperidone dose was reduced to 2 mg daily and completely withdrawn shortly thereafter (Bienentreu & Kronmuller, 2005).

3.5.1.AY Levodopa

1) Interaction Effect: loss of levodopa efficacy
2) Summary: Because risperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is expected to antagonize the effects of levodopa (Prod Info Stalevo(TM), 2003; Prod Info Risperdal(R) Consta(TM), 2003g).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of risperidone in patients with parkinsonism should be avoided. If concurrent use cannot be avoided, monitor the patient for loss of levodopa therapeutic efficacy.
7) Probable Mechanism: pharmacologic antagonism

3.5.1.AZ Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as risperidone that prolong the QT interval (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with risperidone as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: additive cardiac effects

3.5.1.BA Levorphanol

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients
2) Summary: A patient stabilized on levorphanol 14 mg daily for neck pain experienced opioid cravings and cramps following three days of risperidone therapy. Discontinuing risperidone resolved her symptoms of withdrawal. Possible mechanisms for this effect include risperidone accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorption or secretion of the opioid, altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risperidone is concurrently prescribed.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 31-year-old female with a lengthy history of drug dependency, including opioids, was being treated with fluoxetine 40 mg daily for depression and levorphanol 14 mg daily for chronic severe neck pain. Because of recurring nightmares and flashbacks, risperidone 0.5 mg daily was initiated and increased to 1.5 mg daily within two days. While her dissociative symptoms improved, she complained of cramps, gooseflesh, and opioid cravings. Risperidone was decreased to 1 mg daily but her dissociative symptoms worsened. Her risperidone was again increased to 2 mg daily, but she experienced an increase in her withdrawal symptoms which persisted for days. Risperidone therapy was eventually discontinued (Wines & Weiss, 1999).

3.5.1.BB Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999i), haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001l), risperidone (Duenas-Laita et al, 1999r), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BC Linezolid

1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: In a review of post-marketing data, 1 case of serotonin toxicity was reported with the concurrent use of linezolid and risperidone, which was coadministered with other serotonergic agents (Lawrence et al, 2006) . Risperidone, in combination with other serotonergic agents, has been associated with the serotonin syndrome (Springuel & McMorran, 2003). There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents (Wigen & Goetz, 2002; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). Although coadministration of linezolid and serotonergic agents did not result in serotonin syndrome in phase 1, 2, or 3 clinical trials, linezolid is a reversible, non-selective MAOI and can potentially interact with serotonergic agents, precipitating the serotonin syndrome. If concurrent use of linezolid and a serotonergic agent is clinically warranted, monitor patients closely for signs and symptoms of serotonin syndrome. Consider discontinuing either one or both agents if these symptoms occur, keeping in mind that discontinuation of the concomitant serotonergic agent may result in associated discontinuation symp-

toms (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Serotonin toxicity has been reported in 1 individual with the concurrent use of linezolid and risperidone, which was coadministered with other serotonergic agents (Lawrence et al, 2006). If concurrent use of linezolid and risperidone, particularly with additional serotonergic agents, is clinically necessary, monitor patients closely for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005). Keep in mind that discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) In a review of post-marketing data, one case of serotonin toxicity was reported in the concurrent use of linezolid and risperidone, which was coadministered with other serotonergic agents. A review was conducted of post-marketing adverse events reported to the US Food and Drug Administration's Adverse Event Reporting System (AERS) database between November 1997 and September 2003 regarding serotonin toxicity with linezolid use. A serotonin toxicity case was defined as having: (a) linezolid as the primary suspect drug, (b) concomitant administration of 1 or more secondary suspect drug with CNS serotonergic activity, and (c) serotonin toxicity, as defined by the modified Hunter Serotonin Toxicity Criteria or by the reporter of the adverse event. A total of 29 cases were identified (age range 17 to 83 years), where linezolid was used concomitantly with 1 drug (n=20), with 2 drugs (n=6), and with 3 or more drugs (n=3). While SSRIs were the most common class of drugs received concomitantly with linezolid (n=26), other drug classes included tricyclic antidepressants (n=6), and atypical antidepressants (n=4). Additionally, drugs used concurrently included carbidopa-levodopa (n=2), dextromethorphan (n=1), lithium (n=1), metoclopramide (n=1), risperidone (n=1), and tramadol (n=1). Symptoms of serotonin toxicity included tremor, fever, seizure, clonus, sweating, agitation, akathesia, rigors, twitching, and muscle rigidity. Intervention including hospitalization was required in 13 patients, and 3 deaths were reported with concurrent SSRI use. For the 1 case identified with the concurrent use linezolid and risperidone, additional coadministered serotonergic drugs included bupropion, sertraline and trazodone (Lawrence et al, 2006).

3.5.1.BD Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).
b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients

developed symptoms within eight days of initiating combination therapy.
c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.
d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.
e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazinecardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).
f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).
g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BE Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as lorcainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lorcainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BF Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, caution is advised if mefloquine is used with other drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with significant

QT prolongation in a study of 46 healthy subjects (Davis et al, 1996). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998d), quetiapine (Owens, 2001w), risperidone (Prod Info Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999u), sertindole (Agelink et al, 2001s); sultopride (Lande et al, 1992t), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if mefloquine and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BG Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999g), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BH Methadone

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients
2) Summary: A patient stabilized on methadone 50 mg daily experienced aches, nasal congestion, and irritability within three days of starting risperidone therapy. Discontinuing risperidone resolved his symptoms of withdrawal. Possible mechanisms for this effect include risperidone accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorption or secretion of the opioid, altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risperidone is concurrently prescribed.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 26-year-old male with a long history of chemical dependency was receiving a methadone maintenance dose of 50 mg daily when he was hospitalized for an exacerbation of paranoia and agitation. Risperidone 0.5 mg twice daily was initiated, and within three days the patient complained of feeling "dope sick", with symptoms of aches, nasal congestion, and irritability. These symptoms worsened as risperidone was increased to 2 mg daily and dissipated when risperidone was discontinued. His paranoia was successfully treated with chlorpromazine with no further signs of opioid withdrawal (Wines & Weiss, 1999b).

3.5.1.BI Metoclopramide

1) Interaction Effect: an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome
2) Summary: Concomitant use of metoclopramide with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as tardive dyskinesia, or neuroleptic malignant syndrome and is contraindicated (Prod Info METOZOLV ODT orally disintegrating tablets, 2009). If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide when patient develops signs and symptoms of extrapyramidal reactions. Inject diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of metoclopramide with antipsychotic agents is contraindicated. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide when patient develops signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome. Inject diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).
7) Probable Mechanism: unknown

3.5.1.BJ Midodrine

1) Interaction Effect: an increased risk of acute dystonia
2) Summary: A case report described development of acute dystonia in a 33-year-old female following concomitant administration of midodrine and risperidone (Takahashi, 2000). Patients receiving this combination may need to be monitored for increased risperidone adverse events, including signs and symptoms of acute dystonia.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if midodrine and risperidone are prescribed concurrently. Monitor for signs and symptoms of acute dystonia or other risperidone adverse events.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 33-year-old female developed acute dystonia after addition of midodrine to treat orthostatic hypotension secondary to risperidone therapy. The patient had a 12-year history of catatonic schizophrenia, which was adequately controlled with a stable dose of risperidone 6 mg/day. Two days after addition of midodrine 4 mg/day to treat complaints of orthostatic hypotension, the patient exhibited manifestations of acute dystonia, including tongue protrusion, retrocollis, and oculogyric crisis. Intramuscular injection of anticholinergics immediately resolved all symptoms. Midodrine was discontinued and risperidone 6 mg/day monotherapy was continued. After two weeks without dystonic symptoms, midodrine 4 mg/day was added again to therapy to treat continuing complaints of orthostatic hypotension. A similar acute dystonic reaction recurred one day later and was successfully treated with one intramuscular injection of an anticholinergic. Again, midodrine was discontinued and the patient remained on risperidone 6 mg/day without dystonic symptoms. Two weeks later, the risperidone dose was decreased to 3 mg/day due to persistent orthostatic hypotension, and the patient was free of catatonic and dystonic symptoms at a 3-month follow-up. Increased risperidone-associated central noradrenergic activity due to the peripheral alpha-1 receptor activity of midodrine was a postulated mechanism for this interaction (Takahashi, 2000).

3.5.1.BK Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.BL Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including octreotide, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999o), haloperidol (O'Brien et al, 1999m), risperidone (Duenas-Laita et al, 1999w), sertindole (Agelink et al, 2001o), quetiapine (Owens, 2001q), sultopride (Lande et al, 1992o), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BM Paroxetine

1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of paroxetine (potent CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by paroxetine. Two studies demonstrated increased risperidone levels resulting in a greater frequency of extrapyramidal symptoms in patients treated concurrently with paroxetine and risperidone (Saito et al, 2005; Spina et al, 2001a). One of these studies showed an association between paroxetine dose increases and greater risperidone plasma concentrations (Spina et al, 2001a). In a case report, serotonin syndrome was observed in a patient who had already been receiving risperidone and was initiated on paroxetine (Hamilton & Malone, 2000). Monitoring the patient for increased risperidone plasma levels side effects may be necessary. The risperidone dose should be reevaluated if paroxetine is initiated or discontinued. Concomitant use of a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2001a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of paroxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Saito et al, 2005; Spina et al, 2001a; Hamilton & Malone, 2000). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when paroxetine is coadministered with risperidone. Reevaluate the dose of risperidone when concomitant paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008). Coadministering a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Saito et al, 2005).
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Paroxetine (a potent CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) by 3- to 9- fold. Paroxetine also lowered the concentration of 9-hydroxyrisperidone by about 10%. In postmarketing surveillance of risperidone, torsade de pointes has been reported with combined overdose of risperidone and paroxetine. The dosage of risperidone should be reevaluated when paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).
b) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizophrenia and negative symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receiving risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared with baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg

paroxetine dose; increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by 4.2-fold (95% CI, 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 to 26.8) with 40 mg. Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal symptoms scores were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine with risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

c) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the duration of the study. A significant elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant paroxetine treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministration. Total plasma levels of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The occurrence of extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharmacodynamic effect of paroxetine (Spina et al, 2001a).

d) Serotonin syndrome occurred in a patient using concomitant paroxetine and risperidone, an antipsychotic agent with potent serotonin antagonism and dopamine blocking activity . A 53-year-old male with a 7-month history of psychotic depression was being treated with risperidone 3 mg/day and paroxetine 20 mg/day for 10 weeks before presentation. Nine weeks into therapy, the patient showed decreased motivation and bilateral jerking movements of the mouth and legs. The patient discontinued his medication during the week before his admission. Upon presentation he was apathetic, confused, disorganized, and talked to himself. The doses of paroxetine and risperidone were doubled to 40 mg/day and 6 mg/day, respectively. Within 2 hours of taking his medication, he experienced bilateral jerking movements, ataxia, tremor, and shivering. He presented to the emergency room with involuntary jerking movements and lethargy. His mental status exam was notable for depression with psychomotor agitation, difficulty being aroused, and auditory hallucinations. Differential diagnosis included recurrent psychotic depression, neuroleptic malignant syndrome (NMS), drug overdose, and serotonin syndrome. Nortriptyline 100 mg at bedtime, haloperidol 10 mg twice daily and diphenhydramine 50 mg at night were initiated at discharge. The patient returned to baseline 9 months after discharge and is without symptoms of depression or psychosis (Hamilton & Malone, 2000).

3.5.1.BN Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including pentamidine, is not recommended (Agelink et al, 2001p; Owens, 2001r; Prod Info Haldol(R), 2001a; Prod Info Solian(R), 1999p; Duenas-Laita et al, 1999x; Duenas-Laita et al, 1999x; Prod Info Nipolept(R), 1996a; Metzger & Friedman, 1993d; Lande et al, 1992p).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BO Phenobarbital

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyrisperidone
2) Summary: Concomitant use of phenobarbital may reduce plasma concentrations of risperidone. Patients should be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of phenobarbital therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003d).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenobarbital during the first 4-8 weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinuation of phenobarbital therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients currently maintained on the lowest available dose (25 mg) risperidone, it is recommended to continue with that dose unless an interruption of treatment is necessary.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by phenobarbital

3.5.1.BP Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.BQ Phenytoin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyrisperidone
2) Summary: Concomitant use of phenytoin may reduce plasma concentrations of risperidone. Upon initiation of therapy with phenytoin, patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone may need to be adjusted. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of phenytoin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenytoin higher risperidone doses may be needed. Monitor patients during the first 4-8 weeks of coadministration with phenytoin and risperidone; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinuation of phenytoin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients currently maintained on the lowest available dose (25 mg) risperidone, it is recommended to continue with that dose unless an interruption of treatment is necessary.
7) Probable Mechanism: induction of risperidone metabolism through cytochrome P450 enzymes by phenytoin

3.5.1.BR Pimozide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration of pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R) pimozide, 1999). Risperidone has been reported to prolong the QTc interval (Prod Info Risperdal(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as pimozide and risperidone, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999e).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999n; Ravin & Levenson, 1997e; Gesell & Stephen, 1997a; Lo Vecchio et al, 1996a; Brown et al, 1993a).

3.5.1.BS Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BT Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets,

2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BU Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998c), quetiapine (Owens, 2001s), risperidone (Prod Info Risperdal(R) risperidone, 2000a), amisulpride (Prod Info Solian(R), 1999r), sertindole (Brown & Levin, 1998e); sultopride (Lande et al, 1992q), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if probucol and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BV Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BW Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999v), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992n), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BX Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as propafenone, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of propafenone and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BY Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.BZ Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Risperidone can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes, and its use with other agents that may prolong the QT interval, such as quetiapine, is not recommended (Prod Info Risperdal(R), 2002c; Owens, 2001u). Coadministration of risperidone 3 mg twice daily with quetiapine 300 mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Because of the potential additive effects on the QT interval, the concurrent administration of quetiapine and risperidone is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999aa; Ravin & Levenson, 1997j; Gesell & Stephen, 1997e; Lo Vecchio et al, 1996e; Brown et al, 1993e).

3.5.1.CA Ranitidine

1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and ranitidine resulted in a 26% increase in the bioavailability of risperidone. The AUC of the active metabolite, 9-hydroxyrisperidone, and risperidone combined was increased by 20% (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009). Use caution if these agents are used concomitantly. Monitor patients for increased risperidone adverse events (sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with ranitidine and risperidone has resulted in increased risperidone bioavailability (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009). Caution is advised if these agents are used concomitantly. Consider monitoring for increased risperidone adverse events, including sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth.
7) Probable Mechanism: unknown

3.5.1.CB Rifampin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyrisperidone
2) Summary: Concomitant use of rifampin may reduce plasma concentrations of risperidone (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). Patients should be closely monitored if concomitant use is required. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of rifampin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of rifampin during the first 4 to 8 weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone 2 to 4 weeks before the discontinuation of rifampin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients currently maintained on the lowest available dose of risperidone long-acting injection (25 mg), it is recommended to continue with that dose unless an interruption of treatment is necessary

(Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2008).
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by rifampin

3.5.1.CC Ritonavir

1) Interaction Effect: increased risperidone serum concentrations and potential toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of risperidone, resulting in risperidone toxicity (Jover et al, 2002a; Kelly et al, 2002a)A risperdal dose decrease may be required when coadministered with ritonavir (Prod Info NORVIR(R), 2005).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of neuroleptic toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias). Reduce doses of risperidone as required.
7) Probable Mechanism: decreased risperidone metabolism
8) Literature Reports
a) Increases in risperidone serum concentration occurred in a patient taking concomitant ritonavir. A 48-year-old man previously diagnosed with acquired immunodeficiency syndrome (AIDS) was admitted to a psychiatric hospital for manic symptoms. His current medications included zidovudine 250 mg twice daily, didanosine 300 mg once daily, indinavir 400 mg twice daily, and ritonavir 200 mg twice daily. He was given risperidone 3 mg twice daily upon admission. After receiving two doses of risperidone he became ataxic, progressively drowsy and disoriented. He then became lethargic and comatose. Physical exam revealed a Glasgow coma score of 7/15 points with miotic pupils. Laboratory tests were normal. A toxic or metabolic etiology was suspected to be the cause of the coma and all medication was discontinued. Twenty-four hours later, his neurologic status returned to baseline and progressively the manic symptoms reappeared. The author suggests that an interaction between risperidone, indinavir and ritonavir may have caused a reversible toxic coma (Jover et al, 2002).
b) Extrapyramidal symptoms (EPS) occurred in a patient initiated on ritonavir and indinavir while taking risperidone for a tic disorder. A 35-year-old white male with AIDS received risperidone 2 mg twice daily for treatment of Tourette's-like tic disorder. The patient had an 8 month history of hand tremor, twitching and jerky involuntary movements of the face, shoulders, arms, and legs. His current medications were dapsone, pyrimethamine, azithromycin, and hydroxyzine. Risperidone was initiated at 1 mg twice daily for 2 weeks and then increased to 2 mg twice daily. Indinavir 800 mg twice daily and ritonavir 200 mg twice daily was initiated at the same time the risperidone dosage was increased. One week later he experienced significantly impaired swallowing, speaking, and breathing, and worsening of his existing tremors. Ritonavir and indinavir were discontinued. One month later the patient agreed to try indinavir/ritonavir therapy again. At the same time he increased the risperidone dose to 3 mg twice daily. Symptoms worsened over the next 3 days. All laboratory parameters were unremarkable and vital signs were stable. Risperidone was discontinued and clonazepam initiated. Three days later the patients symptoms improved. Caution is warranted when risperidone is prescribed with ritonavir/indinavir (Kelly et al, 2002).

3.5.1.CD Ropinirole

1) Interaction Effect: diminished effectiveness of ropinirole
2) Summary: Theoretically, risperidone may oppose the dopaminergic effect of dopamine agonists, such as ropinirole (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info REQUIP(R) oral tablets, 2006). If concurrent use of ropinirole and a dopamine antagonist is clinically warranted, monitor patients closely for loss of ropinirole efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concurrent use of risperidone and ropinirole as this may result in reduced effectiveness of ropinirole due to the antagonistic dopaminergic effect of risperidone (Prod Info REQUIP(R) oral tablets, 2006). If concurrent use of ropinirole and a dopamine antagonist is clinically warranted, monitor patients closely for signs and symptoms of diminished effectiveness of ropinirole, such as worsening of extrapyramidal movements, rigidity, tremor, or gait disturbances.
7) Probable Mechanism: pharmacological antagonism

3.5.1.CE Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sematilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as sematilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CF Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sertindole with other drugs that potentiallly prolong the QTc interval, such as risperidone, should be approached with caution (Brown & Levin, 1998a; Prod Info Risperdal(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risperidone and sertindole, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999c; Ravin & Levenson, 1997a; Gesell & Stephen, 1997; Lo Vecchio et al, 1996; Brown et al, 1993).
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001b).
c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).

3.5.1.CG Simvastatin

1) Interaction Effect: increased simvastatin serum concentrations with an increased risk of myopathy or rhabdomyolysis
2) Summary: Concomitant use of risperidone and simvastatin may increase the bioavailability of simvastatin. Risperidone and simvastation are both metabolized by cytochrome P450-3A4 (CYP3A4). Although risperidone is predominantly metabolized by CYP2D6, individuals having a slow metabolizer phenotype due to possession of a CYP2D6 polymorphic genotype may convert to CYP3A4 as the primary isoform for risperidone metabolism. As a result, risperidone may competitively inhibit simvastatin metabolism, thereby increasing the risk of myopathy and rhabdomyolysis. In a case report, a patient developed rhabdomyolysis complicated by acute compartment syndrome after receiving simvastatin concomitantly with risperidone (Webber et al, 2004).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of risperidone with simvastatin is not recommended. If concurrent therapy is required, monitor patient for signs and symptoms of myopathy or rhabdomyolysis (muscle pain, tenderness, or weakness). Monitor creatine kinase (CK) levels and discontinue use if CK levels show a marked increase, or if myopathy or

rhabdomyolysis is diagnosed or suspected.
7) Probable Mechanism: competitive inhibition of cytochrome P450-3A4-mediated simvastatin metabolism
8) Literature Reports
a) Rhabdomyolysis occurred in a 22-year-old man after simvastatin 10 milligrams (mg) daily was added to a stable treatment regimen comprising clonazepam 2 mg and risperidone 4 mg daily. Approximately 5 days after beginning simvastatin treatment, the patient presented with right ankle and heel pain. Over the next 24 hours, the pain advanced proximally and increased in severity, with the extremity showing signs of warmth, erythema, rash, and pronounced tenseness of the distal muscle compartments. Serum creatine kinase (CK), aspartate and alanine aminotransferase concentrations were 12, 408 units/liter (L), 296 International Units (IU)/L, and 97 IU/L, respectively. CK concentrations peaked at 25, 498 units/L. Simvastatin was withdrawn and the patient required emergent decompression fasciotomies due to acute compartment syndrome of the right lower extremity. Risperidone and clonazepam were continued without incident (Webber et al, 2004).

3.5.1.CH Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sotalol and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sotalol and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as sotalol and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CI Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including spiramycin, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999c), quetiapine (Owens, 2001g), risperidone (Duenas-Laita et al, 1999i), sertindole (Agelink et al, 2001e), sultopride (Lande et al, 1992d), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CJ Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999n), quetiapine (Owens, 2001t), risperidone (Duenas-Laita et al, 1999z), sertindole (Agelink et al, 2001q), sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CK Sultopride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sultopride with other drugs that potentiallly prolong the QTc interval, such as risperidone, should be approached with caution (Lande et al, 1992x; Montaz et al, 1992a; Harry, 1997b; Prod Info Risperdal(R), 2002d).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risperidone and sultopride, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ae; Ravin & Levenson, 1997l; Gesell & Stephen, 1997f; Lo Vecchio et al, 1996f; Brown et al, 1993f).
b) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992w; Montaz et al, 1992; Harry, 1997a).

3.5.1.CL Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of tedisamil and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tedisamil and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as tedisamil and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CM Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001c; Owens, 2001c; Prod Info Haldol(R), 1998a; Lande et al, 1992a). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of telithromycin and an antipsychotic is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999e; Ravin & Levenson, 1997c).

3.5.1.CN Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002b; Owens, 2001ad; Prod Info Orap(R), 1999g). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999f).

3.5.1.CO Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyramidal disorders
2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, risperidone) should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008) In addition to QT prolongation, tetrabenazine may also cause adverse reactions such as neuroleptic malignant syndrome and extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic drugs (eg, risperidone) (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with risperidone or other neuroleptic drugs may increase tetrabenazine adverse reactions, such as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neuroleptic malignant syndrome and extrapyramidal disorders may be enhanced when given with a dopamine agonist such as risperidone (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.CP Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001d), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992b), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CQ Topiramate

1) Interaction Effect: decreased risperidone exposure
2) Summary: Concurrent administration of topiramate (200 mg/day) with a single, 2 mg dose of risperidone in healthy subjects (n=12) resulted in a 25% decrease in risperidone exposure. Patients receiving risperidone and topiramate together should be monitored closely for clinical response to risperidone (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: If risperidone and topiramate are administered concurrently, monitor patients closely for clinical response to risperidone (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CR Tramadol

1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.CS Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999v), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992n), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CT Trimethoprim

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999n), quetiapine (Owens, 2001t), risperidone (Duenas-Laita et al, 1999z), sertindole (Agelink et al, 2001q), sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CU Trimipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.CV Valproic Acid

1) Interaction Effect: increased plasma valproic acid concentrations
2) Summary: The addition of risperidone to valproic acid produces a significant increase in the peak plasma concentration (Cmax) of valproic acid (Prod Info Risperdal(R) Consta(TM), 2003f) as well as marked increases in ammonia levels (Carlson et al, 2007). The high protein capacity of risperidone could lead to a competition for protein-binding with the high protein-binding capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (van Wattum, 2001). However, Valproic acid can be added safely to a treatment regimen consisting of risperidone (Spina et al, 2000c). Monitoring of ammonia levels may be warranted in patients who exhibited new or increased manic behavior when taking valproic acid and risperidone, especially in patients vulnerable to valproic acid-induced hyperammonemia, including the young, on valproate polytherapy, severely handicapped, or suffering from malnutrition, protein load, and decreased free serum carnitine (Carlson et al, 2007). In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperidone concentrations does not appear to be warranted.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor for increased ammonia levels and plasma valproic acid concentrations with the addition of risperidone to drug therapy or changes in risperidone dose.
7) Probable Mechanism: unknown
8) Literature Reports
a) In 2 case reports of 11 year-old boys, there were marked exacerbations in manic behavior and a 2 to 4-fold increase in serum ammonia levels when risperidone and valproic acid were concomitantly administered. The first patient, who had a history of Asperger's disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, and manic symptoms, was admitted for increasing aggressive behavior. Chlorpromazine was added as needed and risperidone was added to replace his aripiprazole. Following the initiation of valproic acid 250 mg twice daily, the patient experienced a qualitative exacerbation of manic behavior. The risperidone dosage was eventually adjusted to 2 mg/day and valproic acid to 625 mg/day. The patient's valproate level ranged from 87 to 90 and ammonia level was 213. When valproic acid was discontinued, and the ammonia level fell to 55, his manic behavior stopped. The second patient, with a history of absence epilepsy and ADHD, was on stable doses of valproic acid. Because of his psychotic symptoms, risperidone was started and increased to 1.125 mg/day over 5 weeks. The patients exhibited markedly pronounced manic behavior and had a serum ammonia level of 113, despite a normal valproic acid level of 71. Upon discontinuation of risperidone and valproic acid, the ammonia level normalized to 55 and the manic behavior resolved. One month later when the patient was rechallenged with risperidone (in the absence of valproic acid), there was no return of either mania or hyperammonemia (Carlson et al, 2007).
b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic acid. Steady state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in patients

treated with risperidone alone or in patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder, were stabilized with risperidone alone or in combination with valproic acid. The results demonstrate that valproic acid given at doses up to 1200-1500 mg/day had clinically insignificant effects on plasma concentrations of risperidone and its active metabolite. Valproic acid can be added safely to a treatment regimen consisting of risperidone. In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperidone concentrations does not appear to be warranted (Spina et al, 2000b).
c) The combination of valproic acid and risperidone led to significantly increased levels of valproic acid in one case . A 10-year-old male suffered from mood swings and increasingly aggressive behavior. Valproic acid treatment was initiated and titrated up to 1750 mg/day. Valproate serum levels were in the therapeutic range. After 10 days of treatment, risperidone 2 mg/day was added, which was increased to 3 mg/day on day 4. On day 5 after risperidone was started, the patients symptoms improved but valproic acid levels were above the therapeutic range at 191 mg/L. Valproic acid was decreased to 1000 mg/day and the level normalized to 108 mg/L within 3 days and subsequently stabilized. The author concludes that the high-protein-binding capacity of risperidone could lead to a competition for protein-binding with the high protein-binding capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (Van Wattum, 2001).
d) In 21 patients, repeated oral doses of risperidone 4 mg daily did not affect the pre-dose or average plasma concentrations or exposure (area under the concentration-time curve) of valproate 1000 mg daily compared to placebo. There was, however, a 20% increase in valproate maximum plasma concentration (Cmax) after risperidone coadministration (Prod Info Risperdal(R) Consta(TM), 2003e).

3.5.1.CW Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Antipsychotics and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Owens, 2001f; Prod Info Solian(R), 1999c; Duenas-Laita et al, 1999h; Brown & Levin, 1998b; Harry, 1997; Prod Info Nipolept(R), 1996; Metzger & Friedman, 1993a; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as antipsychotics and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CX Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998g), quetiapine (Owens, 2001ab), risperidone (Prod Info Risperdal(R) risperidone, 2000c), amisulpride (Prod Info Solian(R), 1999y), sertindole (Agelink et al, 2001x); sultopride (Lande et al, 1992z), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QT interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and antipsychotics is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.CY Zotepine

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures (Hori et al, 1992). In addition, coadministration of drugs that potentiallly prolong the QTc interval, such as zotepine and risperidone, should be approached with caution (Sweetman, 2004; Prod Info Risperdal(R), 2002e).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical

6) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking large doses of zotepine; (2) have a history of seizure disorders; (3) are of young age; or (4) have a past history of brain injury. The concurrent administration of agents that prolong the QT interval, such as zotepine and risperdone, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2004).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ai; Ravin & Levenson, 1997o; Gesell & Stephen, 1997g; Lo Vecchio et al, 1996g; Brown et al, 1993g).

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Bipolar Disorder
1) A prolonged time to relapse to any mood episode (depression, mania, hypomania, or mixed) is indicative of a therapeutic response. Improvement of Young Mania Rating Scale (YMRS) has been used to evaluate the efficacy of therapy.
b) Schizophrenia
1) Positive and Negative Syndrome Scale (PANSS), which measures positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility or excitement, and anxiety or depression, evaluates response to therapy.
c) Irritability Associated with Autistic Disorder
1) Reduction in irritability (eg, aggression, deliberate self-injury, temper tantrums, and quickly changing moods) in autistic patients is indicative of efficacy. The Aberrant Behavior Checklist Irritability subscale (ABC-I) has been used to evaluate efficacy.
d) Maintenance Therapy
1) Reassess patients periodically to determine the need for continued treatment (all indications) (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).
B) Toxic
1) Laboratory Parameters
a) Perform a fasting blood glucose test at the beginning of risperidone treatment and regularly during treatment in patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) or for worsening of glucose control in patients with confirmed diabetes mellitus (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) Frequently monitor CBC during the first few months of therapy in patients with a history of clinically significant low WBC or drug-induced leukopenia or neutropenia (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) Physical Findings
a) Monitor ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004).
b) Monitor orthostatic vital signs in patients especially during the initial dose-titration period in the elderly, renal or hepatic impairment and in patients predisposed to hypotension, including dehydration and hypovolemia, known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), and cerebrovascular disease (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
c) Closely supervise patients at high-risk for suicide during risperidone therapy due to the increased risk of suicide attempts in patients with schizophrenia or bipolar disorder (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

4.2 Patient Instructions

A) Risperidone (By mouth)
Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to risperidone.

How to Use This Medicine:
Tablet, Liquid, Dissolving Tablet
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. You may mix your dose with water, low-fat milk, coffee, or orange juice. Do not mix with cola or tea.
If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not open the blister pack that contains the tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the tablet out. Do not push the tablet through the foil. Place the tablet in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Do not freeze the oral liquid.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
There are many other medicines that you should not use while you are taking risperidone. Taking risperidone with certain other medicines may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other medicines you are using.
Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine, furosemide (Lasix®), levodopa, fluoxetine (Prozac®), paroxetine (Paxil®), phenobarbital, ranitidine, or valproate (Depakene®, Depakote®). Tell your doctor if you are using clozapine (Clozaril®), quinidine, phenytoin (Dilantin®), or rifampin (Rifadin®). Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, and Zestril®.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, plan to become pregnant, or if you are breast feeding. Tell your doctor if you have a history of liver disease, kidney disease, stroke, or breast cancer. Make sure your doctor knows if you have heart problems, Parkinson's disease, seizures, or trouble swallowing.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat

this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoid sunlamps and tanning beds.
Risperdal® M-Tab® contains aspartame (phenylalanine). If you have phenylketonuria (PKU), talk to your doctor before using this medicine.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Confusion, weakness, and muscle twitching.
Constant muscle movement that you cannot control (often in your lips, tongue, arms, or legs).
Dry mouth, increased thirst, muscle cramps, nausea or vomiting.
Fast, slow, irregular (uneven), or pounding heartbeat.
Fever, sweating, muscle stiffness.
In males: Painful, prolonged erection of your penis.
Lightheadedness, fainting, or seizures.
Severe diarrhea, vomiting, or stomach pain.
Skin rash.
Sudden or severe headache, problems with vision, speech, or walking.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Anxiety, trouble sleeping, increased dreaming.
Constipation, diarrhea, nausea, or upset stomach.
Darkening of your skin.
Drooling, or stuffy nose.
In women: Unusually heavy bleeding during your menstrual period.
Severe tiredness.
Trouble having sex.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Risperidone (Injection)
Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to risperidone.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine. This medicine is usually given every 2 weeks.

If a Dose is Missed:

This medicine needs to be given on a fixed schedule. If you miss a dose or forget to use your medicine, call your doctor or pharmacist for instructions.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

There are many other medicines that you should not use while you are taking risperidone. Taking risperidone with certain other medicines may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other medicines you are using.

Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine (Tagamet®), furosemide (Lasix®), levodopa (Larodopa®), fluoxetine (Prozac®), paroxetine (Paxil®), phenobarbital (Luminal®), ranitidine (Zantac®), or valproate (Depakene®, Depakote®). Tell your doctor if you are using clozapine (Clozaril®), quinidine, phenytoin (Dilantin®), or rifampin (Rifadin®). Make sure your doctor knows if you are also using medicine to lower blood pressure (such as atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®).

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or if you plan to become pregnant while you are using this medicine, or during the 12 weeks after you stop using it. Do not breastfeed while you are using this medicine and for at least 12 weeks after you receive the last shot.

Make sure your doctor knows if you have kidney disease, liver disease, diabetes, breast cancer, bone problems, brain tumor, bowel blockage, Reye's syndrome, Parkinson's disease, trouble with swallowing, or a history of seizures or neuroleptic malignant syndrome (NMS). Tell your doctor if you have any kind of blood vessel or heart problems, including low blood pressure, heart failure, a low amount of blood, heart rhythm problems, or a history of a heart attack or stroke.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using a medicine for diabetes, your doctor may need to change your dose.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has forgetfulness or confusion related to aging (such as Alzheimer's disease or dementia).

Stop taking this medicine and check with your doctor right away if you have any of the following symptoms while using this medicine: convulsions (seizures), difficulty with breathing, a fast heartbeat, a high fever, high or low blood pressure, increased sweating, loss of bladder control, severe muscle stiffness, unusually pale skin, or tiredness. These could be symptoms of a serious condition called neuroleptic malignant syndrome (NMS).

Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

This medicine may make you dizzy, lightheaded, or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. Change positions slowly when getting up from a lying or sitting position.

This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

This medicine may cause some people to be agitated, irritable, or display other abnormal behaviors. It may also cause some people to have suicidal thoughts and tendencies or to become more depressed. If you or your caregiver notice any of these adverse effects, tell your doctor right away.

This medicine may increase your weight. Your doctor may need to check your weight regularly during treatment with this medicine.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Chills, cough, sore throat, and body aches.
Dry mouth, increased hunger or thirst, or muscle cramps.
Fast, slow, pounding, or uneven heartbeat.
Feeling depressed, agitated, or nervous.
Fever, sweating, confusion, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Mood or behavioral changes, or thoughts of hurting yourself or others.
Numbness or weakness in your arm or leg, or on one side of your body.
Painful, prolonged erection of your penis (in males).
Problems with balance or walking.
Seizures or tremors.
Swelling in your hands, ankles, or feet.
Trouble with speaking or swallowing.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision or change in vision.
Constipation, diarrhea, nausea, vomiting, or stomach pain or upset.
Dry mouth or drooling.
Headache.
Pain, swelling, or a lump under your skin where the shot is given.
Rash or itching skin.
Stuffy or runny nose.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including risperidone) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current risperidone users in 24,589 person-years was 2.91 (95% CI, 2.26 to 3.76, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should an age-dependent justification required prior to administration. It has also been suggested (although not

formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Schizophrenia

1) Risperidone is a benzisoxazole derivative. It is approved for the treatment of schizophrenia. It blocks both serotonin 5-HT(2) and dopamine D(2) receptors. It is effective in chronic schizophrenia for positive and negative symptoms with a response rate of 50% to 75% (Foster & Goa, 1998; Rossi et al, 1997; Smith et al, 1996). At doses of 8 milligrams or less risperidone is associated with a lower risk of extrapyramidal symptoms than conventional antipsychotics (Foster & Goa, 1998). Comparative efficacy with haloperidol and other conventional neuroleptics in schizophrenia has shown that risperidone has a significantly higher clinical response rate and allows for significantly less prescribing of anticholinergic medications (Davies et al, 1998; Bech et al, 1998; Luebbe, 1996). Risperidone has also shown some efficacy in psychotic disorders associated with dementia, HIV, levodopa, and other medical conditions. Refractory obsessive-compulsive disorder and refractory depressions have also been relieved by risperidone in select cases.

C) Bipolar Mania

1) Long-acting injection risperidone alone or in combination with lithium or valproate is approved for the maintenance treatment of bipolar I disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Oral risperidone alone or in combination with lithium or valproate is approved for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

D) Irritability associated with Autistic Disorder

1) Risperidone is approved for the treatment of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) In vitro studies have shown that risperidone acts primarily as a serotonin (5-HT2) and dopamine (D2) antagonist. It binds with highest affinity to serotonergic receptors. Risperidone also binds to alpha-1 and alpha-2 adrenergic and histamine H1 receptors, although with much less affinity. Dissociation from 5-HT2 and H1 receptors is slow; however, the drug rapidly dissociates from dopaminergic and alpha adrenergic receptors. The potency of risperidone as a dopamine D2 antagonist is less than that of haloperidol, and its 5-HT2 antagonist potency is greater than that of ritanserin. Risperidone interacts weakly or not at all with other receptor and neurotransmitter systems, including cholinergic receptors (Anon, 1991; Anon, 1993a; Gerlach, 1991; Leysen et al, 1988; Niemegeers et al, 1988).

2) Studies have shown that there is an exponential dose-response relationship between the daily dose of risperidone and the dopamine D(2) receptor occupancy (Dresel et al, 1998; Remington et al, 1998). The slope of the curve is between that of haloperidol and clozapine but more closely resembles haloperidol. One study did find that extrapyramidal effects were linked to D(2) occupancy with those individuals manifesting symptoms having the highest percentage of binding (Remington et al, 1998). The other study found no clear relationship between symptoms and D(2) occupancy. They hypothesized that the decreased incidence of extrapyramidal effects seen with risperidone is not due to the low binding at the D(2) receptor but to risperidone's high 5-HT(2) affinity providing a relative protection from symptoms (Dresel et al, 1998).

3) Animal studies have shown that risperidone inhibits tryptamine- and serotonin-induced cyanosis and 5-hydroxytryptophan-induced head twitching; it also blocks central and peripheral manifestations of dopaminergic stimulation, including apomorphine-induced emesis and apomorphine- or amphetamine-induced stereotypy or hypermotility (Anon, 1991; Megens et al, 1988). Risperidone is several times less potent than haloperidol in the inhibition of locomotion and induction of catalepsy; in addition, risperidone causes a significant increase in deep sleep, corresponding to the effect of ritanserin (Gerlach, 1991).

4) Potent alpha-2 adrenoceptor blockade has been demonstrated with risperidone, as it reverses clonidine inhibition of potassium-induced norepinephrine release in occipital cortex. It also exhibits complete and potent lysergic acid diethylamide (LSD) antagonism in animals (Anon, 1991; Leysen et al, 1988; Niemegeers et al, 1988).

B) REVIEW ARTICLES

1) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999)(Brown et al, 1993h), and children (Malone et al, 1999; Lewis, 1998; Toren et al, 1998) has been reviewed.

2) A pharmacoeconomic review of risperidone's use in schizophrenia has been published (Foster & Goa, 1998a).

3) Meta-analyses of risperidone versus haldoperidol's efficacy and safety (Davies et al, 1998) and cost-effectiveness (Davies et al, 1998a) have been published.

4) Risperidone's role in the treatment of schizophrenia has been reviewed by the American Psychiatric Association (Anon, 1997).

5) Risperidone controlled trials, clinical observations, and reports of side effects have been reviewed (Marder, 1996).

6) The Consensus Study Group on Risperidone Dosing has published guidelines on transitioning patients to risperidone (Bo-

rison et al, 1992a).
7) A review of new neuroleptics with emphasis on risperidone as a new prototype is published in the German literature (Moeller, 1996).
8) New generation neuroleptics in the treatment of patients with negative symptomology are reviewed in the German literature (Kurtz, 1996).
9) Risperidone is examined with respect to its clinical profile and its place in therapy; in the German literature (Tauscher et al, 1997).
10) A literary review rating the therapeutic actions of risperidone with a focus on negative symptomology, cognitive limits, and quality of life aspects is published in the German literature (Franz & Gallhofer, 1997).

4.5 Therapeutic Uses

4.5.A Agitation, acute - Psychotic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Olanzapine orally disintegrating tablets and risperidone oral solution yielded similar improvements on the Excited Component for Positive and Negative Syndrome Scale and the Clinical Global Impression scale in 87 patients treated for acute psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study(Hatta et al, 2008)
3) Adult:
a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvements on the Excited Component for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated for acute psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased over time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated measures of analysis of PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of treatment or in the interaction of treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in the olanzapine ODT group compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences between the treatment groups for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.5.B Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.C Autistic disorder - Irritability

FDA Labeled Indication
1) Overview
FDA Approval: Adult, no; Pediatric, yes (5 years and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category A
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Risperidone was more effective than placebo in improving the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in short-term (8 weeks), placebo-controlled studies (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets,

2006; McCracken et al, 2002); additionally, continued risperidone therapy maintained efficacy up to 6 months and led to lower relapse rates compared to placebo (McCracken et al, 2002).

Treatment with oral risperidone was well tolerated and more effective in improving autism symptoms compared to placebo in children in a randomized, double-blind study (n=40) (Nagaraj et al, 2006).

3) Pediatric:

a) Risperidone was more effective than placebo for the short-term treatment of severe behavioral problems in children with autism in a randomized, double-blind, placebo-controlled study (n=101). Patients (ages 5 to 17 years) with autism accompanied by serious behavioral problems (tantrums, aggression, or self-injurious behavior) received placebo (n=49) or risperidone 0.5 to 3.5 milligrams (mg)/day (n=52; mean dose during last week, 1.8 mg/day) for 8 weeks. Primary efficacy measures were the score at eight weeks on the Irritability subscale of the Aberrant Behavior Checklist and the rating on the Clinical Global Impressions-Improvement (CGI-I) scale. A positive response was defined as a 25% or greater reduction in the Irritability score and a rating of much improved or very much improved on the CGI-I scale. The mean Irritability score for the risperidone group decreased by 56.9% following 8 weeks of treatment as compared with a 14.1% reduction in the placebo group (p less than 0.001). The rate of positive response was significantly higher in risperidone-treated patients as compared with placebo (69% vs 12%, respectively; p less than 0.001). Risperidone was generally well tolerated and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism (McCracken et al, 2002). Among secondary endpoints, risperidone significantly decreased the overall score on the Ritvo-Freeman scale, which was modified from an observational measure to a parent rating scale and included subscales for assessing sensory motor behaviors, social relatedness, affectual reactions, sensory responses, and language (subscales I, II, III, IV, and IV, respectively). Specifically, significant treatment and time interactions were noted for subscales I (effect size, 0.45; p=0.002), III (effect size, 1.1; p less than 0.001), and IV (effect size, 0.77; p=0.004). There was no statistically significant effect on the subscales scores for social relatedness (subscale II) or language (subscale V). The mean +/- standard deviation Children's Yale-Brown Obsessive Compulsive scale score (modified to only assess the compulsion subscale; total score range, 0 to 20) decreased from a baseline score of 15.51 +/- 2.73 to 11.65 +/- 4.02 in the risperidone group compared to 15.18 +/- 3.88 at baseline to 14.21 +/- 4.81 in the placebo group. For the total Maladaptive Behavior Domain (measured using the Vineland Adaptive Behavior Scales, there was a significant treatment and time interaction during the 8-week trial (effect size, 1.03; p less than 0.001), with decreases from mean baseline scores of 33.26 and 33.51 to 7.93 and 8.87 for the risperidone and placebo groups, respectively (McDougle et al, 2005).

1) Long-Term Extension

a) In a 24-week extension of the aforementioned study that included a 4-month, open-label extension followed by an 8-week, blinded placebo-controlled discontinuation phase, continued risperidone therapy maintained efficacy for autism and led to lower relapse rates compared to the placebo group. Following 8 weeks of double-blind therapy in 101 patients, a total of 63 responders (mean age, 8.6 years) from both the risperidone and placebo groups received open-label risperidone for another 16 weeks; risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 milligrams (mg)/day in children weighing 15 to 45 kilograms (kg) and up to 4.5 mg/day for children weighing over 45 kg. Response was defined as at least 25% reduction on the irritability subscale of the Aberrant Behavior Checklist (ABC) and a rating of much improved or very much improved on the Clinical Global Impressions-Improvement (CGI-I) scale). Responders to the 4-month open-label extension therapy were randomized in a double-blind fashion either to continue risperidone at the same dose or to gradual placebo substitution (risperidone dose reduced by 25%/week) over 8 weeks and assessed for relapse (defined as a 25% increase in the ABC-Irritability (ABC-I) subscale score and a CGI-I scale rating of much worse or very much worse for at least 2 consecutive weeks). At the end of the 4-month, open-label extension, an intention-to-treat analysis revealed a minor but clinically insignificant increase in ABC-I score, going from a baseline (end of 8 weeks of initial therapy) mean +/- standard deviation (SD) score of 9.5 +/- 6.8 to 10.8 +/- 7.1. There was a significant time effect on the ABC-I scale at the end of the 4-month extension phase (p=0.02), Additionally, among 51 patients who completed the extension phase, 82.5% had a much improved or very much improved rating on the CGI-I scale. A preplanned interim analysis during the discontinuation phase revealed higher relapse rates in the placebo group compared to the risperidone group (62.5% (n=10) vs 12.5% (n=2); p=0.01), with a median time to relapse was 34 days and 57 days, respectively. This prompted early termination of the study (Research Units on Pediatric Psychopharmacology Autism Network, 2005). For secondary outcomes, improvements seen in the subscales I, III, and IV scores of the modified Ritvo-Freeman scale, the Children's Yale-Brown Obsessive Compulsive scale scores, and the total scores on the Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scales, after 8 weeks of initial therapy were maintained over the 4-month extension phase (McDougle et al, 2005).

b) Risperidone was more effective than placebo in improving the irritability symptoms of autism in an 8-week, placebo-controlled trial of children and adolescents with autistic disorder. Children (n=55; 5 to 12 years of age) with autistic disorder received placebo or risperidone 0.02 to 0.06 mg/kg/day once or twice daily, starting at 0.01 mg/kg/day (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day). Efficacy was evaluated using the Aberrant Behavior Checklist (ABC). The change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I) was the primary outcome measure.

This subscale evaluated the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Risperidone significantly improved scores on the ABC-I subscale compared with placebo (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

c) Treatment with oral risperidone was more effective in improving autism symptoms compared to placebo in children in a randomized, double-blind study (n=40). Consecutive children up to 12 years of age diagnosed with autism according to the DSM-IV criteria, with varying symptoms that included hyperactivity, aggression, stereotypies, and language difficulties were randomized to receive an oral suspension of either risperidone (initiated at 0.5 milligrams (mg)/day, increased to 1 mg/day 2 weeks later; n=19; mean age, 57.95 months) or placebo (n=20; mean age, 63 months) for 6 months. The primary efficacy measures were changes from baseline in the median Childhood Autism Rating Scale (CARS) and the mean Children's Global Assessment Scale (CGAS) scores at end of treatment. Among the study population, irritability was the most common autism symptom (92%). At endpoint, 63% (n=12/19) of children in the risperidone group showed an improvement of at least 20% from baseline CARS scores compared to none in the placebo group. Median CARS scores decreased from 39.5 (range, 32.5 to 46) at baseline to 32 (range, 24.5-40.5) at the end of treatment for the risperidone group compared to a decrease from 38.5 (range, 31.5-43 at baseline to 37.5 (30-42.5) at end of treatment for the placebo group (p less than 0.001). On the CGAS, significantly more patients in the risperidone group had improvements (ie, increase in CGAS score of at least 20% from baseline) compared to the placebo group (n=17 vs n=2). Mean CGAS scores increased from 29.79 and 32.65 at baseline in the risperidone and placebo groups, respectively, to 40.94 and 35.2, respectively, at the end of treatment (p =0.035). Among secondary endpoints, based on an internally-validated, 12-item parent questionnaire, risperidone improved functioning in domains of social responsiveness (n=7/19; p=0.014), nonverbal communication (n=8/19; p=0.008), decreased hyperactivity symptoms (n=7/19; p=0.002), and aggression and irritability (n=5/19; p=0.016). However, there were no significant improvements in the domains of restricted interests, emotional interaction, or verbal communication or speech. Overall, risperidone was well tolerated. Mild and transient dyskinesias occurred in 3 children. There was a nonstatistically significantly higher mean weight increase from baseline among risperidone-treated children (2.81 kilograms (kg; 17%) vs 1.71 kg (9.3%)) (Nagaraj et al, 2006).

4.5.D Behavioral syndrome - Dementia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved target symptoms of agitation, aggression, hallucinations, and delusions in demented elderly

Cerebrovascular adverse events (stroke, transient ischemic attack) have occurred in elderly individuals (mean age 85 years old) who received risperidone for treatment of dementia-related psychosis (Prod Info Risperdal(R), 2004)

Improved management of behavioral and psychological symptoms in elderly patients with dementia (De Deyn et al, 2005)

3) Adult:

a) Risperidone and haloperidol produced similar reductions in severity of behavioral symptoms, especially aggression, in elderly, demented patients (DeDeyn et al, 1999). In a double-blind, 12-week study, agitated patients (55 years and older) with Alzheimer's disease, vascular dementia, or a mixed dementia were randomized to receive risperidone (n=115), haloperidol (n=115), or placebo (n=114). Outcomes were assessed using the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Both medications were initiated at 0.25 milligrams (mg) daily and increased by 0.25 mg every 4 days up to 1 mg twice daily. If indicated, the patient's dose could be further increased to a maximum of 2 mg twice daily. At the end of 12 weeks mean doses were risperidone 1.1 mg/day and haloperidol 1.2 mg/day. Percent of patients having at least a 30% improvement at 12 weeks was similar at 72% for risperidone, 69% for haloperidol, and 61% for placebo (p not significant). However, risperidone showed significantly greater improvements in mean BEHAVE-AD total score at week 12 over placebo (p=0.05). Risperidone also had a significantly greater improvement than placebo and haloperidol in the BEHAVE-AD aggression cluster (p=0.002; p=0.05). Somnolence occurred in 18% of haloperidol patients, 12% of risperidone, and 4% of placebo patients.

b) In a retrospective chart review, demented patients treated with risperidone were shown to benefit from therapy in 56% of cases (Irizarry et al, 1999). Charts of patients with Alzheimer's disease, Lewy body dementia, or a mixed dementia who had received risperidone for behavior problems were reviewed. The average dose of risperidone used was 1.8 milligrams for a mean duration of 4 months. A complete response occurred in 15% of patients treated, 41% had a partial response, and 44% had no response. Approximately half of the patients experienced adverse effects including extrapyramidal symptoms in 32%, sedation in 17%, or worsening agitation in 7%.

c) In a case series of 22 patients with dementia and behavioral disturbances, risperidone in doses ranging from 0.5 milli-

grams (mg) every other day to 3 mg twice daily resulted in substantially improved behavior in 11 patients (50%). All patients met DSM-IV criteria for dementia; 14 patients with dementia of the Alzheimer's type, 6 with vascular dementia, and 2 with Lewy body dementia. The most frequently occurring target symptoms were agitation, aggression, hallucinations, and delusions. The mean dose of risperidone used was 1.5 mg per day. Using the Clinical Global Impression scale, 6 patients (27%) were rated as very much improved, 5 patients (23%) were rated as much improved and 6 patients (27%) were rated as minimally improved. Eleven patients (50%) experienced extrapyramidal symptoms and 3 patients discontinued therapy within the first two weeks due to side effects (Herrmann et al, 1998).

d) In a pooled analysis, risperidone therapy was superior compared to placebo in managing behavioral and psychological symptoms of dementia in elderly nursing home residents. The pooled data was from three randomized, placebo-controlled, double-blind, multicenter, parallel group, Phase III trials. The efficacy analysis was preceded by a one week single-blind washout period during which all other psychotropic medications were discontinued. Patients were then randomized to receive risperidone (n=722) or placebo (n=428) for 12 weeks at a dose range of 0.25 to 1 milligram (mg) twice daily. Overall, the demographics and baseline characteristics were similar with the majority of patients being women, Caucasian, and suffering from dementia for an average of 5 or more years. Agitation and aggressive behaviors were assessed using the Cohen-Mansfield agitation inventory (CMAI) scores. Risperidone produced significantly greater improvements compared to placebo in CMAI total scores from week 4 through week 12 (mean change from baseline to end point: -11.8 versus -6.4, respectively; p less than 0.001). Decreases in the total aggression and total non-aggression scores were also both statistically significant in favor of risperidone (p less than 0.001). The severity of behavioral and psychological symptoms associated with dementia were assessed using the rating scale for behavioral pathology in Alzheimer's disease (BEHAVE-AD). At all evaluation points, scores on the BEHAVE-AD total scale were significantly more improved with risperidone versus placebo (mean change from baseline to end point: -6.1 versus -3.6, respectively; p less than 0.001). The psychotic symptoms subscale of the BEHAVE-AD found that risperidone produced significantly greater improvements than placebo in patients with psychosis at baseline (mean change from baseline: -3.5 +/- 0.21 (n=434) versus -2.5 +/- 0.32 (n=252), respectively; p=0.003). The paranoid and delusional symptoms were significantly improved in the risperidone group compared to placebo (-1.7 versus -1; p less than 0.002). However, there was no significant difference between the groups regarding improvement in hallucinations (risperidone -0.4, placebo -0.3; p=0.191). The clinical global impression (CGI) scores were also significantly improved in the risperidone group versus the placebo group. A subgroup analysis on dementia type (Alzheimer's disease, vascular dementia and mixed dementia) found that the CMAI and BEHAVE-AD total scores were significantly improved in the risperidone group in both Alzheimer's disease and vascular dementia, but not in the mixed dementia subjects. Treatment-emergent adverse events were comparable between risperidone (84.3%) and placebo (83.9%). However, the number of patients who discontinued therapy due to treatment-emergent adverse events was higher in the risperidone treated group (16.7%) versus placebo (11.2%). Common adverse events leading to discontinuation in the risperidone group were somnolence, agitation, extrapyramidal disorders, aggressive reaction, pneumonia, injury, cerebrovascular disorder, and fall (De Deyn et al, 2005).

4.5.E Behavioral syndrome - Mental retardation

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone moderately improved aberrant behavior in adults with mental retardation compared with placebo in a 4-week, randomized, double-blind, placebo-controlled study (n=77) with continued improvement over 48 weeks in an open-label, extension study (n=58) (Gagiano et al, 2005)

A post hoc analysis (n=163) of two, 6-week, multicenter, double-blind, placebo-controlled studies demonstrated reduced aggression scores after treatment with risperidone in boys with below normal intelligence and either conduct disorder (CD) or oppositional defiant disorder (ODD) with or without attention-deficient hyperactive disorder (LeBlanc et al, 2005).

In a 1-year, open-label, multicenter, multinational, trial (n=504), risperidone moderately improved behavior and cognitive function in children with disruptive behavior disorders and borderline intellectual functioning or mild to moderate mental retardation (Croonenberghs et al, 2005).

Risperidone was safe and effective as a short- and long-term therapy (48 weeks) for the reduction of severe behavior problems in children with mild or moderate intellectual disabilities; below average intelligence; and a diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified, in a 6-week, randomized, double- blind, placebo controlled study (Findling et al, 2004; Aman et al, 2002).

3) Adult:

a) Risperidone moderately improved aberrant behavior in adults with mental retardation compared with placebo in a 4-week, randomized, double-blind, placebo-controlled study (n=77). Adults (18 to 65 years of age) with conduct disorder, oppositional defiant disorder, antisocial personality disorder, disruptive behavior disorder, or intermittent explosive disorder and borderline intellectual functioning or mild to moderate mental retardation (Wechsler or Stanford-Binet Intellectual Quotient of 35 to 84) were randomized to risperidone (n=39) or placebo (n=38). The initial oral dose was 0.5 milligrams/day (mg/day) on days 1 and 2, 1 mg/day on day 3, and based on response the dose could be increased by 1 mg/day at weekly intervals up to a maximum of 4 mg/day. The dose was reduced if movement disorders developed and anticholinergic drugs could be started if the movement disorders persisted. Other medications allowed were antidepressants, lithium, carbamazepine, and valproic acid. The primary efficacy endpoint was the change from baseline in the total Aberrant Behavior Checklist (ABC) score at 4 weeks. The mean risperidone dose was 1.45 +/- 0.08 mg/day (range, 1 to 4 mg/day). Concomitant anti-psychotropic drugs were used in 53.8% and 65.8% of the risperidone- and placebo-treated patients, respectively. Baseline total ABC scores were 51.7 +/- 4.2 and 47.6 +/- 3.5 for the risperidone- and placebo-treated patients, respectively. The risperidone-treated group experienced a 52.8% improvement compared with a 31.3% improvement (-27.3 +/- 3.3 vs -14.9 +/- 4; p=0.036) in total ABC score at 4 weeks. Improvement was noted at 2 weeks (p less than or equal to 0.07). The mean change from baseline ABC irritability subscale improved significantly compared with placebo (p less than or equal to 0.05) but the other subscales of lethargy/social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech did not improve compared with placebo. Behavior Problems Inventory (BPI) subscale of stereotypical behavior improved at week 4 for risperidone compared with placebo (-0.8 +/- 0.4 vs -0.2 +/- 0.3, respectively, p less than 0.05); however, other subscales of BPI (total score and self-injurious behavior, aggressive/destructive behavior) did not improve compared with placebo. Responder rates (response defined as not ill, very mildly ill, or mildly ill) based on the Clinical Global Impressions-Severity scale were 45.8% and 25%, respectively. The most disturbing behaviors identified by caregivers were aggressive behavior, which improved on the visual analog scale for the risperidone compared with the placebo group (-31.3 vs - 12.8, respectively, p less than 0.001). Risperidone- and placebo-treated patients experienced somnolence (23.1% vs 15.8%, respectively), injury (17.9% vs 13.2%, respectively), and headache (12.8% vs 7.9%, respectively). Mild movement disorders were reported in 3 risperidone-treated and 4 placebo-treated patients. Extrapyramidal Symptom Rating Scale (ESRS) did not increase for either the risperidone or placebo group. The median weight gain was 1 kilogram for the risperidone group and 0 kg for the placebo group (Gagiano et al, 2005).

1) Behavior continued to improve over 48 weeks in an open-label, extension, study (n=58). From the above double-blind study, 31 on placebo and 27 on risperidone chose to continue for another 48 weeks on risperidone. The mean modal dose of risperidone was 1.81 +/- 0.13 milligrams/day. For all patients the total Aberrant Behavior Checklist (ABC) score decreased by 9 points from baseline to endpoint (p=0.012). ABC subscales significantly decreased (p less than or equal to 0.001 compared with double-blind baseline) by 10.7 +/- 1.5 for irritability, 3.3 +/- 0.9 for lethargy/social withdrawal, 0.8 +/- 0.2 for stereotypic behavior, 10.4 +/- 1.5 for hyperactivity, and 2.4 +/- 0.4 for inappropriate speech. Responder rates (response defined as not ill, very mildly ill, or mildly ill) based on the Clinical Global Impressions-Severity scale increased to 64.7% after 1 month and to 76.7% at endpoint. The most disturbing behaviors identified by caregivers were aggressive behavior, which went from a mean baseline visual analog score of 47.1 +/- 3.6 to 28.2 +/- 3.5 at endpoint. Cognition did not change over the 48 weeks as measured by the Cognition measured by Continuous Performance Task (CPT) and a modified version of the California Verbal Learning Test-Adult Version. Extrapyramidal Symptom Rating Scale (ESRS) or any of the ESRS subclusters did not increase between baseline and endpoint. One patient developed tardive dyskinesia, which resolved without sequelae after risperidone was stopped. The overall mean weight increase from baseline to 48 weeks was 3.8 +/- 0.6 kilograms (p less than or equal to 0.001) (Gagiano et al, 2005).

b) In one double-blind, placebo-controlled crossover study, 37 patients with behavioral abnormalities such as hostility, aggressiveness, irritability, agitation, hyperactivity, automutilation, and autism despite current therapy improved on risperidone versus placebo. The medications were given orally for 3 weeks, followed by 3 weeks of crossover treatment. Doses of risperidone were initially 2 milligrams twice a day; at weekly evaluations, daily dosage was increased by 4 mg/day up to a maximum total dose of 12 mg/day if no improvement in Clinical Global Impression (CGI) scores occurred. Risperidone caused significant improvement in CGI parameters throughout the duration of the study; placebo was not effective. No extrapyramidal symptoms occurred. No significant cardiovascular, biochemical, or urinalysis changes were reported (Vanden Borre et al, 1993a).

4) Pediatric:

a) A post hoc analysis (n=163) of two, 6-week, multicenter, double-blind, placebo-controlled studies demonstrated reduced aggression scores after treatment with risperidone in boys with below normal intelligence and either conduct disorder (CD) or oppositional defiant disorder (ODD) with or without attention-deficient hyperactive disorder. The 2 placebo-controlled studies (n=288) enrolled male and female patients, aged 5 to 12 years, with a diagnosis of CD, ODD, or disruptive behavior disorder not otherwise specified, who had a parent/caregiver-assessed rating of 24 or more on the conduct problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF); mild mental retardation, moderate mental retardation, or borderline intellectual functioning (intelligence quotient (IQ) of 36 to 84); and a Vineland Adaptive Behavior Scale score of 84 or less. The patients were randomized to either placebo or risperidone with starting oral doses of 0.01 milligrams/kilogram/day (mg/kg/day) and titrating to response up to a maximum of 0.06 mg/kg/day for a total of 6 weeks. The

post hoc analysis was limited to boys with a diagnosis of CD or ODD who were subsequently assessed by an aggression score (AS) using 6 core aggression items from the N-CBRF. The mean age of the boys was 8.5 years and IQ of low-normal intellectual functioning to moderate mental retardation. The daily dose of risperidone over the 6-weeks was 0.04 mg/kg/day (range, 0.01 to 0.06 mg/kg/day) and the mean duration was 38.7 days (range, 1 to 49 days). At 6-weeks, the AS was 4.5 +/- 4.3 compared with 10.1 +/- 4.1 at baseline in boys treated with risperidone. At 6-weeks, the AS for placebo-treated boys was 8.3 +/- 5 compared with 10.6 +/- 3.9 at baseline. Boys with higher AS at baseline had greater responses than those with lower AS at baseline (LeBlanc et al, 2005).

b) In a 1-year, open-label, multicenter, multinational, trial (n=504), risperidone moderately improved behavior and cognitive function in children with disruptive behavior disorders and borderline intellectual functioning or mild to moderate mental retardation. Children (5 to 14 years old) with conduct disorder, oppositional defiant disorder, or disruptive behavior disorder; a score of 24 or more on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF); mild mental retardation, moderate mental retardation, or borderline intellectual functioning (intelligence quotient (IQ) of 36 to 84); and a Vineland Adaptive Behavior Scale score of 84 or less received risperidone once daily in the morning or afternoon. The initial oral dose was 0.01 milligrams/kilograms/day (mg/kg/day) on days 1 and 2, 0.02 mg/kg/day on days 3, with subsequent dose increases based on response at weekly intervals not to exceed 0.02 mg/kg/day increases and a maximum dose of 0.06 mg/kg/day. Doses could be reduced if extrapyramidal symptoms (EPS) developed and an anticholinergic could be used for persistent EPS. The only psychotropic medications allowed were psychostimulants for attention-deficit/hyperactivity disorder as long as a constant dose in the previous 30 days was used and for premedication with benzodiazepines for medical procedures. Sleep and anxiety medications were not allowed. At baseline, the median age was 10 years (4 to 14 years) with a primary diagnosis of conduct disorder (45%) or oppositional defiant disorder (36%) with or without attention deficit hyperactivity disorder. The mean IQ was 64.2 +/- 13.4 and the mean Vineland Adaptive Behavior Scale score was 52.7 +/- 13.4. The median dose was 1.5 mg/day (range, 0.1 to 4.3 mg/day) with a mean duration of 307.3 +/- 5 days. Fourteen percent of the patients were on concomitant methylphenidate. At 1 year, the mean changes in the modification of the children's version of the California Verbal Learning Test (MCVLT-CV) were 0.7 +/- 0.1 for total long delay-free recall, 2.9 +/- 0.4 for the total short delay-free recall, and 0.7 +/- 0.2 for total correct (each p less than 0.001 compared with baseline). For the Continuous Performance Task easy and hard tests the mean change scores were 1.6 +/- 0.3 and 1.6 +/- 0.4, respectively for total hits; -2.9 +/- 0.6 and -4.2 +/- 0.7, respectively, for total false alarms; and -1.5 +/- 0.3 and -1.4 +/- 0.4, respectively, for total misses (each p less than 0.001 compared with baseline). The mean N-CBRF score decreased from 32.9 +/- 7.5 to 17 +/- 11 at 1 year, representing a mean change of -15.8 +/- 0.5 (p less than 0.001). Improvements were demonstrated as early as 1 week. The subscales of N-CBRF (compliant/calm, adaptive/social, insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive all significantly improved (p less than 0.001). At baseline, 72% of patients had marked to extremely severe symptoms based on the Clinical Global Improvement Severity scale compared with 12% at 1-year. Sixty-six percent were rated as not ill or having mild symptoms. At baseline, the mean aberrant Behavior Checklist total scores were 64.3 +/- 25 compared with 37.4 +/- 27 at 1-year representing a 28.3 +/- 1.4 decrease from baseline (p less than 0.001). The visual analog scale scores of the most troublesome symptoms (aggression, oppositional defiant behavior, and hyperactivity) improved by 40.3 +/- 1.3 from baseline (p less than 0.001). In general, adverse events were mild or moderate with the most common being somnolence (30%), rhinitis (27%), and headache (22%). At month 12, the mean Extrapyramidal Symptom Rating Scale total score changes from baseline was -0.4+/-0.2 (p less than 0.001). Antiparkinsonian medications were necessary in 5 patients (1%) and EPS led to discontinuation in 6 patients (1%). Tardive dyskinesia, which resolved after stopping risperidone, was experienced in 2 patients. Prolactin elevation in 32 patients (6.4%) may have resulted in adverse events. Mild to moderate gynecomastia was experienced in 22 boys and 3 girls. Other possible prolactin-related events, most of which were mild and resolved after risperidone discontinuation, were menstrual disturbances (6 patients) and galactorrhea (1 patients). Mean body weight increased by 7 +/- 2.1 kilogram (p less than 0.001) in children, half of this weight gain could be attributed to expected growth. Normal sexual maturation was observed (Croonenberghs et al, 2005).

c) Risperidone was safe and effective as a short- and long-term therapy for the reduction of severe behavior problems in children with mild or moderate intellectual disabilities. In a 6-week, randomized, double- blind, placebo controlled study, patients (ages 5 to 12 years) with below average intelligence (IQ, 36 to 84) and a diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified received placebo (n=63) or risperidone (n=55) 0.02 to 0.06 milligrams (mg)/kilogram/day (mean dose, 1.16 mg/day). Efficacy of risperidone was assessed according to the change in score from baseline to endpoint on the conduct problem subscale of the Nisonger Child Behavior Rating Form. Patients treated with risperidone showed a significantly larger reduction in mean conduct problem subscale scores from baseline to endpoint as compared with placebo (-15.2 vs -6.2, respectively; p less than 0.001). Risperidone- treated patients also showed significantly better improvements than did placebo-treated patients on all other subscales of the Nisonger Child Behavior Rating Form. Risperidone was generally well tolerated and most adverse effects were mild to moderate, including somnolence (51%) and headache (29%). As a long-term, open-label extension, 107 patients from this controlled study received risperidone (initial, 0.01 mg/kg/day, titrated up to maximum of 0.06 mg/kg/day; mean dose 1.51 mg/day) for 48 weeks. Throughout the 48-week extension, symptom improvement was maintained in patients treated with risperidone during the controlled trial and significant symptom improvement was observed in patients

who had received placebo during the controlled trial. Risperidone was generally well tolerated throughout the extension phase of the trial. Adverse events included headache (32.7%), somnolence (32.7%), rhinitis (28%), increased appetite (9.3%), weight gain (20.6%; mean increase from baseline, 5.5 kilograms), and transient, mild elevations in prolactin levels (mean maximum level, 27.6 nanograms/milliliter (ng/mL) in boys; 23.9 ng/mL in girls). Additional studies are needed to investigate the safety and efficacy of risperidone therapy beyond 1 year for the treatment of severe, disruptive behavior in pediatric patients (Findling et al, 2004; Aman et al, 2002).

4.5.F Bipolar I disorder

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (10 years and older, oral only)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Intramuscular long-acting risperidone is indicated as monotherapy or in combination with lithium or valproate for the maintenance treatment of bipolar I disorder in adults (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

Oral risperidone is indicated for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in children aged 10 years of age and older and adults (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

Oral risperidone, at doses ranging from 0.5 to 6 milligrams per day for 3 weeks, was effective in the treatment of acute manic or mixed episodes of bipolar I disorder in children aged 10 to 17 years in a multicenter, randomized, double-blind, placebo-controlled trial (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Adult:

a) Monotherapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV diagnostic criteria for bipolar disorder type I and who were stable on medications or experiencing an acute manic or mixed episode, long-acting intramuscular (IM) risperidone was effective for the maintenance treatment of bipolar I disorder. During a 26-week open-label period, a total of 501 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up if clinically desirable (or 12.5 mg in patients not tolerating the starting dose). Of the 501 treated patients, 303 (60%) were deemed to be stable and were randomized to double-blind treatment with either the same dose of IM risperidone or placebo. The results of the study showed that when compared to placebo, patients receiving monotherapy IM risperidone were delayed to reaching the study primary endpoint, which was the time to relapse to any mood episode (depression, mania, hypomania, or mixed). The majority of relapses were due to manic rather than depressive symptoms and based on their history of bipolar disorder, these patients had, on average, more manic episodes than depressive episodes (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral

a) Risperidone monotherapy was effective in the acute and continuation treatment of mania in patients with bipolar disorder. In an open- label, multicenter study, patients with acute mania and a score of at least 20 on the Young Mania Rating Scale (YMRS) received six months of risperidone monotherapy at a mean dose of 4.2 milligrams (mg) daily (range 1.5 to 4.5 mg/day). Significant improvements in the YMRS score were observed from baseline to weeks 1, 2, 4, 6, 12, and 24 (p less than 0.0001). Additionally, improvements in Clinical Global Impression and Positive and Negative Syndrome Scale scores were significant from week 4 onward as compared with baseline (p less than 0.0001). Extrapyramidal symptoms (ie, dystonia, hypokinesia) were significantly increased by week 4 (p=0.015) (correlating with the highest mean doses of risperidone), but then decreased significantly by study endpoint (p=0.027). Other adverse events included impotence, drowsiness, weight gain (mean increase, 3.2 kilograms), restlessness, dizziness, hypotension, incontinence, and galactorrhea. Within the initial 4 weeks of treatment, increased severity of manic symptoms was seen in four patients (4.2%) and the appearance of a depressive episode was observed in seven patients (7.3%). Randomized, controlled studies are needed to confirm the safety and efficacy of risperidone monotherapy for the long-term treatment of bipolar mania (Vieta et al, 2004).

b) In two placebo-controlled trials, risperidone monotherapy was more effective than placebo in reducing manic symptoms in patients with bipolar disorder. Patients meeting DSM-IV criteria for bipolar I disorder with manic or mixed episodes and with or without psychotic features received risperidone (1 to 6 milligrams (mg)/day; mean modal dose, 4.1 to 5.6 mg/day) or placebo for 3 weeks (n=246; n=286). In both trials, risperidone was more effective than placebo

in the reduction of the Young Mania Rating scale (YMRS) scores of these patients (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV diagnostic criteria for bipolar disorder type I and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12 months and at least 2 episodes in the 6 months prior to starting the trial, long-acting intramuscular (IM) risperidone was effective for bipolar I disorder when used as combination therapy with lithium or valproate. During a 16-week open-label period, a total of 240 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up if clinically desirable (or 12.5 mg in patients not tolerating the starting dose) in addition to continuing their usual bipolar disorder therapy with all oral antipsychotics discontinued after the first 3 weeks of the initial injection of IM risperidone. Of the 240 treated patients, 124 (51.7%) were deemed to be stable for at least the last 4 weeks and were randomized to double-blind treatment with either the same dose of IM risperidone or placebo in addition to their usual bipolar disorder therapy for 52 weeks. The results of the 52-week study showed that when compared to placebo, patients receiving IM risperidone as combination therapy were delayed to reaching the study primary endpoint, which was the time to relapse to any new mood episode (depression, mania, hypomania, or mixed) compared to placebo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral

a) The efficacy of risperidone as a combination therapy for the treatment of manic or mixed episodes associated with bipolar disorder was established in one controlled trial, while a second controlled trial failed to show efficacy. In a randomized, controlled, combination trial, patients (n=148) on lithium or valproate therapy (therapeutic range, 0.6 to 1.4 mEq/L or 50 to 125 mcg/mL, respectively) with bipolar I disorder with or without psychotic features and with inadequately controlled manic or mixed symptoms received risperidone (1 to 6 mg/day; mean modal dose, 3.8 mg/day), an active comparator, or placebo in combination with their original therapy. Combination therapy with adjunctive risperidone was more effective than lithium or valproate alone in the reduction of the YMRS total score. However, in a second combination trial in 142 patients on lithium, valproate, or carbamazepine with inadequately controlled manic or mixed symptoms, the addition of risperidone (1 to 6 mg/day; mean modal dose, 3.7 mg/day) was not superior to lithium, valproate, or carbamazepine (therapeutic range, 0.6 to 1.4 mEq/L, 50 to 125 mcg/mL, or 4 to 12 mcg/mL, respectively) alone in the reduction of the YMRS total score. The failure of this trial could be due to induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Risperidone (median modal dose of 4 milligrams) may be more effective in the treatment of manic episodes associated with bipolar disorder than placebo when combined with mood stabilizing drugs. Bipolar patients, aged 18 to 65 years of age, presenting with a manic or mixed episode and a score of at least 20 on the Young Mania Rating Scale (YMRS) were enrolled in a 3-week, double-blind, placebo-controlled study. To be eligible for this study the patient also had to be taking a mood stabilizer (lithium, divalproex or carbamazepine) for a minimum of 2 weeks prior to randomized assignment into treatment groups. The primary efficacy measure was the change in YMRS score from baseline to endpoint. There was a decrease of 14.5 and 10.3 points on the YMRS score for the risperidone and placebo groups, respectively, at the end of the 3 weeks (p=0.089). Risperidone was equally effective in patients with or without psychotic features. When combined with carbamazepine, risperidone median dose-normalized plasma concentrations decreased by 40%. Due to a high number of dropouts in both groups the study was inadequately powered to determine the true treatment effects. Additional studies are ongoing (Yatham et al, 2003).

c) Risperidone was associated with significantly greater improvement compared with placebo. A multisite, double-blind, parallel-group study investigated adding risperidone, haloperidol, or placebo to a mood stabilizer (lithium or valproate) in 158 patients with acute mania. After completing the 3 week, double-blind phase of the study, patients were offered open-label risperidone therapy for an additional 10 weeks of follow-up. Improvement on the Young Mania Rating Scale and the Clinical Global Impressions-Improvement scale was greater with risperidone at 3 weeks. The investigators concluded that risperidone is a safe and effective addition to lithium or valproate for the treatment of bipolar mania (Ghaemi & Sachs, 1997).

d) An improvement was seen in all patients who completed another small, 6-week, open label study, which evaluated risperidone (mean dose, 3 mg per day) and concurrent mood-stabilizing drugs in the treatment of acute psychotic mania. Eight patients were enrolled and by week 6, all of the completers had a 50% improvement as assessed by the Young Mania Rating Scale (Tohen et al, 1996).

e) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorder and schizoaffective disorder, bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorder who were in a manic, hypomanic, depressive, or mixed episode (n=541; 430 completed the study) were given risperidone in combination with lithium, anticonvulsants, and antidepressants to clinical response and tolerability. The aver-

age dose of risperidone at the start of the study was 4 milligrams (mg) per day and at the end of the study, 3.9 mg/day. For all patients, scores on the Young Mania Rating Scale (YMRS) were significantly reduced at week 1 and at every point thereafter (p less than 0.001 for all but the subgroup of depressed patients, for whom p was less than 0.05). Mean scores on the YMRS decreased from 25.6 at baseline to 2.4 at 6 months. Likewise, scores on the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced from baseline at all evaluation times (p less than 0.0001), with scores declining from 12.8 at baseline to 4.1 at 6 months. Scores on the Positive and Negative Syndrome Scale (PANSS) declined from 72 at baseline to 40 at 6 months (p less than 0.0001). According to the Clinical Global Impressions scale (CGI), no patients were free from symptoms at baseline and only 5% were rated as "mildly ill." At study endpoint, 44% of patients showed no symptoms of mania or depression and a further 30% were "mildly ill." During the study, 25% of the patients experienced relapses into a mood state different from that at the start of the trial. Scores for extrapyramidal symptoms were lower at the end of study than at baseline (p less than 0.0001). There were significant reductions in dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia subscores. There were no cases of new-emergent tardive dyskinesia. Nonextrapyramidal adverse reactions included increase in weight (2.4% of patients), drowsiness (1.3%), impotence (0.7%), and dysarthria (0.7%). There was a very low incidence of exacerbation mania in the first 6 weeks (1.8%) (Vieta et al, 2001).

f) Long-term use of adjunctive risperidone for breakthrough episodes of mania or depression was reported useful in a small open study. A group of outpatients (n=12) with bipolar disorder type I, who experienced breakthrough episodes despite adequate maintenance medication, were treated with a mean dose of 2.75 mg per day of risperidone. Scores on the Global Assessment of Functioning scale improved from 10 to 25 points in 4 of the 8 patients who completed 6 months of treatment. No patient experienced worsening of mania (Sachs G, 1999).

g) In an open study, 10 patients with rapid cycling bipolar disorder (type I or type II) improved with risperidone therapy (Vieta et al, 1998). Patients were allowed to continue thyroid medications and benzodiazepines but had all antidepressants and antipsychotics discontinued. Risperidone was started at 1 milligram twice daily and titrated as needed. After 6 months patients had a decrease from 5.5 affective episodes during the previous 6 months to 2 episodes while receiving risperidone (p less than 0.02). Mean Hamilton Rating Scale for Depression scores also decreased from 14 to 6.

h) Open studies using risperidone 1 to 6 milligrams as adjunct therapy in the treatment of refractory bipolar disorder has shown some efficacy. In one study, 9 out of 14 patients were rated as much improved on the Clinical Global Impression (CGI) rating scale. Among the other 5 patients, 3 stopped due to ataxia and dizziness or weight gain and 2 experienced no change in mood (Ghaemi et al, 1997). In another study, 4 of 7 patients had a mild to moderate improvement on the CGI rating scale, and 3 patients had no change after therapy (McIntyre et al, 1997). A controlled trial is needed to establish the benefits of risperidone for bipolar disorder.

4) Pediatric:

a) Monotherapy

1) In a multicenter, randomized, double-blind, placebo-controlled trial, oral risperidone, at doses ranging from 0.5 to 6 milligrams (mg) per day, was effective in the treatment of mania in children aged 10 to 17 years. Patients who were experiencing a manic or mixed episode of bipolar I disorder were randomized to receive either risperidone 0.5 to 2.5 mg/day (n=50; mean modal dose, 1.9 mg), risperidone 3 to 6 mg/day (n=61; mean modal dose, 4.7 mg), or placebo (n=58) for 3 weeks. Risperidone was initiated at 0.5 mg/day and titrated up to the target dose by day 7, with further increases to the maximum tolerated dose by day 10. Compared to placebo, both risperidone dose groups showed a significant reduction from baseline in the total Young Mania Rating Scale (YMRS) score. The YMRS score reductions seen in the 3 to 6 mg/day dose group were comparable to those seen in the 0.5 to 2.5 mg/day dose group, with no additional benefit evident at doses higher than 2.5 mg/day. Adverse events reported at a higher incidence than placebo in both risperidone groups included fatigue (18%-30%), dizziness (13%-16%), dystonia (8%-13%), abdominal pain (15%-18%), nausea (13%-16%), vomiting (10%-12%), somnolence (42%-56%), and abnormal vision (4%-7%) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) In a case series including 11 children and adolescents aged 5 to 16 years with difficult to manage mood disorders (suggestive of bipolar disorder) and aggressive behavior, 8 had therapeutic responses to risperidone 0.75 to 2.5 milligrams (mg) daily. The patients and symptoms were clinically very diverse and most were taking concurrent medications, such as mood stabilizers. No standardized psychometric instruments were used for assessment, so improvement was purely subjective. Seven patients were considered to have marked improvement and one patient was considered moderately improved. Side effects reported included sedation, weight gain and anxiety (Schreier, 1998).

4.5.G Borderline personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Has reduced aggressive behavior and hostility in patients with borderline personality disorder

3) Adult:

a) Treatment with risperidone was associated with improvement in aggression, mood, and anergy in 13 patients with borderline personality disorder. In an 8-week open label study, patients were given risperidone, starting at 1 milligram (mg) per day and increasing on an individual basis to a maximum of 4 mg/day. The average final dose was 3.27 mg/day. Scores on the Brief Psychiatric Rating Scale (BPRS) were reduced by an average of 21% (p=0.003), with improvements specifically on the anergia scale (p=0.0033) and the hostility and suspicion scale (p=0.0144). Depression was reduced (p=0.0025) and, according to the self-rated Aggression Questionnaire, aggressive behavior was reduced by 18% (p=0.0057). Four patients experienced insomnia and 3 experienced agitation. Somnolence, anxiety, and headache were each reported by 2 patients (Rocca et al, 2002).

b) A 31-year-old woman with comorbid borderline personality disorder and dysthymia was successfully treated with the addition of risperidone (Szigethy & Schulz, 1997). She had been hospitalized 5 times and had failed therapy with fluoxetine, sertraline, trifluoperazine, and perphenazine. She had been maintained on fluvoxamine but after an exacerbation of symptoms, risperidone 1 milligram/day was added. She sustained improvement over the next 3 months. Risperidone was increased and a fluvoxamine taper was unsuccessfully initiated. With the resumption of fluvoxamine she was again able to return to her full-time job.

c) A 31-year-old woman was successfully treated with risperidone for her extreme impulsivity associated with self-mutilation and borderline personality disorder (Khouzam & Donnelly, 1997). After being refractory to multiple antipsychotics, antidepressants, methylphenidate, lithium, carbamazepine and valproate, she went into remission on risperidone 4 milligrams daily.

4.5.H Catatonia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
One case report documents the successful use of risperidone for catatonia

3) Adult:

a) A 47-year-old man with persistent organic catatonia responded to risperidone 4 milligrams twice daily therapy after unsuccessful treatment with psychotherapy and pharmacologic therapy that included antidepressants, lithium carbonate, and various antipsychotic agents (Cook et al, 1996).

4.5.I Cocaine dependence

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Risperidone is not effective in reducing cocaine use
Risperidone reduced craving and relapses in cocaine-dependent patients with schizophrenia

3) Adult:

a) Cocaine Dependence Only

1) There was no reduction in cocaine use associated with risperidone. A 12-week, randomized, double-blind, placebo-controlled trial evaluated using risperidone for the treatment of cocaine dependence. Cocaine-dependent subjects (n=193) initially received placebo or 4 or 8 mg of risperidone, with a subsequent change to active doses of 2 mg and 4 mg. Subjects attended the clinic twice each week, provided urine samples, obtained medication, and underwent one

behavioral therapy session per week. The study was terminated at the interim analysis. Retention was worse for the 4 and 8 mg medication groups. Side effects were primarily associated with the 8 mg dose, although neither the 2 nor 4 mg dose was well accepted by subjects. Risperidone is unlikely to find broad acceptance for use in treating cocaine dependence (Grabowski et al, 2000).

b) Schizophrenia With Concomitant Cocaine Dependence

1) The results of a pilot study suggest that risperidone therapy reduced craving and relapses in cocaine-dependent patients with schizophrenia. In this 6-week, open label trial, patients with a dual diagnosis of schizophrenia and cocaine dependence (6 grams or more of cocaine/month) received risperidone (n=8; initial, 2 milligrams (mg)/day, titrated to maximum dose of 6 mg/day) or continued typical neuroleptic medication treatment (n=10; haloperidol, fluphenazine, or chlorpromazine). Patients in the risperidone group had significantly less cue reactivity in regard to the intensity (p=0.005) and depression (p=0.031) dimensions of craving as compared with conventional therapy, but there was no statistical difference on the energy and feeling sick dimensions. Risperidone-treated patients also had a significantly lower rate of relapse (defined as any substance abuse) than did patients on typical neuroleptic therapy (12.5% vs 70%, respectively; p=0.025). Although not significant, a tendency toward a greater reduction in negative and global symptoms of schizophrenia was seen in risperidone-treated patients. Larger, double-blind studies are needed to substantiate these findings (Smelson et al, 2002).

4.5.J Cognitive function finding

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone-treated patients have shown some positive results in their neurocognitive abilities

3) Adult:

a) In a small randomized study (n=13), risperidone demonstrated an advantage over haloperidol for improving neurocognitive functioning (Addington & Addington, 1997). Patients received either risperidone or haloperidol over a 6 week period. There was improvement for risperidone subjects on executive functioning (Wisconsin Card Sorting Test), on a measure of sustained attention (Continuous Performance test), and on delayed verbal recall.

b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatment-resistant schizophrenic patients than did haloperidol therapy (Green et al, 1997a). In a randomized, double-blind comparison of treatment with risperidone (n=30) and haloperidol (n=29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose and flexible dose regimen. Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from baseline performance at both the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated patients did not change significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on neurocognitive abilities.

c) Risperidone improved neuropsychological impairment in withdrawn cocaine-dependent patients (Smelson et al, 1990). In an open design, patients received either risperidone 2 to 4 milligrams or no drug. Neuropsychological testing was done before therapy and after 7 days. The group receiving risperidone showed improvement in the Digit Symbol test (p less than 0.01), the Trails Part A (p less than 0.001), and the Grooved Peg Board dominant (p less than 0.003) and nondominant tests (p less than 0.06). No difference was found in the other group.

4.5.K Delusional disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone has been effective in the treatment of delusional disorder in case reports and open trials
Risperidone was effective treatment of monosymptomatic hypochondriacal psychosis

3) Adult:

a) Risperidone reduced most delusional parameters in a 50-year-old female with persecutory delusions (Fear & Libretto,

2002). Previous treatment with sulpiride, 200 to 800 milligrams (mg) daily, produced side effects and resulted in patient noncompliance. In this case study, the patient was originally part of a 24-week, double-blind, randomized, placebo-controlled, crossover trial (1 to 4 mg oral risperidone daily vs placebo) with 4 participants; all other participants dropped out of the study. A collaborative approach was used to ensure patient participation in the study. In this approach the delusions are not challenged from the outset. The certainty with which the patient held beliefs did not change, but these beliefs were qualitatively different; the persecution had happened in the past, but was not currently happening. Assessment tools used were the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) and the Maudsley Assessment of Delusions Schedule (MADS). During the placebo phase (weeks 0 to 11) there was no change in delusional condition. After trial crossover (weeks 12 to 24), the patient received 2 weeks of 1 mg risperidone, which was then titrated to 2 mg according to response. Four weeks after trial crossover, MADS results indicated improvement in delusional condition had begun; substantial improvement was noted after 2 months of risperidone treatment. The final trial dose was 2 mg of risperidone at night. By the end of the 24-week trial, efficacy assessments indicated a marked reduction or absence of delusions, suspicions, anxiety, tension, and depression.

b) Risperidone eliminated or reduced delusions of theft in 17 of 18 patients treated for 12 weeks in an open-label study. The change in burden on the caretaker was evaluated for 16 of the responding patients. The mean daily risperidone dose for those 16 responders was 1.06 milligrams. There were significant reductions in Neuropsychiatric Inventory (NPI) scores for delusion (p less than 0.000), agitation/aggression (p=0.002), anxiety (p=0.017), irritability/lability (p=0.023), and aberrant motor behavior (p=0.011) with risperidone treatment. Scores on the Zarit Caregiver Burden Interview (ZBI) dropped from 41 at the start of the study to 23 at 12 weeks (p less than 0.001) (Shigenobu et al, 2002).

c) An 81-year-old male presented with tactile hallucinations and DELUSIONS OF INFESTATION at which time risperidone therapy was initiated and started gradually. The patient was asymptomatic 3 months later. After 9 months he returned with extrapyramidal side effects with haloperidol that had been prescribed by another physician. Haloperidol was discontinued and low dose risperidone was started. One month later his symptoms recurred and the risperidone dose was increased. At the time of publication he was symptom-free (Freyne et al, 1999).

d) A 23-year-old male presented with ocular complaints. He was suffering from continuous pain and the feeling that his eyes were sliding down his face. Risperidone 2 milligrams per day was started and increased to 4 milligrams per day 3 days later. He was completely improved after 2 weeks and discharged at 4 weeks (Cetin et al, 1999).

4.5.L Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.M Dementia - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Reduces frequency and severity of delusions and agitation

Cerebrovascular adverse events (stroke, transient ischemic attack) have occurred in elderly individuals (mean age, 85 years) who received risperidone for treatment of dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

3) Adult:

a) Low-dose risperidone was efficacious in the treatment of behavioral and psychological symptoms of dementia in a small, open study. This 8-week study included 34 patients, ranging in age from 53 through 89 years (35% between 70 and 79 years; 44% 80 to 89 years) and exhibiting dementia and at least one of the following symptoms: delusions, hallucinations, agitation/aggression, irritability, or disinhibition. The primary diagnosis of 59% of the patients was Alzheimer's type dementia. At baseline, the illness of 71% of patients was categorized as "severe" or "very severe." By the end of the study, the mean dose of risperidone was 1.1 milligram (mg) per day. Fifty percent of patients received 1 mg/day, 18% received 0.5 mg/day, and 32% more than 1 mg/day. Both frequency and severity of delusions and hallucinations were significantly reduced by week 8 (p=0.0002 and p=0.0033, respectively for the product of frequency and severity scores). Irritability/lability was also significantly reduced (p=0.0452). Fifty-nine percent of patients were rated as "much" or "very much improved," and 82% showed some degree of improvement, according to the Clinical Global Impression of Change scale. Cognition was unaffected throughout the study. The mean increase in the Extrapyramidal Symptom Rating Scale (ESRS) score was 0.8 (p less than 0.01). Orthostatic dysregulation, sedation, and vertigo occurred in a few patients. No patient

withdrew because of extrapyramidal symptoms or any other side effect (Rainer et al, 2001).
b) Risperidone was effective and well-tolerated for the treatment of psychotic symptoms and behavioral disturbances in elderly patients with comorbid medical illnesses and medications (Zarate et al, 1997). In a review of medical records, 122 hospitalized psychogeriatric patients newly treated with risperidone were assessed. Patients received risperidone for agitation or psychosis associated with dementia (53%), a major mood disorder (29%), or other disorder (18%). Most were also medically ill and received other psychotropic (76%) or cardiovascular drugs (70%). Risperidone appeared to be effective in 85% of cases. In the demented group of patients with agitation or psychotic features, 82% were rated as improved. Patients starting on low doses and undergoing slow dosage increases, were less likely to have any adverse drug events (p=0.002). Risperidone was discontinued in 11% due to side effects and in 7% due to lack of efficacy.
c) Two cases of patients with psychotic symptoms secondary to Lewy-Body dementia responsive to risperidone have been reported (Hussain & Hussain, 1998; Geizer & Ancill, 1998). The first was a 59-year-old man with depressive illness, anxiety, aggressive outbursts, pseudo-hallucinations, and hallucinations (Hussain & Hussain, 1998). He had some relief of symptoms with trifluoperazine and clomipramine. Risperidone 2 milligrams twice daily increased to 3 mg twice daily made the visual hallucinations disappear after 7 days. The other case was a 74-year-old male with visual hallucinations, persecutory delusions, and agitation. He was started on risperidone 0.25 mg with some relief in his psychotic experiences. He then had donepezil added and within 2 weeks had complete resolution of psychosis.

4.5.N Depression, Refractory; Adjunct

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Improvement was demonstrated with risperidone compared with placebo augmentation of antidepressant therapy in difficult-to-treat depression in a double-blind, 4-week, placebo-controlled, study (n=97); however, the treatment effect was diminished around week 4 (Keitner et al, 2009).
There were modest but statistically significant improvements in treatment-resistant depression with 6 weeks of risperidone augmentation to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized trial in adults (n=274) (Mahmoud et al, 2007).
Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was not sustained in the long-term (9 months) in a multinational, double-blind, placebo-controlled study (n=243) (Rapaport et al, 2006).

3) Adult:
a) General Information
1) Risperidone, as augmentation to antidepressant medication, has provided some benefit in the short-term (4 to 6 weeks) in patients with treatment-resistant or difficult-to-treat depression (Mahmoud et al, 2007), (Keitner et al, 2009); however, continuation of risperidone augmentation for 24 weeks failed to prevent relapse of depression (Rapaport et al, 2006). There were modest but statistically significant improvements with 6 weeks of risperidone augmentation compared with placebo in a multicenter, double-blind, placebo-controlled, randomized trial (n=274) (Mahmoud et al, 2007). In another double-blind, 4-week, placebo-controlled, study (n=97), initial improvement demonstrated with risperidone compared with placebo augmentation diminished around 4 weeks (Keitner et al, 2009). Risperidone augmentation did not prevent relapse in the long-term (9 months) in a multinational, double-blind, placebo controlled study (n=243) (Rapaport et al, 2006).

b) Clinical Trials
1) Improvement was demonstrated with risperidone compared with placebo augmentation of antidepressant therapy in difficult-to-treat depression in a double-blind, 4-week, placebo-controlled study (n=97); however, the treatment effect was diminished around week 4. Patients (n=147) with unipolar, nonpsychotic major depression were enrolled in an open-label treatment phase to receive antidepressant monotherapy for 5 weeks if they were currently not on antidepressant drugs, if they were not currently receiving antidepressant therapy at an adequate dose and duration, or if they had poorly documented antidepressant therapy. At the end of the open-label phase, partial responders and non-responders with a Montgomery-Asberg Depression Rating Scale (MADRS) rating of 15 or more were enrolled in the double-blind, randomized phase (n=43). Additionally, patients (n=54) with well documented failure of current antidepressant therapy of adequate dose and duration were enrolled in the double-blind phase directly, without going through the open-label phase. Patients with bipolar I, bipolar II, or psychotic features were among those excluded. During the double-blind phase, patients continued on the same dose of their antidepressant drug and were randomized to additionally receive either risperidone (n=62) or placebo (n=33) for 4 weeks. Risperidone was initiated at 0.5 milligrams (mg) per day, and the dose was increased, if necessary, to 2 mg/day by day 21 and 3 mg/day thereafter (mean dose at end of 4 weeks, 1.6 mg/day).

Based on Clinical Global Impression (CGI) scores, the majority of patients were moderately ill at baseline (risperidone, 68.8%; placebo, 69.7%) and mean baseline MADRS scores were 25.8 +/- 5.7 and 25.5 +/- 5.4 in the risperidone and placebo groups, respectively. In the modified intent-to-treat population (received at least 1 dose of study drug and competed at least 1 set of assessments), the primary outcome of remission (MADRS rating of 10 or less) was achieved in 51.6% (n=32/62) and 24.2% (n=8/33) of patients in the risperidone- and placebo-treated groups, respectively, at the end of 4 weeks (p=0.011). The corresponding rates of remission for those who completed all 4 weeks of treatment (n=82) were 52.7% and 29.6%, respectively (p=0.052). Treatment difference was evident after 2 weeks, with remission rates of 37.3% and 15.6% in the risperidone and placebo groups, respectively. Notably, while both treatments demonstrated improvement over time, the difference in treatment was not statistically significant at week 4. The odds ratio for remission with risperidone compared with placebo was 3.33 (95% CI, 1.303 to 8.526; p=0.011). Among other outcomes, rates of response (50% decrease from baseline MADRS rating) at 4 weeks were 54.8% and 33.3% in the risperidone and placebo groups, respectively (p=0.049), with significant differences seen after 1 week of treatment (24.2% and 6.1%, respectively; p=0.031). When remission and response were evaluated on the Hamilton Depression Scale (HAM-D), treatment differences between risperidone and placebo were not statistically significant. Patient ratings of overall life satisfaction and contentment were significantly better in the risperidone group compared with the placebo group (from 1.3 to 2.5 and 1.2 to 1.7, respectively, p=0.014), with differences apparent by 2 weeks of treatment. The overall frequency of side effects was similar in the risperidone (84.4%) and placebo (81.8%) groups (Keitner et al, 2009).

2) There were modest but statistically significant improvements in treatment-resistant depression with 6 weeks of risperidone augmentation to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized trial in adults (n=274). An open-label, 4-week, run-in period identified 274 patients (age range, 18 to 65 years) with unremitting major depression, with a Clinical Global Impression-Severity of Illness (CGI-S) score of 4 or more, and a Carroll Depression Scale score of 20 or more while on their current antidepressant monotherapy at the recommended dosage. These patients were then randomized to 6 weeks of augmentation therapy with either oral risperidone (n=141) or placebo (n=133). The risperidone dose was 0.25 milligrams (mg) every day for 3 days, then 0.5 mg every day for days 4 to 15, followed by 1 mg every day for days 16 to 28. At the investigator's determination of ineffective treatment on day 29, risperidone was either continued at 1 mg/day or the dose was increased to 2 mg/day, or double-blind treatment was discontinued. At the start of randomization, the mean time since diagnosis of depression was 16.7 +/- 12.3 years, and mean Hamilton Rating Scale for Depression 17-item (HRSD-17) scores for the risperidone- and placebo-treated patients were 24.3 and 24.9 (p=0.73), respectively. All patients continued on their baseline antidepressant regimen, which consisted of a selective serotonin reuptake inhibitor (risperidone group, 59.1%; placebo group, 59.5%), a serotonin-norepinephrine reuptake inhibitor (22.6% and 19.8%, respectively), or other agents such as bupropion and trazodone (17.6% and 19.9%, respectively). The primary outcome was the change from baseline to 6 weeks in the HRSD-17 total score; response was defined as a 50% or more reduction in score and remission was defined as a total score of 7 or less. The final risperidone dose was 1 mg for 65.7% and 59.5% of risperidone- and placebo-treated patients, respectively. Results for the primary outcome are listed in the table below (Mahmoud et al, 2007).

Outcome
Risperidone
Placebo
Difference (95% CI)
p value
Mean (+/- SE) HRSD-17
Week 4*
15.4 +/- 0.52
17.3 +/- 0.52
-1.9 +/- 0.69 (95% CI, -3.3 to -0.5)
p=0.006
Week 6**
13.4 +/- 0.54
16.2 +/- 0.53
-2.8 +/- 0.72 (95% CI, -4.2 to -1.4)
p less than 0.001
Remission Rates
Week 4*
13.6%
6%
--
p=0.041
Week 6**
24.5%

10.7%
--
p=0.004
Response Rates
Week 4*
35.6%
18.8%
--
p=0.002
Week 6**
46.2%
29.5%
--
p=0.004
KEY: SE = standard error; CI = confidence interval; HRSD-17 = Hamilton Rating Scale for Depression 17-item score *risperidone: n=118; placebo: n=117 ** risperidone: n=106; placebo: n=112.

Secondary outcomes, which included clinician-rated measures (measured by CGI-S) and patient-rated measures (measured by Quality of Life Enjoyment and Satisfaction Questionnaire, Patient Global Improvement Scale, Sheehan Disability Scale), improved significantly more with risperidone compared with placebo at week 6. The number needed to treat with 6 weeks of risperidone augmentation to achieve 50% baseline symptom improvement in treatment-resistant depression was 6. Risperidone was well-tolerated, with premature study discontinuation due to adverse effects occurring in 5.8% of risperidone-treated patients and 2.3% of placebo-treated patients. Frequency of motor events was similar between the risperidone and placebo groups (akathisia, 0.7% and 0%, respectively; dystonia, 0% and 0.8%; tremor, 0.7% and 0.8%) and did not require use of benztropine (Mahmoud et al, 2007).

3) Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was not sustained in the long-term (9 months) in a multinational, double-blind, placebo-controlled study (n=243). The study design consisted of the following 3 phases: 4 to 6 weeks of open-label citalopram monotherapy (initial dose, 20 milligrams (mg); target dose range, 40 mg to 60 mg), 4 to 6 weeks of open-label risperidone augmentation, and a 24-week double-blind, placebo-controlled continuation of the risperidone phase. Patients (n=502) enrolled in the open-label citalopram monotherapy phase had major depressive disorder, single or recurrent episode, with or without psychotic features, a score of 20 or more on the Hamilton Rating Scale for Depression (HAMD-17), and were treatment-resistant (failure to respond to at least 1 but not more than 3 antidepressant trials of at least 6 weeks' duration at the labeled doses). Patients who either failed to respond (less than 50% reduction in HAMD-17 total score) after 6 weeks or were unchanged or worse after 4 weeks with citalopram were augmented with open-label, oral risperidone (n=390). For patients aged 18 to 54 years, risperidone was initiated at 0.5 mg/day and increased up to 2 mg/day (goal, 1 mg/day); patients aged 55 to 85 years old received 0.25 mg/day initially, with dose increases permitted up to 1 mg/day (goal, 0.5 mg/day). Patients achieving a HAMD-17 score of 7 or less or a Clinical Global Impressions (CGI)-Severity score of 1 or 2 during the risperidone augmentation (n=243, 63% of the open-label risperidone phase) were then randomized to receive either placebo (n=120; mean age, 48.4 years) or to continue on risperidone (n=123; mean age, 47.8 years) for 24 weeks. Time to relapse, the primary outcome, was defined as 1 or more of the following: 6 (much worse) or 7 (very much worse) on the CGI-Change score, 16 or higher on the HAMD-17 score, lack of efficacy leading to discontinuation, or intentional self-injury or suicidal ideation. There were more women than men in the double-blind continuation phase (71.3% vs 56.3%). The mean duration of illness in the risperidone and placebo groups at baseline was 17.9 +/- 12.3 years and 17.6 +/- 13.9 years, respectively. Among those entering the double-blind phase, 63.1% were complete non-responders (less than 25% reduction in HAMD-17 score) and 36.9% were partial responders (25% to 49% reduction in HAMD-17) to open-label citalopram. Based on Kaplan-Meier analysis, the median time to relapse was 102 days and 85 days (p=0.52) for the risperidone augmentation group and placebo augmentation group, respectively, with relapse rates of 53.3% and 54.6%, respectively. The HAMD-17 baseline scores worsened by 7.6 +/- 8.8 points from a baseline (start of double-blind phase) score of 6 +/- 3 in the risperidone group and by 7.9 +/- 8.1 points from a baseline score of 6.3 +/- 2.9 in the placebo group (for both, p less than 0.001 compared with baseline). The Montgomery-Asberg Depression Rating Scale scores worsened by 11.2 +/- 12.6 points from a baseline score of 6.8 +/- 4.7 in the risperidone group and 10.4 +/- 11.2 points from a baseline score of 8.1 +/- 4.6 (for both, p less than 0.001 compared with baseline) in the placebo group. The mean prolactin concentrations were 35.4 +/- 53.4 nanograms/milliliters (ng/mL) and 6.6 +/- 21 ng/mL (p less than 0.001) in the risperidone and placebo groups, respectively; galactorrhea occurred in 2.5% and 0%, respectively. During the double-blind phase, the mean weight increase was 1.3 +/- 3.8 kilograms (kg) in the risperidone group compared with a mean loss of 0.5 +/- 2.9 kg in the placebo group (Rapaport et al, 2006).

4) Adjunctive risperidone therapy was effective in the treatment of nonpsychotic depressive disorders in patients with suicidal ideation. In a case series, five female patients (ages 48 to 61 years) with treatment-resistant depression and suicidal ideation received risperidone (maximum dose, 1 milligram/day) in addition to their current antidepressant medi-

cation for at least 5 months. At baseline, Clinical Global Impressions-Severity of illness scores were reported as "markedly ill" or "among the most extremely ill" and following at least 3 months of adjunctive therapy, all patients were rated as "very much improved" on the Clinical Global Impressions-Improvement scale. In addition, patients did not report further suicidal ideation. Risperidone was well tolerated. Larger, controlled studies are needed to substantiate these findings (Viner et al, 2003).

5) Eight cases were described of risperidone therapy augmenting selective serotonin reuptake inhibitor (SSRI) therapy in patients with major depressive episodes without psychotic features (Ostroff & Nelson, 1999). All patients had incomplete responses to their SSRI therapy with Hamilton Rating Scale for Depression (HAM-D) scores of 16 to 27. Risperidone 0.5 to 1 milligram was added to their SSRI and HAM-D scores decreased to a range of 0 to 6 within 1 to 7 days.

4.5.O Drug-induced psychosis - Levodopa adverse reaction

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective for levodopa-induced psychotic symptoms

3) Adult:

a) In an open-label trial in 10 patients, low dose risperidone was useful for levodopa-induced psychotic symptoms (hallucinations) in patients with advanced Parkinson's disease and cognitive decline (Meco et al, 1997b). Nine patients improved significantly on the Brief Psychiatric Rating Scale and the Hallucinosis Questionnaire after 2 weeks and peaked after 6 weeks (p less than 0.01). Two patients discontinued risperidone due to worsening Parkinson's disease.

b) In a 26 week-trial, 23 of 39 parkinsonism patients treated with risperidone demonstrated complete or near-complete resolution of hallucinations and delusions and an approximately 50% to 75% reduction was seen in another 4 patients. Six patients experienced less improvement and an additional 6 had rapid and pronounced deterioration of parkinsonism which required risperidone to be discontinued. The mean dose of risperidone was 1.10 milligrams (mg) with a mean duration of treatment of 16.2 weeks. Sixteen patients completed the 26-week trial (Leopold, 2000). Similar results were found in a 12-week open pilot study involving 17 patients receiving an average dose of 1.1 mg per day (Mohr et al, 2000).

4.5.P First episode psychosis

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Treatment with low-dose risperidone was as effective as haloperidol in improving symptom severity of first-episode psychosis (Moller et al, 2008; Schooler et al, 2005; Merlo et al, 2002; Emsley, 1999)
In patients with first-episode psychosis, treatment with low-dose risperidone had less prevalence of extrapyramidal symptoms compared to haloperidol (Moller et al, 2008; Merlo et al, 2002; Emsley, 1999)

3) Adult:

a) Low-dose risperidone significantly delayed the time to relapse and was as effective as haloperidol in treating initial symptoms of first-episode psychosis in a multicenter, double-blind, randomized, controlled flexible-dose study (n=555). Patients diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder based on DSM-IV criteria for no greater than 1 year, had less than 2 hospitalizations for psychosis, had cumulative exposure to antipsychotic agents for less than 12 weeks, and were treated with an antipsychotic agent at the time of enrollment were eligible for the study. They were randomized to receive risperidone (mean age, 25.2 +/- 6.84 years (yr); n=278) or haloperidol (mean age, 25.7 +/- 6.87 yr; n=277). Following a 3- to 7-day washout period, with the exception of extremely ill patients, study medication was started at 1 milligram/day (mg/day) that could be increased to 2 mg/day on day 4 and at 1 mg/day increment each week thereafter, to a maximum dose of 4 mg/day. For patients who did not respond sufficiently at 4 mg/day, the dose could be titrated to 8 mg/day as tolerated. Clinical improvement, relapse and extrapyramidal symptoms were assessed weekly during the first 4 weeks, then every 4 weeks for the next 5 months, every 2 months during months 6 through 15, and every 3

months thereafter, until the last enrolled patient completed 2 years of treatment. After 3 months, 73.6% of patients who received risperidone achieved clinical improvement (greater than 20% decrease on the PANSS score) compared to 76.2% of patients in the haloperidol arm (p=0.48). The total PANSS score improved by 21 +/- 1.46 from baseline of 83.7 +/- 1.24 in the risperidone arm and improved by 20.6+ +/- 1.43 from baseline of 81.1 +/- 1.23 in the haloperidol arm (between-arm difference, p=0.49). At study endpoint, 75.5% and 77.8% achieved clinical improvement in the risperidone and haloperidol arms, respectively. The corresponding median time to clinical improvement was 26 days in the risperidone arm compared with 22 days in the haloperidol arm (p=0.22). Among the 400 subjects who responded, risperidone was associated with fewer relapses (42.1% vs 54.7%) and longer median time from clinical improvement to first relapse (466 days vs 205 days p=0.008) compared with haloperidol. Risperidone was associated with less acute extrapyramidal symptoms (5.09% vs 6.17%; p=0.04). Out of 46 patients expressing suicidal ideation during the study, there were fewer patients (7.2%) and no completed suicides in the risperidone arm compared with 9.4% of the patients and 3 completed suicides in the haloperidol arm. Abnormal prolactin values (males, greater than 18 nanograms/milliliter (mL); females greater than 25 nanograms/mL) were reported in 73.8% of the patients who received risperidone and 49.8% of the patients who received haloperidol. Additionally 14 prolactin-related adverse events (eg, gynecomastia, hyperprolactinemia, galactorrhea) and 1 prolactin-related adverse event (hyperprolactinemia) were reported in the risperidone and haloperidol arms, respectively (Schooler et al, 2005).

b) Treatment with risperidone was as effective as haloperidol in treating negative symptoms among in-patients with first-episode schizophrenia in a 8-week, multicenter, parallel-group, double-blind, randomized, controlled study (n=296); furthermore, risperidone was associated with lower prevalence of extrapyramidal symptoms compared with haloperidol. Patients with acute manifestation of first-episode schizophrenia according to International Classification of Diseases (ICD-10) codes and DSM-IV criteria were randomized to receive either risperidone 2 milligrams/day (mg/day) (mean age, 29.5 +/- 9.5 years (yr); n=148) or haloperidol 2 mg/day (mean age, 30.7 +/- 10 yr; n=148) for 8 weeks. If required, the dose could be adjusted by 1 mg/day to 2 mg/day between days 3 and week 1, and weekly thereafter to a maximum of 8 mg/day, not exceeding 4 mg/day by week 2. Additionally, dosage reduction of 1- to 2-mg decrements was permitted for extrapyramidal symptoms. Patients who had received psychotropic medications underwent a 4- to 7-day washout period. The mean dose taken in the risperidone arm was 3.8 +/- 1.5 mg/day compared to 3.7 +/- 1.5 mg/day in the haloperidol arm. More than one-half of the patients in both treatment arms received concomitant lorazepam. The primary efficacy outcome was assessed based on the negative scale of the Positive and Negative Syndrome Scale (PANSS). The Simpson-Angus Scale (SAS) was used to measure prevalence of extrapyramidal symptoms (primary tolerability criterion). At baseline, the mean PANSS negative score was 19.3 +/- 8.2 overall. Based on the intent-to-treat analysis, both treatment arms demonstrated improvement in the mean PANSS negative scores from baseline to week 8 (p less than 0.001), but there was no difference between the risperidone and haloperidol (16 +/- 6.6 vs 15.8 +/- 7.1; estimated difference, -0.13 ; p=0.85). Clinical response rate (defined as a rating of 3 or less in selected PANSS items, 30% or greater reduction from baseline PANSS total score, and a Clinical Global Impression (CGI) severity score of 4 or less) was 49.3% in the risperidone arm and 49.6% in the haloperidol arm. The corresponding time to response was 41 days and 38.6 days in the risperidone and haloperidol arms, respectively (p=0.753). After 8 weeks, the risk of developing extrapyramidal symptoms was higher in the haloperidol arm compared with the risperidone arm (51.5% vs 36.5%; odds ratio, 2.09; p=0.005) (Moller et al, 2008).

c) Treatment with risperidone 2 milligrams/day (mg/day) was associated with significantly less fine motor dysfunction and was as effective as risperidone 4 mg/day in treating first-episode psychosis symptoms in an 8-week, double blind, randomized, study (n=49). Neuroleptic-naive patients with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder based on DSM-IV criteria, with a intelligence quotient (IQ) greater than 80, and experienced first psychotic episode were randomized to receive risperidone 2 milligrams/day (mg/day) (mean age, 23.2 years (yr) +/- 4.4 yr; baseline Brief Psychiatric Rating Scale (BPRS) total score, 76.2 +/- 15.2; n=23) or risperidone 4 mg/day (mean age, 26 yr +/- 7.2 yr; baseline BPRS total score, 83.3 +/- 20.1; n=26) for 8 weeks. During the first week, the risperidone starting dose of 0.5 mg/day was gradually titrated to the target dose in each treatment arm. At 8 weeks, the total BPRS scores change from baseline in patients who received risperidone 2 mg/day was -32.3 +/- 15.1 compared to -29.3 +/-.7 in patients who received risperidone 4 mg/day; however, there was no significant difference. Two patients in the risperidone 2-mg arm compared to 3 patients in 4-mg arm scored 3 or more ("strong") on the Simpson-Angus Scale (SAS). Additionally, 2 patients in the risperidone 2-mg arm compared with 4 patients in 4-mg arm scored 2 or more ("moderate") on the Barnes Akathisia Scale (BAS). For the Steadiness Test, there were no differences in the number of errors between the 3 groups (2 treatment arms and a control arm of 20 healthy volunteers). For the Line Tracking Test, there were more errors in the risperidone 4-mg arm compared to the control group (p less than 0.05); however, there were no difference between the two risperidone arms. Additionally, the number of hits on the Tapping Test was lower in the risperidone 2-mg group compared with the control group (p less than 0.05). The adverse events were mostly mild to moderate (eg, concentration difficulties, asthenia, fatigue, sedation, weight gain) and occurred in 30% of patients in the risperidone 2 mg/day arm and 50% in the 4 mg/day; additionally, there were no reports of serious adverse events (Merlo et al, 2002).

d) In a multicenter, double-blind, randomized study (n=183), treatment with risperidone was associated with lower occurrence of extrapyramidal symptoms and was as effective as haloperidol in improving symptom severity of first-episode psychosis. Patients with a diagnosis of provisional schizophreniform disorder or schizophrenia based on the DSM-III-R cri-

teria, without prior treatment, with first psychotic episode that required treatment with an oral antipsychotic agent and who received emergency treatment for a maximum of 3 days for the disorder were eligible for the study. The eligible patients were randomized to receive a starting dose of risperidone 2 milligrams/day (mg/day) (median age 26 years (yr), range 15 yr to 50 yr; n=99) or haloperidol 2 mg/day (median age 24 years (yr), range 16 yr to 45 yr; n=94). The dose could be titrated in increments of 2 mg/day to a maximum of 8 mg twice daily for clinical response or reduced at any time to a minimum of 2 mg/day due to adverse effects. At 6 weeks, 79 patients in the risperidone arm compared to 58 patients in the haloperidol arm completed the study. The mean daily dose was 6.1 mg (range, 2 mg to 16 mg) and 5.6 mg (range 2 mg to 16 mg) in the risperidone and haloperidol arms, respectively. According to the total Positive and Negative Syndrome Scale (PANSS) scores change from baseline, 63% of patients who received risperidone compared to 56% of patients who received haloperidol achieved clinical improvement (p=0.19). The corresponding change in PANSS total score from baseline to endpoint was -30.9 +/-2.5 and -29.3 +/-2.7 in the risperidone and haloperidol arms, respectively. The PANSS scores showed clinical improvement in 74% of patients in the low-dose risperidone arm (6 mg/day or less; n=34) compared to 59% in the high-dose risperidone arm (greater than 6 mg/day; n=62). Shifts from baseline to a worst score for the Extrapyramidal Symptoms Rating Scale (ESRS) was greater in the haloperidol arm compared to the risperidone arm; especially in the hyperkinesia factor (p less than 0.01), and in the total ESRS score (p less than 0.05). Furthermore, 75% and 50% of patients required antiparkinsonian medications in the haloperidol and risperidone arms, respectively. The ESRS shifts were worse in the high-dose risperidone arm compared to the low-dose risperidone arm. The most common nonextrapyramidal adverse events reported included insomnia, agitation, headache, and anxiety. Nine patients withdrew from the study due to adverse events or insufficient efficacy in the risperidone arm compared to 17 patients in the haloperidol arm (p=0.03) (Emsley, 1999).

4.5.Q Gilles de la Tourette's syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May be an effective alternative for treatment of Tourette's syndrome

3) Adult:
a) Risperidone was effective in treating patients with Tourette's Syndrome (TS). In a randomized, double-blind, placebo-controlled trial 46 patients with moderate to severe TS received either risperidone 0.5 to 6 milligrams/day or placebo for 8 weeks. Risperidone was introduced at 0.25 mg once daily and increased to 0.5 mg twice daily. Thereafter, the dose could be altered for an individual according to response, not to exceed 6 mg/day. Sixty-one percent of patients in the risperidone group and 26% in the placebo group improved by at least 1 point on the Tourette's Syndrome Severity Scale (TSSS) by 8 weeks (p=0.04). The severity of disease at baseline did not alter the outcome. The risperidone group also showed significantly greater improvement in functioning than did the placebo group (p=0.03), with the greatest benefit occurring in patients with greater impairment in functioning at baseline. Patients treated with risperidone showed significantly more parkinsonism than did patients treated with placebo (p=0.004. An increase in parkinsonism occurred only in patients with average or above-average parkinsonism at baseline. Risperidone caused a greater incidence of fatigue than did placebo (57% vs 17%, p=0.01) and somnolence (35% vs 4%, p=0.02). Depression also occurred more frequently with risperidone, resulting in discontinuation by 3 patients in the risperidone group (Dion et al, 2001).
b) Risperidone treatment resulted in improvement in the severity of Tourette's syndrome tics in an open trial in 38 patients (Bruun & Budman, 1996). All subjects (age range 8 to 53 years) had been treated with clonidine and neuroleptics and had experienced either poor response or unacceptable side effects. The mean risperidone dose was 2.7 milligrams/day (range 0.5 to 9 mg/d). Twenty-five (21%) of the patients also took neuroleptics during the study period. Eight patients dropped out because of side effects; of the original 38 subjects, 22 (58%) experienced improvement. Reported side effects included sedation (18% of patients), akathisia/agitation (10%), dystonic reactions (5%), weakness, insomnia, depression, anxiety, and aggressive behavior (3% each). Risperidone dose, other medications, or concomitant diagnoses did not significantly affect response, and there was no correlation between those factors and the type or severity of side effects.

4) Pediatric:
a) Tourette syndrome patients demonstrated a reduction in aggression in 78.5% of 28 patients and a decrease in the frequency and severity of tics in 61.7% of 28 patients. The average daily dose of risperidone was 2 milligrams daily. The tics and aggressive behavior were evaluated at baseline and 2 weeks to 4 months later (average 2 months) (Sandor & Stephens, 2000).

4.5.R Huntington's disease

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective for the involuntary movements per case reports

3) Adult:
a) Four patients with involuntary movements secondary to Huntington Chorea (and no psychotic symptoms) improved with risperidone therapy (Dallocchio et al, 1999). Patients received an initial dose of risperidone 1 milligram (mg) every 8 hours for 15 days. Thereafter they were increased in 0.5-mg increments per day to 3 mg every 8 hours. There was no significant improvement seen with the initial low dose. The higher doses produced a significant reduction in choreic disturbances as seen on the Marsden and Quinn Scale score (p less than 0.00001). Symptoms worsened again as the patients were withdrawn from risperidone. Another patient with genetically confirmed Huntington Chorea but only with psychosis and no movement disorder also received risperidone 3 mg/day. Her psychiatric condition improved markedly without any side effects.

4.5.S Inhalant abuse

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Risperidone was effective in the treatment of inhalant abuse

3) Adult:
a) A 25-year-old male had a 5-year history of inhalant (gasoline and carburetor cleaning fluid) abuse. Risperidone 0.5 milligram (mg) twice daily was started which effectively reduced hallucinations and paranoia and eliminated aggressive behavior caused by his inhalant abuse. After an increase to 1 mg twice daily paranoid thoughts ceased and craving for inhalants was reduced. He had not relapsed at 12 weeks follow-up (Misra et al, 1999).

4.5.T Obsessive-compulsive disorder, Refractory

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Adjunctive therapy may be effective for obsessive-compulsive disorder refractory to serotonin reuptake inhibitor therapy (Maina et al, 2008; McDougle et al, 2000; Agid & Lerer, 1999; Stein et al, 1997; Saxena et al, 1996).

3) Adult:
a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effective in reducing obsessive-compulsive symptoms in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial; however this conclusion may be limited by the lack of a placebo arm, single-arm design, and underpowered nature of the trial. Following a 16-week prospective, open-label phase of SRI monotherapy (n=96), patients who were treatment-resistant (defined as less than 35% improvement in the total score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and a Clinical Global Impression Severity (CGI-S) score greater than 2) entered an 8-week single-blind phase (n=50). Patients in the single-blind phase received SRI daily doses of clomipramine 200 to 225 mg, citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, paroxetine 50 to 60 mg, or sertraline 200 mg, and were randomized to receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) in addition to the SRI therapy. Administration personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an

intent-to-treat, last-observation carried forward analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S scores by week 8 from baseline. The magnitude of change in mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater improvement in Y-BOCS score versus baseline, and a CGI-I score of 2 or less) was similar between groups.

Primary Efficacy Endpoints at 8 Weeks

Risperidone (n=25)	Olanzapine (n=25)
Responder rates*	
44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	
22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	
-7.5; p less than 0.001	-8.4; p less than 0.001
Mean end-point CGI-S score	
3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	
-1.7; p less than 0.001	-1.9; p less than 0.001

* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity scale

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (24% vs 0%, p=0.022), weight gain (16% vs 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and the absence of an a priori power calculation may have contributed to the limitations of this study (Maina et al, 2008).

c) Obsessive compulsive disorder (OCD) patients with and without comorbid chronic tic disorders or schizotypal personality disorder may respond to the addition of low-dose risperidone to ongoing serotonin reuptake inhibitor (SRI) therapy. A double-blind, placebo-controlled study was designed to determine the short-term efficacy and tolerability of potent SRIs in combination with risperidone in treating OCD patients refractory to SRIs alone. Seventy adult patients with a primary diagnosis of OCD received 12 weeks of treatment with an SRI. Thirty-six patients were refractory to 6 weeks of risperidone (n=20) or placebo (n=16) addition. Behavioral ratings, including the Yale-Brown Obsessive Compulsive Scale, were obtained at baseline and throughout the trial. Placebo-treated patients subsequently received an identical open-label trial of risperidone addition. For study completers, 9 (50%) of 18 risperidone-treated patients were responders (mean daily dose, 2.2 +/- 0.7 mg per day) compared to 0 of 15 in the placebo addition (p less than 0.005). Seven (50%) of 14 patients who received open-label risperidone addition responded. Risperidone addition was superior to placebo in reducing OCD (p less than 0.001), depressive (p less than 0.001), and anxiety (p=0.003) symptoms. Other than mild, transient sedation, risperidone was well tolerated (McDougle et al, 2000).

d) Risperidone (initial dose of 2 milligrams/day) was effective in a 24-year-old patient with methamphetamine-associated obsessive-compulsive disorder-like symptoms (Iyo et al, 1999).

e) Fourteen of 16 patients with obsessive-compulsive disorder had substantial reductions in obsessive-compulsive disorder (OCD) symptoms within 3 weeks of initiating risperidone. Result were usually seen within the first few days. Before the addition of risperidone, all patients received a serotonin reuptake inhibitor (SRI) for at least 12 weeks either alone or in combination with mood stabilizers, neuroleptics, or anxiolytics. In addition to the OCD, patients had horrific mental imagery, comorbid schizophrenia, schizoaffective disorder, or schizotypal disorder (Saxena et al, 1996).

f) In a case series, 3 of 8 patients with obsessive- compulsive disorder (DSM-IV criteria) showed significant improvement on the Clinical Global Impression Change Scale after receiving augmentation with risperidone 1 to 2 milligrams/day. Of the other 5 patients: one patient noted minimal to much improvement, 3 patients had no change in symptoms and 1 patient was unable to tolerate the side effects (Stein et al, 1997).

g) A 25-year-old man with obsessive compulsive disorder refractory to multiple medications improved with risperidone added to his paroxetine (Agid & Lerer, 1999). Risperidone 1.5 milligrams (mg)/day was added to paroxetine 60 mg/day. His score on the Yale-Brown Obsessive Compulsive Scale for obsessions went from 14 to 4 and for compulsions went from 20 to 2. After 2 months he became depressed. The depressed symptoms responded to a decreased dose of risperidone of 0.5 mg/day.

4.5.U Organic psychotic condition

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Has reduced symptoms of psychosis caused by medical conditions

3) Adult:
a) A case series reports the successful use of risperidone in five patients who fulfilled DSM-IV criteria for psychosis due to a general medical condition and two who met the criteria for mood disorder due to a general medical condition with severe psychotic features (Furmaga et al, 1997). All seven responded to treatment including four patients who had previously failed initial treatment with at least one typical antipsychotic agent.
b) In a case series of 21 patients with HIV-related psychotic disorders, 20 patients treated with risperidone had substantial improvement (Singh et al, 1997). Most responded to low doses (mean 3.3 milligrams) and required only a short course (mean 6.4 weeks). No serious adverse effects were reported and no hematological effects were observed.

4.5.V Parkinson's disease - Psychotic disorder

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

4.5.W Pervasive developmental disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective for the treatment of symptoms related to pervasive developmental disorders and autism in adults
In children with autism spectrum disorder, responders to 24 weeks of open-label therapy with oral risperidone therapy had lower relapse rates when randomized to continue additional 8 weeks of double-blind treatment with risperidone versus placebo (Troost et al, 2005).
Treatment with oral risperidone relieved several behavioral symptoms associated with pervasive development disorder in children aged 5 to 12 years in an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) (Shea et al, 2004).

3) Adult:
a) Risperidone therapy was effective in 3 autistic disorder patients. All 3 patients tolerated risperidone well and did not experience unwanted effects. Effective doses in each patient were 5 milligrams daily, 4 milligrams daily, and 1 milligram daily, respectively. Epilepsy was present in 2 of the patients and both showed no increase in seizure frequency. Improved social relations and reduced aggressive behavior were observed in all patients and decreased repetitive behavior in 1 patient (McCartney et al, 1999).
b) In a double-blind, placebo controlled trial including adults with autistic disorder (n=17) or pervasive developmental disorder (n=14), 57% of patients treated with risperidone (mean dose 2.9 milligrams per day) were considered responsive to therapy compared to 0% of placebo recipients (p less than 0.002). At the end of the 12 week trial, patients initially randomized to placebo were treated with open-label risperidone. During open-label treatment, 60% of patients were considered responders. Repetitive behaviors were evaluated using a modified version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and aggression was evaluated with the Self-injurious Behavior Questionnaire (SIB-Q). The Clinical Global Impression (CGI) Scale and the Rivto-Freeman Real-life Rating Scale were also used to evaluate patients. Ratings on the CGI, Y-BOCS, SIB-Q, and overall Rivto-Freeman Scale were significantly improved with risperidone compared to placebo (p less than 0.05 for all analyses). Improvements became evident at 4 weeks and continued throughout the 12-week study period. The most common side effect was transient sedation. Other than one patient who developed gait abnormalities, extrapyramidal side effects were not observed (McDougle et al, 1998).

4) Pediatric:
a) In a double-blind extension phase, continued treatment with risperidone was more effective than placebo in preventing relapse of autism spectrum disorder symptoms among responders to 24 weeks of open-label risperidone therapy. Children

aged 5 to 17 years (n=36) meeting the DSM-IV (Third Revision) criteria for a pervasive development disorder (PDD) and who demonstrated clinically significant tantrums, aggression, self-injurious behavior, or a combination of these problems were enrolled in the open-label phase to receive oral risperidone. In children weighing under 45 kilograms (kg), risperidone was initiated at 0.5 milligrams (mg) at bedtime, increased to 0.5 mg twice daily a week later, and subsequently increased in 0.5-mg increments to a maximum dose of 2.5 mg/day by day 29. Doses could be increased up to 3.5 mg/day by day 29 in children weighing more than 45 kg. Patients with an at least 25% reduction from the baseline Aberrant Behavior Checklist (ABC) Irritability score (baseline mean score, 23) and a rating of much improved or very much improved on the Clinical Global Impression (CGI) of Severity scale after 8 weeks were classified as responders (26/36) and allowed to continue taking risperidone for another 16 weeks. At 24 weeks of open-label treatment, 69% (18/26) of patients were rated as much improved or very much improved on the CGI Symptom Change (CGI-SC) scale, with significant decreases in ABC Irritability subscores as well; most improvements occurred by week 8 of treatment. Completers of the additional 16 weeks of therapy were randomized in a double-blind fashion to either continue taking risperidone (n=12) or placebo (gradual withdrawal for 3 weeks and placebo only for 5 weeks; n=12) for 8 weeks. Relapse was defined as the occurrence of CGI Symptom Change (CGI-SC) scores of much worse or very much worse for at least 2 consecutive weeks and a minimum increase of 25% from the last ABC Irritability score. An intention-to-treat analysis revealed relapses (primary endpoint) in 3 and 8 patients in the risperidone and placebo groups, respectively (p=0.049), with a longer mean time to relapse in patients maintained on risperidone (7 vs 6 days; p=0.0475). Compared to mean +/- standard deviation (SD) ABC Irritability subscale scores of 11.1 +/- 8.1 and 12.7 +/- 7.7 in the risperidone and placebo groups, respectively, at week 24, scores at the end of the study (week 32) were 12.6 +/- 9.8 (14% increase) and 20.3 +/- 10.2 (60% increase; p=0.043), respectively. Improvements noted at week 24 among other ABC subscales, such as social withdrawal, stereotypy, hyperactivity, and inappropriate speech, were fairly well maintained until the end of the study in the risperidone, there were no statistically significant differences between the groups at study end. Treatment-emergent adverse events were mild to moderate and included increased appetite (62%), anxiety (39%), fatigue (35%), and increased thirst (26%). At week 24, the mean weight gain from baseline was 5.7 +/- 2.8 kg (range, 1.2 to 11.7 kg; p less than 0.0001). It should be noted that the majority (75%; n=18/24) of the study population had a form of PDD other than autistic disorder and 63% (n=15/24) had average or above-average intelligence (Troost et al, 2005).

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) in children, treatment with oral risperidone relieved several behavioral symptoms associated with pervasive development disorder (PDD). Pediatric outpatients aged 5 to 12 years (mean age, 7.5 years; greater than 75% male) with a DSM-IV Axis I diagnosis of PDD and a total score of 30 or more on the Childhood Autism Rating Scale (CARS), with or without mental retardation were randomized to receive either an oral solution of either risperidone (n=40) or placebo (n=39) in 1 or 2 divided doses for 8 weeks. Risperidone was initiated at 0.01 milligram/kilogram/day (mg/kg/day) and increased to 0.02 mg/kg/day on day 3. At day 8, the dose was further increased at a maximal increment of 0.02 mg/kg/day, and subsequent increments or decrements were allowed up to a maximum daily dose of 0.06 mg/kg/day. Using the Aberrant Behavior Checklist (ABC), efficacy was primarily assessed for change in irritability from baseline to endpoint on the irritability subscale of the ABC. Secondary assessments included scores on the other 4 ABC subscales (hyperactivity/noncompliance, inappropriate speech, lethargy/social withdrawal, and stereotypic behavior), the parent-rated Nisonger Child Behavior Rating Form (N-CBRF), and the Clinical Global Impression-Change (CGI-C; 7-point scale ranging from very much improved to very much worse). At baseline, autistic disorder was the most common form of PDD (risperidone, 67.5%; placebo, 71.8%), and 57.5% and 53.8% of patients in the risperidone and placebo groups, respectively, were diagnosed with severe autism. At endpoint, patients in the risperidone group had received a mean risperidone daily dose was 0.05 mg/kg/day (mean daily dose, 1.48 mg) for a mean duration of 52.7 days (range, 2 to 62 days). An intention-to-treat analysis (included all patients receiving at least 1 study dose and with at least 1 postbaseline assessment) at endpoint revealed greater decreases from baseline irritability scores in the risperidone group (64% improvement) compared to placebo (30.7% improvement). Based on CGI-C scores, global improvements occurred in 87.2% and 39.5% of risperidone- and placebo-treated patients, respectively, with 54% and 18% of patients, respectively, reporting a rating of much improved or very much improved (p less than 0.001). Additionally, there was a greater decrease in the Visual Analog Scale score of aggression (most frequently reported troublesome symptom; 23.4%) in the risperidone-treated patients compared to placebo (mean score decrease, 38.4 vs 26.2, respectively; p less than or equal to 0.05). Results of the primary and key secondary endpoints are listed in the table below. Treatment-emergent adverse events were mild in severity, with somnolence (72.5% vs 7.7%), upper respiratory tract infection (37.5% vs 15.4%), rhinitis (27.5% vs 10.3%), and increased appetite (22.5% vs 10.3%) being the most commonly reported among risperidone-treated patients (Shea et al, 2004).

Efficacy measure
Risperidone (n=39)
Placebo (n=38)
Baseline
Endpoint (change from baseline)
Baseline
Endpoint (change from baseline)

ABC subscale (mean +/- SD)
Irritability
18.9 +/- 8.8
-12.1 +/- 5.8*
21.2 +/- 9.7
-6.5 +/- 8.4
Hyperactivity/noncompliance
27.3 +/- 9.7
-14.9 +/- 6.7*
30.9 +/- 8.8
-7.4 +/- 9.7
Inappropriate speech
4.6 +/- 3.4
-2.6 +/- 2.6**
4.8 +/- 3.7
-1.6 +/- 3
Lethargy/social withdrawal
13.7 +/- 7
-8.6 +/- 5.9***
14.3 +/- 8.2
-5.7 +/- 6.9
Stereotypic behavior
7.9 +/- 5
-4.3 +/- 3.8**
8.1 +/- 5.6
-2.4 +/- 4
N-CBRF (parent version) subscale (mean +/- SD)
Conduct problem
16.8 +/- 9.4
-10.4 +/- 7.4*
23.3 +/- 12
-6.6 +/- 9.5
Hyperactive
17.2 +/- 5.8
-8.1 +/- 4.6**
18.9 +/- 5.3
-5.6 +/- 6.6
Self-Isolated/ritualistic
7.5 +/- 4.1
-4.8 +/- 3.9
8.2 +/- 4.5
-3.6 +/- 4.6
Insecure/anxious
8.7 +/- 8.1
-4.6 +/- 6.5**
10.6 +/- 7.6
-3.5 +/- 5.5
Overly sensitive
6.9 +/- 3.4
-3.8 +/- 2.8**
7.4 +/- 3.5
-2.7 +/- 3.2
Self-injurious/sterotypic
4.2 +/- 4.2
-2.6 +/-3.3
3.5 +/- 4.2
-1.3 +/- 2.8
Key: n=number of subjects; ABC=Aberrant Behavior Checklist ; N-CBRF=Nisonger Child Behavior Rating Form; SD=standard deviation*p less than or equal to 0.001 vs placebo**p less than or equal to 0.05 vs placebo***p less than or

equal to 0.01 vs placebo

b) Risperidone improved functionality on the Children's Global Assessment Scale in 13 out of 14 cases in an open trial of children and adolescents (ages 9 to 17 years) treated for pervasive developmental disorders. Starting doses of 0.25 milligrams (mg) twice daily were increased in 0.25 mg/day increments every 5 to 7 days to optimal doses ranging from 0.75 to 1.5 mg daily in divided doses. Improvements occurred in attention, lessening of obsessional behaviors, decrease in agitation and anxiety and improvement in social awareness (Fisman & Steele, 1996).

c) Behavioral symptoms improved in a series of 6 children (ages 7 to 15) with pervasive developmental disorder. After a mean duration of treatment for 5 months (range 1-8 months) at a mean optimal dose of 2.7 milligrams (mg) daily (range 1 to 6 mg daily) in an open label trial, patient rating scores decreased, which reflected improvements in aggression, temper tantrums, and mood instability. Three patients were followed for more than 2 years, of whom one discontinued risperidone due to increased liver enzymes; one patient was switched to another new agent, and the third patient continued risperidone with good response (Perry et al, 1997)

4.5.X Pick's disease

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in one case report

3) Adult:

a) A 42-year-old woman with a presumptive diagnosis of Picks Disease was treated with risperidone (titrated to 3 mg twice daily) and demonstrated significant improvements and cognitive stabilization. The author suggested that controlled trials with this agent or other atypical antipsychotics in treating Picks Disease need to be performed and might produce promising results (Curtis & Resch, 2000).

4.5.Y Posttraumatic stress disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Possibly effective in treating patients with irritable aggression in posttraumatic stress disorder
Possibly effective in treating intrusive thoughts associated with posttraumatic stress disorder

3) Adult:

a) Risperidone was effective in a 48-year-old male war veteran demonstrating increased irritability and anger associated with posttraumatic stress disorder. Fluoxetine and diazepam were ineffective. With the addition of risperidone 1 milligram daily to paroxetine and diazepam, he reported less intensity in his anger and more confidence in his ability not to act on it (Monnelly & Ciraulo, 1999).

b) Two patients with posttraumatic stress disorder responded favorably to risperidone 6 milligrams daily and 2 milligrams daily, respectively. Other agents were ineffective (Krashin & Oates, 1999).

4.5.Z Schizophrenia

FDA Labeled Indication

1) Overview
FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (13 years and older, oral only)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone is indicated for the treatment of schizophrenia in adults (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)and pediatric patients 13 years of age and older (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

Approved for maintenance treatment of schizophrenia in adults (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

Oral risperidone, at doses ranging from 1 to 6 milligrams per day, was effective in the treatment of schizophrenia in adolescents aged 13 to 17 years in 2 short-term (6 and 8 weeks), double-blind, controlled trials (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult:

a) General Information

1) Risperidone is effective for the positive and negative symptoms associated with chronic schizophrenia with a response rate of 50% to 75% (Foster & Goa, 1998b; Rossi et al, 1997a; Smith et al, 1996a). Dose ranges of risperidone 4 to 16 milligrams have shown statistically greater improvement than placebo in Clinical Global Impression (CGI) and total Positive and Negative Syndrome Scale (PANSS) scores. The 4 to 6 milligram dose appears to be the most effective (Marder & Meibach, 1994a; Chouinard et al, 1993b; Marder, 1992; Muller-Spahn, 1992a). At doses of 8 milligrams or less risperidone is associated with a lower risk of extrapyramidal symptoms than conventional antipsychotics (Foster & Goa, 1998b). Comparative efficacy with haloperidol and other conventional neuroleptics has shown that risperidone has a significantly higher clinical response rate and allows for significantly less prescribing of anticholinergic medications (Davies et al, 1998)(Bech et al, 1998a; Luebbe, 1996a). Patients treated with risperidone have a lower relapse rate than those treated with haloperidol (Csernansky et al, 2002a). Patients have also been successfully switched from depot antipsychotics to risperidone (Desai et al, 1999).

b) Monotherapy

1) Intramuscular

a) Long-acting injectable risperidone was significantly more effective than placebo in the treatment of patients with schizophrenia. In a randomized, double-blind, placebo-controlled, multicenter study, patients (n=400) with schizophrenia received intramuscular injections of long-acting risperidone (25 milligrams (mg), 50 mg, or 75 mg) or placebo every two weeks for 12 weeks. During a one week run-in period, patients received oral risperidone (titrated to a dose of 4 mg/day) for at least 3 days. Patients also received oral risperidone (2 mg/day, 4 mg/day, or 6 mg/day) or placebo for the first three weeks of the double-blind period of the study. Mean Positive and Negative Syndrome Scale (PANSS) total scores were significantly more improved in patients receiving long-acting risperidone 25 mg, 50 mg, or 75 mg as compared with those who received placebo (p=0.002, p less than 0.001, p less than 0.001, respectively). Improvements in positive and negative symptoms were also significantly greater in all three long-acting risperidone groups as compared with the placebo group (p less then or equal to 0.05, all values). Clinical improvement was defined as at least a 20% reduction in PANSS total scores and was observed in only 17% of placebo patients as compared with 47%, 48%, and 39% of patients in the 25 mg, 50 mg and 75 mg long-acting risperidone groups, respectively (p less then 0.001). While the 75 mg dose of long-acting risperidone was efficacious, it offered no additional benefit over the 25 mg and 50 mg doses. Long-acting risperidone was well tolerated and extrapyramidal adverse events were mild throughout the study period. Small increases in body weight from baseline to endpoint were observed in risperidone-treated patients and these changes appeared to be dose- related (Kane et al, 2003).

2) Oral

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in elderly patients. In an international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventional antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=nonsignificant). The severity of EPS symptoms was reduced in both groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients as compared with those who received risperidone

(14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean QTc changes were not considered clinically relevant (Jeste et al, 2003a).

b) Risperidone treatment resulted in mild to substantial improvement in psychotic symptoms in approximately two-thirds of the elderly Chinese patients (age 65 years or greater) participating in an open, 4-week study. Doses of risperidone were titrated on the basis of clinical responses and adverse effects and ranged from 0.25 to 7 milligrams (mg) per day (mean 2.1 mg/day). The mean dose for functional psychoses was greater than that for organic mental disorders (2.8 mg/day vs 1.6 mg/day, p=0.001). Patients with schizophrenia received the highest mean dose (4.1 mg/day). With improvement defined as a reduction of 25% or more in baseline scores on various rating instruments, improvement occurred in 61% to 78% of patients. Patients with vesicular dementia responded better than Alzheimer's patients. Of the 110 patients, 81 had one or more adverse effects. Weakness of the legs or walking problems, dizziness, and peripheral edema were the most common side effects (Hwang et al, 2001a).

c) Risperidone is beneficial in the treatment of patients with chronic schizophrenia, compared with conventional neuroleptics (CNs), and these benefits may appear only after longer-term treatment. A randomized, open, parallel, multicenter study compared the long-term (12 months) effectiveness of risperidone with that of CNs. One hundred eighty-four subjects were randomized to receive either risperidone or CN and 165 of them completed the follow-up. Outcome measures were taken at 3, 6, and 12 months and included in the Positive and Negative Syndrome Scale (PANSS) and the Extrapyramidal Symptom Rating Scale. Within this 12-month follow-up, risperidone was found to be superior to CNs in terms of both the average change in score from baseline on the PANSS (p=0.006) and the proportion of good responders (as defined by a 20% decrease in total PANSS scores; p=0.03). For positive symptoms, the effectiveness of the risperidone treatment tended to increase over time and at 12 months, the percentage of good responders in the risperidone group was twice as large as that in the CN group (30% vs 15%; p=0.03). A worsening of akathisia was less frequent in subjects receiving risperidone than in those receiving CNs (p=0.02) (Bouchard et al, 2000).

d) In an open, multicenter trial, risperidone was found to be effective in outpatients (Chouinard et al, 1998). Patients (n=333) with subchronic or chronic schizophrenia treated on an outpatient basis were screened initially while on their current neuroleptic therapy. Their current therapy was discontinued and risperidone started at 2 milligrams (mg) daily and increased to 6 mg daily over 3 days. After 2 weeks the dose could be titrated to a maximum of 10 mg or a minimum of 4 mg. At the end of the 8-week study, the mean risperidone dose was 6.1 mg daily in 244 patients completing the study. The mean total Positive and Negative Syndrome Scale (PANSS) for schizophrenia decreased significantly from 86.3 to 63.6 (p=0.0001). Clinical improvement (20% or more decrease from baseline in total PANSS score) was seen in 85% of patients. The most frequent adverse events reported were insomnia, nausea, headache, somnolence, dizziness, fatigue, anxiety, vomiting, and ejaculation failure/disorder.

e) In an open multicenter trial, risperidone was viewed as an efficacious and well tolerated medication which demonstrated good overall antipsychotic action and above standard improvement in negative symptomology in 254 chronic schizophrenic patients with and without exacerbation who were treated with risperidone 1 to 5 milligrams twice daily for 8 weeks, following an abrupt discontinuation of previous psychotropic medications; significant improvement in the overall Brief Psychiatric Rating Scale was observed at every evaluation time (p less than 0.0001); 73% of patients showed improvement in negative symptomology; a significant improvement was noted in the extrapyramidal symptom scores in all patients, including those who discontinued therapy early (p less than 0.0001); the Clinical Global Impression scores significantly improved for those finishing the study (p less than 0.0001); 98% of those finishing the study tolerated risperidone very well or well; 32% of patients discontinued treatment early, of which 51% dropped out within the first 2 weeks, probably due to adverse reactions stemming from the abrupt discontinuation of all previous psychotropics; the research team now recommends initial overlapping of therapies, especially for those patients previously medicated with sedatives (Phillip, 1997).

c) Combination Therapy

1) Addition of celecoxib to risperidone therapy for patients with an acute exacerbation of schizophrenia resulted in greater improvement than did risperidone therapy alone. In a randomized, double-blind study, 25 patients were given risperidone 2 to 6 milligrams (mg) per day plus celecoxib 400 mg/day and 25 patients were given risperidone plus placebo. Both groups showed improvement in psychopathology over the 5- week study, mainly with reductions in scores on the positive symptoms subscale of the Positive and Negative Syndrome Scale (PANSS) (p=0.006) and on the general psychopathology subscale (p=0.01). Negative symptoms were not significantly affected. Celecoxib therapy resulted in an improvement in total PANSS score relative to that of the placebo group (p=0.05). There were no significant effects of celecoxib on the group-by-time interaction on any of the subscales, although a trend favoring celecoxib was evident on all subscales. The main influence of celecoxib occurred in weeks 2 to 4, resulting in earlier improvement. The use of biperiden for treating side effects of risperidone was not significantly different for the 2 groups. The use of benzodiazepines for treating anxiety and agitation appeared less in the celecoxib group, but the difference for the 2 groups was not statistically significant. Side effects of celecoxib were not observed (Muller et al, 2002).

2) In an open trial, risperidone added to clozapine was well tolerated and produced significant reductions of symptoms after 4 weeks as measured by the Brief Psychiatric Rating Scale (42.2 to 30.3, p=0.0002). Patients enrolled had either persistent psychotic or negative symptoms despite optimal doses of clozapine (n=10) or a maximal clozapine dose lim-

ited by significant side effects (n=2). Clozapine doses were kept constant while risperidone doses were increased to a maximum of 6 milligrams (mg) per day. The two agents were well-tolerated, however, complaints included mild akathisia, hypersalivation, and worsening fatigue (Henderson & Goff, 1996). Two other cases of refractory schizophrenic patients responding to combination therapy have been reported (Morera et al, 1999). Doses used were clozapine 300 mg with risperidone 4.5 mg, and clozapine 400 mg with risperidone 6 mg.

3) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorder and schizoaffective disorder, bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorder who were in a manic, hypomanic, depressive, or mixed episode (n=541; 430 completed the study) were given risperidone in combination with lithium, anticonvulsants, and antidepressants to clinical response and tolerability. The average dose of risperidone at the start of the study was 4 milligrams (mg) per day and at the end of the study, 3.9 mg/day. For all patients, scores on the Young Mania Rating Scale (YMRS) were significantly reduced at week 1 and at every point thereafter (p less than 0.001 for all but the subgroup of depressed patients, for whom p was less than 0.05). Mean scores on the YMRS decreased from 25.6 at baseline to 2.4 at 6 months. Likewise, scores on the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced from baseline at all evaluation times (p less than 0.0001), with scores declining from 12.8 at baseline to 4.1 at 6 months. Scores on the Positive and Negative Syndrome Scale (PANSS) declined from 72 at baseline to 40 at 6 months (p less than 0.0001). According to the Clinical Global Impressions scale (CGI), no patients were free from symptoms at baseline and only 5% were rated as "mildly ill." At study endpoint, 44% of patients showed no symptoms of mania or depression and a further 30% were "mildly ill." During the study, 25% of the patients experienced relapses into a mood state different from that at the start of the trial. Scores for extrapyramidal symptoms were lower at the end of study than at baseline (p less than 0.0001). There were significant reductions in dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia subscores. There were no cases of new-emergent tardive dyskinesia. Nonextrapyramidal adverse reactions included increase in weight (2.4% of patients), drowsiness (1.3%), impotence (0.7%), and dysarthria (0.7%). There was a very low incidence of exacerbation mania in the first 6 weeks (1.8%) (Vieta et al, 2001).

d) Refractory

1) Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were considered treatment- refractory, approximately 45% showed sufficient clinical improvement after 3 months of treatment with olanzapine or risperidone to be discharged from the hospital. The 79 patients were not suited to treatment with clozapine either because of medical contraindications or because of unwillingness to submit to the weekly blood drawings. Patients were given olanzapine 10 to 30 milligrams (mg) per day or risperidone 4 to 10 mg/day. Treatments were titrated quickly to the maximum tolerated dose and continued for 3 months. Mean scores on the Brief Psychiatric Rating Scale decreased from 67 to 53 for the olanzapine group (n=32) and from 63 to 52 for the risperidone group (n=47) (p less than 0.001 for both groups). Of the 34 patients who were discharged from the hospital, only 3 required rehospitalization during the 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months (Dinakar et al, 2002).

e) Schizophrenia With Concomitant Cocaine Dependence

1) The results of a pilot study suggest that risperidone therapy reduced craving and relapses in cocaine-dependent patients with schizophrenia. In this 6-week, open label trial, patients with a dual diagnosis of schizophrenia and cocaine dependence (6 grams or more of cocaine/month) received risperidone (n=8; initial, 2 milligrams (mg)/day, titrated to maximum dose of 6 mg/day) or continued typical neuroleptic medication treatment (n=10; haloperidol, fluphenazine, or chlorpromazine). Patients in the risperidone group had significantly less cue reactivity in regard to the intensity (p=0.005) and depression (p=0.031) dimensions of craving as compared with conventional therapy, but there was no statistical difference on the energy and feeling sick dimensions. Risperidone-treated patients also had a significantly lower rate of relapse (defined as any substance abuse) than did patients on typical neuroleptic therapy (12.5% vs 70%, respectively; p=0.025). Although not significant, a tendency toward a greater reduction in negative and global symptoms of schizophrenia was seen in risperidone-treated patients. Larger, double-blind studies are needed to substantiate these findings (Smelson et al, 2002).

4) Pediatric:

a) In 2 short-term (6 and 8 weeks), double-blind, controlled trials, oral risperidone, at doses ranging from 1 to 6 milligrams (mg) per day, was effective in the treatment of schizophrenia in adolescents aged 13 to 17 years. Patients met the DSM-IV diagnostic criteria for schizophrenia and were experiencing an acute episode at the time of enrollment. In the first trial (trial 1), patients were randomized to receive either risperidone 1 to 3 mg/day (n=55; mean modal dose, 2.6 mg), risperidone 4 to 6 mg/day (n=51; mean modal dose, 5.3 mg), or placebo (n=54) for 6 weeks. In the second trial (trial 2), patients were randomized to receive either risperidone 0.15 to 0.6 mg/day (n=132; mean modal dose, 0.5 mg) or risperidone 1.5 to 6 mg/day (n=125; mean modal dose, 4 mg). In both studies, risperidone was initiated at 0.5 mg/day and titrated up to the target dose range by approximately day 7 (except for the risperidone 0.15 to 0.6 mg/day group in trial 2, where risperidone was initiated at 0.05 mg/day). Eventually, the dosage was increased to the maximum tolerated dose by day 14. Compared to placebo, a significant reduction occurred in the Positive and Negative Syndrome Scale (PANSS) score in all risperidone dose groups ranging from 1 to 6 mg/day (primary efficacy endpoint). Reductions in the PANSS scores in the 1 to 3 mg/day

group were comparable to the 4 to 6 mg/day group in trial 1 and to the 1.5 to 6 mg/day group in trial 2. The 1.5 to 6 mg/day group showed statistically significantly greater efficacy than the 0.15 to 0.6 mg/day group in trial 2, with no additional benefit evident beyond the 3 mg/day dose. Adverse events reported at a higher incidence than placebo in both the risperidone 1 to 3 mg/day and 4 to 6 mg/day dose groups in trial 1 included parkinsonism (13%-16%), tremor (10%-11%), dystonia (9%-18%), dizziness (7%-14%), akathisia (7%-10%), somnolence (12%-24%), and anxiety (6%-7%) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) The results of a small study suggest that risperidone may be effective in the treatment of schizophrenia in adolescent patients. In a prospective, open-label trial, eleven patients (mean age, 17.27 years) with first-episode, early-onset schizophrenia received risperidone (initial, 0.5 milligrams (mg)/day, titrated based on clinical response and adverse effects; mean dose, 3.14 mg/day) for 6 weeks. At 6 weeks, the Positive and Negative Syndrome Scale (PANSS) total score and positive symptoms score were significantly reduced from baseline (p less than 0.01 and p less than 0.0001, respectively), however, a significant reduction was not observed for the negative symptoms score on the PANSS (p=ns). Total scores for the Brief Psychotic Rating Scale were significantly reduced from baseline to week 6 (p less than 0.01). From baseline to endpoint, Clinical Global Impression-Severity (CGI-S) scores decreased by 31.6% (p less than 0.001) and CGI-Improvement scores decreased by 45.5% (p less than 0.0001). The most common adverse events observed were weight gain (72%), somnolence (72%), depression (63%), orthostatic hypertension (45%), emotional indifference (45%), akathisia (36%). Because three patients in this study improved significantly at a dose of only 1 mg/day, the authors suggest that lower initial doses of risperidone should be utilized in adolescents, as compared with adults, in order to minimize the risk of extrapyramidal side effects. Larger, controlled studies are needed to further define the safety and efficacy of risperidone for the treatment of schizophrenia in pediatric patients (Zalsman et al, 2003).

c) A 15-year old boy, with a diagnosis of simple deteriorative disorder (DSM-IV criteria or simple schizophrenia), showed significant improvement following risperidone therapy. He was started on 2 mg daily and this dosage was increased to 3 mg per day the following week. He did not report any significant side effects and showed clinical improvement. The author advocates the further study of the efficacy of risperidone in the treatment of simple schizophrenia (Hirose, 2000).

4.5.AA Schizotypal personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Appeared to effective in the treatment of schizotypal personality disorder

3) Adult:

a) Risperidone treatment was more effective than placebo in reducing the symptoms of schizotypal personality disorder. In a 9-week, randomized, double-blind, placebo-controlled study, patients (n=25) with schizotypal personality disorder received placebo or risperidone (0.25 milligrams (mg)/day for 1 week, then titrated by 0.5 mg/day every 2 weeks for 8 weeks; final dose, 2 mg/day). Five (20%) patients had comorbid borderline personality disorder. Weekly measurements of symptoms were taken using the Positive and Negative Syndrome Scale (PANSS), the Hamilton Rating Scale for Depression (HAM-D), and the Clinical Global Impressions Scale (CGI). The Schizotypal Personality Questionnaire (SPQ) was administered biweekly. Total PANSS scores were significantly lower in risperidone-treated patients as compared with placebo at weeks 3, 5, 7, and 9 (p=0.021, p=0.003, p=0.003, and p=0.013, respectively). PANSS negative symptom scores were lower in patients in the risperidone group than in the placebo group at all time points, with the difference reaching significance at 3, 5, and 7 weeks (p=0.027, p=0.006, and p=0.01, respectively). Patients in the risperidone group had significantly lower PANSS general symptom scores than patients in the placebo group at weeks 3, 5, 7, and 9 (p=0.042, p=0.007, p=0.005, and p=0.013, respectively). Risperidone-treated patients had significantly lower PANSS positive symptom scores at weeks 7 and 9 as compared with placebo (p=0.028 and p=0.009, respectively). At the end of treatment, SPQ and CGI scores showed greater reductions in the risperidone group than in the placebo group, however this difference was not significant. The change in HAM-D scores was non- significant in both groups. Adverse events included weakness, decreased sexual arousal, delayed ejaculation, mild dystonic reaction and dry mouth. Larger studies are needed to confirm these findings (Koenigsberg et al, 2003).

4.5.AB Stuttering

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Risperidone may be beneficial

3) Adult:
a) Risperidone may be effective in the treatment of developmental stuttering. A small, randomized, double- blind, placebo-controlled study was conducted to assess the efficacy of risperidone in the treatment of developmental stuttering in 16 adults. Eight subjects received placebo and eight received risperidone at 0.5 mg once daily at night, increased to a maximum of 2 mg per day. After 6 weeks of treatment, decreases in all measures of stuttering severity were greater in the risperidone group than in the placebo group; the between-treatment difference was significant (p less than 0.05) on the most important measure, the percentage of syllables stuttered. In the risperidone group, reductions from baseline in scores for the percentage of syllables stuttered, time stuttering as a percentage of total time speaking, and overall stuttering severity were significant (p less than 0.01); changes in scores on the fourth measure of stuttering, duration, were not significant. No significant differences occurred in the placebo group. Five of the eight patients in the risperidone group responded best to the 0.5 mg per day dose, with stuttering recurring at higher doses. Risperidone was generally well-tolerated (Maguire et al, 2000).
b) In one small study (n=21), patients were randomized to receive risperidone (n=10) up to 2 milligrams daily or placebo (n=11) for 6 weeks. Every 2 weeks stuttering severity, adverse events, compliance, and tolerability were assessed. Risperidone treatment significantly decreased the mean stuttering severity compared to placebo (3.93 and 5.23, respectively (p less than 0.05). However, elevated cognitive impairment and social alienation-personal disorganization did not (Maguire et al, 1999).

4.5.AC Tardive dyskinesia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in reducing tardive dyskinesia in some patients when substituted for conventional antipsychotics
See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

3) Adult:
a) Risperidone treatment was more effective than withdrawal of antipsychotic therapy in reducing symptoms of severe tardive dyskinesia. In a randomized, double-blind, placebo-controlled study (n=42), schizophrenic patients with persistent, severe tardive dyskinesia received risperidone (initial, 2 milligrams (mg)/day titrated in 2 mg increments to 6 mg/day over 6 weeks) or placebo for 12 weeks following a 4-week washout period from all original conventional antipsychotic medications. Response was defined as a decrease of at 3 or 4 in the Abnormal Involuntary Movement Scale (AIMS) total score. Risperidone- treated patients showed a significantly greater reduction in the total mean AIMS score from baseline to endpoint, as compared with placebo (5.5 vs 1.1, respectively; p=0.001). This significant difference of change in the total AIMS score between groups was observed from week 8 to endpoint, and grew more distinct over time. In addition, the responder rate was significantly higher in the risperidone group as compared with the placebo group (68%(15) vs 30%(6), respectively; p=0.029). The tardive dyskinesia improvement in the risperidone group was noted mainly in the buccolinguomasticatory area rather than in the choreoathetoid movement of the extremities. Additional studies are needed to evaluate the long-term efficacy of risperidone for the treatment of tardive dyskinesia and whether symptoms reemerge when the risperidone dosage is withdrawn or reduced (Bai et al, 2003).
b) Five of nine patients with tardive dyskinesia showed a lessening of severity of tardive dyskinesia when risperidone was substituted for the conventional antipsychotic drug they had been taking. After a tapering of the previous antipsychotic and antiparkinsonian drug regimen, patients were prescribed risperidone 2 milligrams (mg) per day. The dose was gradually increased over 4 weeks to 8 mg/day and later adjusted to maintain the least severity of tardive dyskinesia. Over the year-long study, 5 patients showed improvement of more than 4 points in score on the Abnormal Involuntary Movement Scale (AIMS) (responders). The dose for maximum effect in responders was 6 mg/day. Mean improvement in AIMS score was 7 for responders and 0.5 for nonresponders (Chen et al, 2001).
c) Tardive movements were resolved with the addition of risperidone and a reduction in doses of trihexyphenidyl and diazepam in a 47-year-old schizophrenic patient (Chong et al, 1999).

d) Tardive dyskinesia was diminished in a 54-year-old schizophrenic woman after switching to risperidone therapy (Santone et al, 1997a). Risperidone 2 milligrams daily resolved her schizophrenic symptoms. At 8 months, her tardive dyskinesia was no longer present and at 10 months, her parkinsonism had also resolved.

4.5.AD Trichotillomania

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Augmented therapy in patients with trichotillomania
3) Adult:
a) In a case series, 3 of 5 patients with trichotillomania disorder (DSM-IV criteria) showed significant improvement on the Clinical Global Impression Change Scale after receiving augmentation with risperidone 1 milligram/day (Stein et al, 1997).

4.5.AE Water intoxication syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
No effect on self-induced water intoxication
3) Adult:
a) Risperidone had no significant effect in treating self-induced water intoxication. In a prospective, 11 month open-label study of risperidone in 8 men with chronic schizophrenia and a history of polydipsia and episodic water intoxication, fluid intake was monitored through 6 months of 4 times daily weights. Risperidone was increased in doses up to 16 milligrams per day. Though there was a trend toward decreased fluid intake, there was no significant change in body weight over the study period (Milson et al, 1996).

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Amisulpride

4.6.A.1 Schizophrenia

a) Amisulpride and risperidone therapies were equally effective in the treatment of positive and negative symptoms in Taiwanese patients with schizophrenia. In a randomized, double-blind, multi-center study, schizophrenic patients with productive positive symptoms received oral amisulpride 400 to 800 milligrams (mg) per day (mean dose, 630 mg/day) or risperidone 4 to 8 mg per day (mean dose, 6.88 mg/day) for 6 weeks following a 3-to-6-day washout period. At 6 weeks, patients in both treatment groups showed significant improvements in the Positive and Negative Symptom Scale (PANSS) total score and the three PANSS sub- scale scores, but no significant differences existed between treatment groups. The occurrence of adverse events was also similar between groups. Akathisia (16%), tremor (12%), and constipation (12%) were most commonly reported with risperidone administration while insomnia (17.3%) and constipation (17.3%) were most frequently reported in the amisulpride group (Hwang et al, 2003).

4.6.B Chlorpromazine

4.6.B.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of risperidone was 4 milligrams/day (equivalent to

chlorpromazine 200 milligrams/day) (Woods SW, 2003).

4.6.C Clozapine

4.6.C.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000).

4.6.C.2 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.C.3 Parkinson's disease - Psychotic disorder

a) In subjects with Parkinson's Disease (PD), risperidone may be considered as an alternative to clozapine however, risperidone may worsen extrapyramidal symptoms more than clozapine and therefore must be used with caution. A small (n=10) double-blind trial compared the efficacy and safety of risperidone and clozapine for the treatment of psychosis in patients with PD. Five patients were randomized to receive clozapine and five patients received risperidone. Clozapine was started at 12.5 mg at bedtime and risperidone was started at 0.5 mg per day and both were titrated to symptomatic improvement was achieved or intolerable side effects emerged. Each subject received drug for 3 months and was assessed prior to initiation of treatment and after 2, 4, 8, and 12 weeks of treatment. Assessment was based on scores from the Brief Psychiatric Rating Scale and the Unified Parkinson's Disease Rating Scale. Mean improvement in the Brief Psychiatric Rating Scale psychosis score was similar in the clozapine and the risperidone groups (p=0.23). Although the mean motor Unified Parkinson's Disease Rating Scale scores worsened in the risperidone group and improved in the clozapine group, this difference did not reach statistical significance. Risperidone may be a reasonable alternative to clozapine in the treatment of psychosis in patients with PD however, it must be used with caution since it may worsen extrapyramidal side effects (Ellis et al, 2000).

4.6.C.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global

neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002).

b) Clozapine was superior to risperidone for improving positive and negative symptoms of schizophrenia in patients with poor previous response to treatment. In a prospective, double-blind study, patients meeting DSM-IV criteria for schizophrenia and having had poor response to previous treatment underwent a single-blind placebo run-in period when all psychotropic and anticholinergic medications were withdrawn. They were then randomly assigned to treatment with clozapine (n=138) or risperidone (n=135). Starting with daily doses of clozapine 12.5 milligrams (mg) and risperidone 1 mg, dosages were titrated over a period of 4 weeks to a minimum of 300 mg/day and 4 mg/day, respectively, and possibly to 600 mg/day and 6 mg/day. Patients unable to tolerate the minimum dose were withdrawn from the study. During the next 8 weeks, doses were adjusted at 2-week intervals within the range of 200 to 900 mg/day for clozapine and 2 to 15 mg/day for risperidone. For patients who completed the 12-week study (n=201), median final daily doses were 600 mg for clozapine and 9 mg for risperidone. Changes in the Positive and Negative Syndrome Scale of the BPRS (Brief Psychiatric Rating Scale) and in the Clinical Global Impression (CBI) scale were significantly greater in the clozapine group than in the risperidone group for the intent-to-treat population (those who received at least one dose of treatment medication and had one post-dose BPRS evaluation) and in the per- protocol population (those who completed the 28-day dose-setting period) (p less than 0.008 for all comparisons). Eighty-six percent of patients in the clozapine per-protocol population and 70% in the risperidone per-protocol population showed 20% or more improvement in the BPRS score (for difference between groups, p less than 0.01). By the end of the study, 94 (76%) patients in the clozapine group and 81 (64%) in the risperidone group no longer met the severity of psychopathology inclusion criteria (p less than 0.05). Extrapyramidal symptoms occurred significantly less frequently in the clozapine group than in the risperidone group (13% vs 28%, p=0.008). However, convulsions, dizziness, sialorrhea, tachycardia, and somnolence occurred significantly more frequently among those receiving clozapine. No case of agranulocytosis was observed during the study. Granulocytopenia occurred with low incidence in both groups (1% clozapine, 2% risperidone). Low neutrophil count was significantly more frequent among risperidone-treated patients (3% vs 11%, p less than 0.01). Hypotension occurred more frequently among risperidone-treated patients (p less than 0.01). Weight gain was significantly greater for the clozapine group (2.4 kilograms vs 0.2 kilograms; p less than 0.002) (Azorin et al, 2001).

c) In the treatment of refractory schizophrenia, giving a risperidone trial before clozapine was more beneficial given its better side effect profile. A retrospective review study compared the relative efficacy profiles of clozapine and risperidone in a group of the most refractory, chronically institutionalized patients. The specific goal was to identify superiority (or lack thereof) of either agent on global clinical outcome as well as on specific symptom domains, including positive symptoms, negative symptoms, and aggressive behavior, compared with a baseline of conventional antipsychotic treatment in a total of 24 patients. Information obtained from systematic retrospective chart review was blindly rated by 2 psychiatrists using the 7-point Clinical Global Impressions Improvement (CGI-I) scale on overall clinical state and along specific symptom domains as above. The mean dose was 520 +/- 94 mg daily for clozapine and 7.5 +/- 2.2 mg daily for risperidone. Fourteen patients (58%) were classified as responders to clozapine, while 6 (25%) responded to risperidone. On specific symptom domains, response rates to clozapine were 38% (9/24) on positive symptoms, 29% (7/24) on negative symptoms, and 71% (12/17) on aggressive behavior. For risperidone, response rates were 17% (4/24) on positive symptoms, 8% (2/24) on negative symptoms, and 41% (7/17) on aggressive behavior. The results of this study would support the utility of first giving a risperidone trial in patients with treatment-refractory schizophrenia because of its better side effect profile compared with clozapine (Sharif et al, 2000).

d) Risperidone and clozapine had similar antipsychotic effects in 59 patients with paranoid schizophrenia. In a double-blind randomized study, patients were divided in three groups receiving either 4 milligrams risperidone, 8 milligrams risperidone, or 400 milligrams clozapine daily for 28 days. The antipsychotic effect was highly significant for both risperidone and clozapine. Patients on 4 milligrams of risperidone better tolerated therapy than those patients receiving clozapine. Withdrawals from clozapine treatment were mostly due to side effects, whereas withdrawals from risperidone treatment occurred from lack of therapeutic response (Heinrich et al, 1994).

e) Similar effectiveness of risperidone and clozapine was also observed in an 8-week, double-blind trial that allowed dose adjustment based on response in 86 patients with treatment-resistant chronic schizophrenia. The mean effective dose was 6.4 milligrams (mg) for risperidone and 291 mg for clozapine. The larger proportion of patients with clinical improvement after 7 and 14 days' treatment with risperidone suggested earlier onset of effect compared to clozapine treatment (Bondolfi et al, 1998)

f) In a prospective, open-label, 12-week trial, risperidone was found to be a poor substitute for clozapine in the treatment of chronic refractory schizophrenia. Six patients with schizophrenia and 4 with schizoaffective disorder were switched from a mean clozapine dose of 565 milligrams(mg)/day to a mean dose of risperidone 8 mg/day at 12 weeks. No subjects im-

proved after being switched. Overall, patients who were switched from clozapine tended to worsen when taking risperidone. Statistically significant increases over baseline in the mean total of the Positive and Negative Syndrome Scale occurred at 9 and 12 weeks (P less than 0.05). The Brief Psychiatric Rating Scale scores also increased significantly over baseline at weeks 6, 9, and 12 (P less than 0.05). Five subjects failed to complete the entire 12 weeks. Of the 5 patients that completed the 12 weeks, the Clinical Global Impressions Scale indicated that 2 patients were unchanged, one was minimally worse, and 2 were much worse. The authors concluded that this study does not support replacing clozapine with risperidone for patients with treatment-resistant schizophrenia (Still et al, 1996).

4.6.C.5) Adverse Effects

a) Adverse effects and death were more commonly reported as the reasons for the discontinuation of clozapine while ineffectiveness was more often reported as the reason for discontinuation of risperidone (long-acting injection) in a retrospective, phase 3 study (n=322). Patients with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders who received clozapine (n=161), and had mean duration of therapy of 12.3 +/- 18.6 months (range, 0.25 to 100 months; median, 3 months) were matched by age (mean age, 40 +/- 12.6 years (yr); range, 18 to 83 yr) and gender at discontinuation to patients who discontinued risperidone long-acting injection (n=161). The risperidone patients (mean age, 39.9 +/- 13.1 yr , range 18 to 83 yr) were matched without knowledge of the reason for discontinuation of therapy (mean duration of therapy of 5.9 +/- 8.7 months; range, 0.5 to 46 months; median, 3 months). The reasons for discontinuation differed significantly between clozapine and risperidone injection; additionally, death as reason for discontinuation was significantly more common with clozapine (13%) vs risperidone injection (1.9%) (Taylor et al, 2009).

Reasons for Discontinuation: Clozapine vs RisperidoneReason
Clozapine (n=161) n (%)
Risperidone (n=161) n (%)
OR (95% CI)
p value
Patient's decision
77 (47.8)
64 (39.7)
1.41 (0.89 to 2.21)
0.139
Adverse effects
57 (35.4)
32 (19.9)
2.19 (1.31 to 3.67)
0.0023
Ineffectiveness
3 (1.9)
59 (36.6)
0.034 (0.01 to 0.14)
less than 0.0001
Death
21 (13)
3 (1.9)
7 (2.09 to 23.5)
0.0003
Other
3 (1.9)
3 (1.9)
-
-

The cause of death reported in clozapine patients (mean age, 49.2 +/- 14.5 yr, range 30 to 83 yr) included: pneumonia (n=5), lung carcinoma (n=3), other carcinoma (n=2), myocardial infarction (n=2), cerebrovascular accident (n=2), clozapine overdose (n=2), gastrointestinal hemorrhage (n=1), cardiac arrest (n=1), left ventricular failure (n=1), asphyxia during restraint (n=1) and sepsis (n=1). There was no incidence of neutropenia or agranulocytosis at the time of death in any of the patients. The cause of death in the risperidone patients included: myocardial infarction (n=1), left ventricular failure (n=1) and sudden unexplained death (n=1). The mortality rate for clozapine patients was 8.5 per 1000 patient-years (95% CI, 5.53 to 13.07) vs 5.3 per 1000 patient-years (95% CI, 1.7 to 16.61) (Taylor et al, 2009).

b) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of pancreatitis than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose,

15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003).
c) Clozapine was associated with fewer extrapyramidal side effects (EPS) than was risperidone (Miller et al, 1998). Outpatients receiving stable doses of clozapine (n=41), risperidone (n=23), or conventional antipsychotics (n=42) were screened for EPS. Utilizing the Barnes Akathisia Scale, akathisia was noted in 7.3% of clozapine patients, 13% of risperidone patients, and 23.8% of conventional antipsychotic users. From the Simpson-Angus scale, rigidity and cogwheeling were noted in 4.9% and 2.4% of clozapine patients, 17.4% and 17.4% of risperidone patients, and 35.7% and 26.2% of conventional antipsychotic users, respectively. However, salivation was noted in 36.6% of clozapine patients, 8.7% of risperidone patients, and 4.8% of conventional antipsychotic users.
d) Insomnia and extrapyramidal side effects were more common with risperidone, and sedation and weight gain were more common with clozapine in a single-blind, crossover pilot study of the side effect profiles of the 2 drugs (Daniel et al, 1996). Twenty outpatients with schizophrenia or schizoaffective disorder were randomized to each drug for 6 weeks separated by a 1-week tapering-off period before crossover. The mean doses at week 6 were 6.1 milligrams/day (range 1 to 10 mg/d) of risperidone and 375 milligrams/day (range 75 to 800 mg/d) of clozapine. Three patients dropped out of the study; there was no significant difference in therapeutic effect between the 2 treatment groups. Mean body weight was greater (p less than 0.005) and sleepiness and lack of alertness were reported more often after the clozapine treatment phase. Restlessness and insomnia were more frequent complaints after the risperidone phase. A longer, double-blind study with a large sample of patients is needed to further elucidate the therapeutic differences and side effect profiles of these 2 drugs.

4.6.D Haloperidol

4.6.D.1 Cognitive function finding

a) Results of a multicenter, randomized, double blind trial assessing cognitive function in patients experiencing their first schizophrenic episode or a related psychosis demonstrated that overall improvement in cognitive functioning was superior with risperidone than with haloperidol. Patients (n=533) were randomized to receive either risperidone or haloperidol on a one-to-one randomization basis for a period of 2 years or more. There were no significant differences in sex, race or ethnicity, age, diagnosis, or previous neuroleptic treatment in either group. Dosing strategies were equivalent in both groups where patients were started on 1 milligram per day (mg/day) of the study drug and titrated up to 4 mg/day, or in some cases, to a maximum of 8 mg/day. Patients in the risperidone group received the trial medication (mean modal total dose 3.3 mg/day) for an average of 192 days while patients in the haloperidol group received treatment (mean modal total dose 2.9 mg/day) for an average of 218 days. Cognitive assessments, performed at several different follow-up intervals, included examinations of verbal and visuospatial episodic memory, vigilance, executive functioning, processing speed, and verbal fluency. An intention-to-treat analysis conducted with a focus on the 3-month assessment revealed that there was significant improvement from baseline in the risperidone group (n=169) for all measures except category verbal fluency and letter verbal fluency (p less than 0.05). In the haloperidol group (n=169), statistically significant improvements from baseline were noted in episodic memory, vigilance, and visuomotor speed but not in executive functioning and verbal fluency. Comparison between the two groups showed that, after 3 months of treatment, the risperidone group was significantly more beneficial than the haloperidol group on the composite measure of cognitive functioning. In addition, cognitive improvement as a result of treatment with risperidone was not affected by changes in symptoms. Risperidone therapy also proved to be superior than haloperidol in relapse prevention and extrapyramidal side effects (Harvey et al, 2005).
b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatment-resistant schizophrenic patients than did haloperidol therapy (Green et al, 1997). In a randomized, double-blind comparison of treatment with risperidone (n = 30) and haloperidol (n = 29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose and flexible dose regimen. Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from baseline performance at both the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated patients did not change significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on neurocognitive abilities.

4.6.D.2 Dementia

a) Some Chinese patients with dementia, who were non-responders to haloperidol, responded to risperidone with decreased behavioral disturbances and improved mood. Thirty-five Chinese patients who had shown insufficient response to an 8-week trial with haloperidol (i.e., having a total score of more than 10 on the Brief Psychiatric Rating Scale (BPRS) at the end of 8 weeks) (typical dose 1 gram/day) were switched abruptly from haloperidol to risperidone 0.5 milligrams (mg) at bedtime for weeks 1 to 4 and then (if tolerated) to 1 mg at bedtime for weeks 5 to 12. At week 13, the regimen was shifted

again to haloperidol at the dose used in the earlier trial. Twenty-nine patients completed the trial. Sixteen patients responded by the end of the risperidone trial (response = a decrease of 25% in the BPRS score). After haloperidol resumption, the mean BPRS score stayed the same, but the number of responders decreased to 15. Patients with vascular dementia were almost 6 times more likely to respond to risperidone than patients with Alzheimer's disease. Mean scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale decreased (6.1 at baseline to 1.9 at 12 weeks of risperidone treatment) and increased after switching back to haloperidol (to 2.4 after 4 weeks of haloperidol). Thirty- four of the 35 patients tolerated both doses of risperidone and haloperidol 1 mg/day. One patient experienced moderate rigidity with risperidone 1 mg/day, which was relieved by reduction of the dose to 0.5 mg/day. Patients experienced fewer extrapyramidal symptoms with risperidone than with haloperidol (Lane et al, 2002).

b) Both risperidone and haloperidol in low doses reduced the severity and frequency of behavioral and psychological symptoms of elderly Chinese patients with dementia. Risperidone was associated with less severe exacerbation of extrapyramidal symptoms (EPS). In a randomized, double-blind trial, 55 elderly Chinese patients (mean age 80 years) with Alzheimer's dementia or vascular dementia and with behavioral disturbance, were given either risperidone or haloperidol for 12 weeks after a 2-week washout period for elimination of psychotropic and antiparkinsonian drugs. The starting dose for both treatment drugs was 0.5 milligrams (mg) at night; doses were adjusted individually in increments of 0.5 mg no faster than every other day, to a maximum of 2 mg/day. At 12 weeks, the mean daily dose of haloperidol was 0.9 mg, and that of risperidone, 0.85 mg. Significant improvements on the Cohen- Mansfield Agitation Inventory (CMAI) were evident in both groups (haloperidol, p less than 0.001; risperidone, p=0.002). Significant reduction was seen at 2 weeks in the risperidone group and at 4 weeks in the haloperidol group. With risperidone, there were significant improvements in scores for psychosis, activity disturbances, aggressiveness and diurnal rhythm disturbances, whereas with haloperidol, improvement in only the aggressiveness score reached statistical significance. However, none of the measures showed a significant difference between the treatment groups. With haloperidol, there was a significant worsening of EPS (p less than 0.001), whereas, with risperidone, EPS scores were only modestly worsened. Final EPS scores were significantly higher for haloperidol (p=0.001) (Chan et al, 2001).

4.6.D.3 Extrapyramidal disease

a) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidone caused few or no extrapyramidal symptoms (Simpson & Lindenmayer, 1997). Mean changes in Extrapyramidal Symptom Rating Scale (ESRS) scores from baseline to worst score were significantly lower in each risperidone group than the haloperidol group (P less than 0.001).

4.6.D.4 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperidol in mania and found comparable results with risperidone. Patients (n=45) were assigned to take risperidone (as monotherapy), dosed at 6 mg per day, haloperidol at 10mg per day, or 800 to 1000 mg daily of lithium. All 3 groups showed a similar improvement on Brief Psychiatric Rating Scale and Young Mania Rating Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worsen in any of the risperidone treated patients (Segal et al, 1998).

4.6.D.5 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002a).

b) The risk of relapse of schizophrenia was significantly less with long-term treatment with risperidone than with haloperidol. In a randomized, double-blind study, 365 patients meeting DSM-IV criteria for schizophrenia or

schizoaffective disorder and in a stable condition were given flexible doses of either risperidone or haloperidol. The trial was continued until the last enrolled patient had completed one year of treatment. Means of modal daily doses were 4.9 milligrams (mg) for risperidone and 11.7 mg for haloperidol. At the end of the study, 25% of the risperidone group and 40% of the haloperidol group had relapsed. The risk of relapse was significantly higher among patients assigned to haloperidol (risk ratio 1.93, p less than 0.001). The risk of premature discontinuation was greater for the haloperidol group than for the risperidone group (risk ratio 1.52), mainly because of relapse. Median duration of treatment for the risperidone group was 364 days and for the haloperidol group, 238 days (p=0.02). The subtypes of relapse (psychiatric hospitalization, clinical deterioration, increase in level of care, suicidal or homicidal ideation) were similar in the 2 groups. In the risperidone group, there were improvements from baseline in positive and negative symptoms, disorganized thoughts, and anxiety- depression, whereas symptoms were not improved with haloperidol. The severity of extrapyramidal symptoms was reduced from baseline in the risperidone group and increased in the haloperidol group. Differences between the groups were significant (p less than 0.02 for total score on the Extrapyramidal Symptom Rating Scale). The most frequent adverse events were somnolence (14% with risperidone and 25% with haloperidol), agitation (10% and 18% respectively), and hyperkinesia (5% and 20%, respectively). Those taking risperidone had a mean increase in body weight of 2.3 kilograms (kg) and those taking haloperidol had a mean decrease of 0.73 kg (p less than 0.001) (Csernansky et al, 2002).

c) Risperidone was more efficacious and had fewer adverse effects than haloperidol when used to treat refractory schizophrenia in Chinese patients. Chinese patients, meeting DSM-III-R criteria for schizophrenia and having a history of treatment failure with 3 conventional neuroleptics given at least 3 months at full dose, were randomly assigned to receive risperidone (n=41) or haloperidol (n=37) for a 12-week, double-blind trial. The dose of risperidone was increased during the first week to 6 milligrams (mg) per day, and the dose of haloperidol to 20 mg/day. By the end of the study, the average score on the Positive and Negative Syndrome Scale (PANSS) had decreased by 39.8% for the risperidone group and by 28.3% for the haloperidol group (p=0.03). The general psychopathology and negative subscores of the PANSS showed greater improvement with risperidone, but there was no difference between treatments in the positive subscore. The proportion of patients rated as responders was higher in the risperidone group (31 of 41 vs 20 of 37, p=0.046). Total scores on the Treatment Emergent Symptoms Scale (TESS) were significantly lower with risperidone than with haloperidol (2.9 vs 6.9, p=0.01). Particular subscores significantly favoring risperidone were those showing symptoms of the nervous system (rigidity, tremor, dystonia, and akathisia) and of the cardiovascular system (hypotension, dizziness, tachycardia, hypertension and electrocardiogram abnormalities) (p=0.02 and p=0.04, respectively). Patients in the risperidone group required less medication for extrapyramidal symptoms during the study than did patients in the haloperidol group. The authors mentioned that the dose of haloperidol was higher than the dose recommended in the United States and Europe and may have accounted for some of the difference between treatments in efficacy and adverse effects (Zhang et al, 2001).

d) Results of a subanalysis of data from the multinational risperidone trial (double-blind, randomized, parallel-group) reported that the reduction in negative symptoms was significantly better in patients receiving risperidone 16 mg/day than haloperidol 10 mg/day (p less than 0.05) (Moller et al, 1997). Patients with chronic schizophrenia (n=169) were treated with risperidone 1 mg, 4 mg, 8 mg, 12 mg, or 16 mg, or haloperidol 10 mg/day for 8 weeks. Improvement was noted in each group. Risperidone onset was faster than haloperidol. An analysis of the Positive and Negative Syndrome Scale cluster scores revealed significantly greater improvement in the risperidone-treated patients than in the haloperidol group on 2 clusters: activity and anxiety/depression (p less than 0.05).

e) Risperidone was significantly better than haloperidol in the treatment of chronic schizophrenia using combined data from 2 studies (Chouinard et al, 1993a; Marder & Meibach, 1994) to evaluate five factors of the Positive and Negative Syndrome Scale (Marder et al, 1997). Data from 513 patients showed that after 6 to 8 weeks of therapy, patients receiving risperidone 6 to 16 milligrams had significantly higher adjusted mean changes in total Positive and Negative Syndrome Scale than patients treated with haloperidol (p less than 0.01). The 5 specific symptom areas that risperidone was significantly superior to haloperidol included: negative symptoms (p less than 0.01), positive symptoms (p less than 0.05), disorganized thought (p less than 0.05), uncontrolled hostility/excitement (p less than 0.01), and anxiety/depression (p less than 0.01). One author, however, noted some positive symptoms that reemerged after an initial response to risperidone (Cung & Stimmel, 1997).

f) In a meta-analysis, risperidone (4 to 8 milligrams(mg)/day) was found to be more effective and produce fewer extrapyramidal effects than haloperidol (4 to 20 mg/day). Seven studies done in a double-blind, randomized fashion were included. The primary outcome measure was clinical improvement defined as a 20% reduction in the total scores on the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale. Results showed that patients identified as treatment failures were 50% of those taking risperidone, 66% on haloperidol, and 83% on placebo. There was a highly significant need for anticholinergic medication in the haloperidol-treated patients as compared to risperidone (P less than 0.00001) (de Oliveira et al, 1996).

g) Risperidone was more effective than haloperidol in a double-blind, placebo-controlled, multicenter study (Marder & Meibach, 1994). 388 schizophrenic patients were randomly assigned to receive 4 fixed doses of risperidone (2, 6, 10, and 16 milligrams/day, on a BID schedule), haloperidol 20 milligrams daily or placebo for 8-weeks (Marder and Meibach, 1994). Patients receiving risperidone 6 to 16 milligrams showed statistically greater improvement than placebo or haloperidol in Clinical Global Impression (CGI) and total Positive and Negative Syndrome Scale (PANSS) scores. Of the

four doses studied, the 6, 10, and 16 milligram doses were all effective with the 6 milligram dose being the most effective. Similar results have been reported (Chouinard et al, 1993a; Marder, 1992).

h) In an 8-week, double-blind study, 1362 schizophrenic patients were randomly assigned to receive either risperidone 1, 4, 8, 12, 16 milligrams/day, on a BID schedule, or haloperidol 10 milligrams daily (Muller-Spahn, 1992). Significantly greater improvement in Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total score, the PANSS General Psychopathology subscale, the BPRS Activity and Anxiety/Depression cluster, was observed in the risperidone 4 milligram and 8 milligram groups versus the haloperidol-treated patients. In addition, a greater percentage of patients treated with risperidone 4 and 8 milligrams achieved clinical improvement on the PANSS and BPRS as compared with the haloperidol group.

i) Risperidone was faster acting, more effective, and had fewer side effects than haloperidol in a study to determine efficacy in treating negative symptoms of schizophrenia (Claus et al, 1992a). The multicenter double-blind study that took place over a period of 15 weeks included a two-week run-in period and a one-week washout period. The patients (n=42) took one to 5 mg bid of either drug for a period of 12 weeks. The Positive and Negative Syndrome Scale for Schizophrenia was the key efficacy parameter. The Schedule for Affective Disorders and Schizophrenia Change Conversion was used as a diagnostic aid and symptom severity measure. The Clinical Global Impression Scale was complete as a global rating. In addition, the occurrence of extrapyramidal side effects was also monitored. The improvement in PANSS was approximately three times greater in the risperidone group, both at week six and at endpoint. In addition, the onset of therapeutic effects was quicker in the risperidone group. Finally, the risperidone group needed 10 times less anticholinergic medication to control the extrapyramidal side effects than did the haloperidol group. According to this study, risperidone showed a greater improvement in schizophrenic symptoms than haloperidol.

j) Risperidone was less effective as monotherapy when compared to combination therapy of haloperidol and amitriptyline in patients with coexisting psychotic and depressive disorders. In this double-blind multicenter study, 123 patients were randomized to receive either risperidone (dose titrated to 8 milligrams (mg) by the end of week 1) or the combination of haloperidol and amitriptyline (doses titrated to 10 mg and 200 mg by the end of week 1). For all patients, doses were then adjusted under double blind conditions over the next 5 weeks based on response. At endpoint, the mean effective daily dose was 6.9 mg risperidone, and 9 mg haloperidol in combination with 180 mg amitriptyline. In the 98 patients who completed at least 3 weeks of treatment, Brief Psychiatric Rating Scale (BPRS) scores decreased in both treatment groups, but the reduction in the combination treatment group was significantly greater than the risperidone treated group (p=0.004). The proportion of patients achieving at least 50% improvement in BPRS scores was also significantly higher with combination therapy (p = 0.002). Greater benefit by combination therapy was still observed in an intent-to-treat analyses of the 123 patients. Use of anticholinergic medication for extrapyramidal symptoms was higher in the risperidone group (Muller-Siecheneder et al, 1998)

4.6.D.6) Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003a).

4.6.E Lithium

4.6.E.1 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperidol in mania and found comparable results with risperidone. Patients (n=45) were assigned to take risperidone (as monotherapy), dosed at 6 mg per day, haloperidol at 10mg per day, or 800 to 1000 mg daily of lithium. All 3 groups showed a similar improvement on Brief Psychiatric Rating Scale and Young Mania Rating Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worsen in any of the risperidone treated patients (Segal et al, 1998a).

4.6.F Olanzapine

4.6.F.1 Agitation, acute - Psychotic disorder

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvements on the

Excited Component for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated for acute psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased over time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated measures of analysis of PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of treatment or in the interaction of treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in the olanzapine ODT group compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences between the treatment groups for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.6.F.2 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000a).

4.6.F.3 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F.4 Dementia - Problem behavior

a) Risperidone and olanzapine were equally effective in the treatment of dementia-related behavioral disturbances in elderly patients at long- term care facilities. In a double-blind, parallel study, patients (mean age, 83 years) with dementia received oral olanzapine (n=20, initial dose, 2.5 milligrams (mg)/day, titrated to maximum dose of 10 mg/day) or risperidone (n=19, initial dose 0.5 mg/day, titrated to maximum dose of 2 mg/day) at bedtime for two weeks following a 3-day washout period of psychotropic drugs. Antidepressants and mood stabilizers were allowed at stable doses and lorazepam was used as a rescue medication at doses of 0.5 to 1 mg as needed for acute agitation. The mean daily doses for olanzapine and risperidone were 6.65 mg (range, 2.5 to 10 mg) and 1.47 mg (range, 0.5 to 2 mg), respectively. Lorazepam was utilized a median of 3.5 days (range 1-12 days) and the median dose was 2 mg (range, 0.2 to 21 mg). Primary outcome measures were the Neuropsychiatric Inventory (NPI) and the Clinical Global Impressions Scale (CGI). Both treatments significantly lowered CGI scores and total NPI scores from baseline to endpoint (p less than 0.0001, both values), however, there was no difference between the two groups. Adverse events were frequent in this elderly population, with the most common including drowsiness, falls, and extrapyramidal symptoms (Fontaine et at, 2003).

4.6.F.5 First episode psychosis

a) Olanzapine and risperidone were equally efficacious in treating patients with first-episode schizophrenia spectrum disorders; however, both medications caused substantial rapid weight gain with significantly more weight gained recorded by olanzapine-treated patients. In this open-label randomized study, patients (mean age 23.3 years; 70% male) with first-episode schizophrenia (75%), schizophreniform disorder (17%), or schizoaffective disorder (8%) and less than 12 weeks of lifetime antipsychotic medication treatment were randomly assigned to treatment with olanzapine (2.5 to 20 mg per day; n=56) or risperdal (1 to 6 mg per day; n=56). Data represents response rates at 4 months in an ongoing study assessing first-episode patients over 3 years. At study entry, patients reported substantial positive symptoms and less pronounced negative symptoms, with a slightly greater than 2 year history of psychotic symptoms. Data analysis included all patients taking 1 dose of medication following randomization. Mean modal doses were 11.8 mg/day and 3.9 mg/day for olanzapine and risperidone, respectively. Response rates were similar with olanzapine (43.7%; 95% CI, 28.8% to 58.6%) and risperidone (54.3%; CI, 39.9% to 68.7%); and mean time to response was 10.9 weeks and 10.4 weeks with olanzapine-treated and risperidone-treated patients, respectively. Mean length of time that patients maintained their responder status was 6.6 weeks (95% CI, 5.6 to 7.7) with olanzapine and 9.5 weeks with risperidone (95% CI, 8.6 to 10.4). The study may have lacked adequate power to detect a difference between these 2 antipsychotics as power was based on recruitment of 130 patients which was not achieved. Weight gain was a significant adverse event in both treatment groups. Mean weight at study entry for all subjects was 70.1 kg. At 4 months, the increase in weight relative to baseline was 17.3% (95% CI, 14.2% to 20.5%) and 11.3% (95% CI, 8.4% to 14.3%) in olanzapine-treated and risperidone-treated patients, respectively. Body mass index at baseline and at 4 months was 24.3 (95% CI, 22.8 to 25.7) and 28.2 (95% CI, 26.7 to 29.7) in olanzapine-treated patients; and 23.9 (95% CI, 22.5 to 25.3) and 26.7 (95% CI, 25.2 to 28.2) in risperidone-treated patients. Differences in extrapyramidal symptom severity scores and prescription-use for extrapyramidal symptoms and akathisia favored olanzapine over risperidone, but did not reach a level of statistical significance (Robinson et al, 2006).
b) In a small observational study comparing olanzapine with risperidone in first episode psychosis in drug-naive patients, both groups showed equal improvement in symptom response, while neither group demonstrated statistically significant differences in motor or cognitive side effects. For this study, 17 pairs of comparable (age, gender, age of onset, marital status, diagnosis and estimated premorbid IQ) patients receiving risperidone (1 to 6 mg) or olanzapine (5 to 20 mg) for 1-year were selected from a parent naturalistic outcome study for analysis. Two subjects from the olanzapine group were excluded (1 due to possible substance-induced psychosis and 1 may have had a brief exposure to risperidone) resulting in an observation group of 17 risperidone-treated patients (mean age 21.7 years) and 15 olanzapine-treated patients (mean age 25.9 years). The majority of patients met DSM-IV criteria for schizophrenia spectrum psychotic disorders. The median antipsychotic dose was 2.5 mg of risperidone and 10 mg of olanzapine. Comparison at baseline and after 1 year of treatment revealed no significant differences in clinical response, cognitive testing, or motor side effects. There was a higher proportion of risperidone-treated patients receiving anticholinergic medications (4 vs 1), and twice (10 vs 5) as many patients on risperidone showed very mild parkinsonism at one year compared with olanzapine, but the difference did not reach a level of statistical significance (Malla et al, 2004).

4.6.F.6 Obsessive-compulsive disorder, Refractory

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effective in reducing obsessive-compulsive symptoms in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial; however this conclusion may be limited by the lack of a placebo arm, single-arm design, and underpowered nature of the trial. Following a 16-week prospective, open-label phase of SRI monotherapy (n=96), patients who were treatment-resistant (defined as less than 35% improvement in the total score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and a Clinical Global Impression Severity (CGI-S) score greater than 2) entered an 8-week single-blind phase (n=50). Patients in the single-blind phase received SRI daily doses of clomipramine 200 to 225 mg, citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, paroxetine 50 to 60 mg, or sertraline 200 mg, and were randomized to receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) in addition to the SRI therapy. Administration personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an intent-to-treat, last-observation carried forward analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S scores by week 8 from baseline. The magnitude of change in mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater improvement in Y-BOCS score versus baseline, and a CGI-I score of 2 or less) was similar between groups.

Primary Efficacy Endpoints at 8 Weeks

Risperidone (n=25)
Olanzapine (n=25)
Responder rates*
44% (11/25)

48% (12/25)
Mean end-point Y-BOCS score
22.6 +/- 7.2
22.2 +/- 7.4
Change in mean Y-BOCS score from baseline
-7.5; p less than 0.001
-8.4; p less than 0.001
Mean end-point CGI-S score
3.2 +/- 1.7
3.1 +/- 1.8
Change in mean CGI-S score from baseline
-1.7; p less than 0.001
-1.9; p less than 0.001
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity scale

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (24% vs 0%, p=0.022), weight gain (16% vs 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and the absence of an a priori power calculation may have contributed to the limitations of this study (Maina et al, 2008).

4.6.F.7 Schizophrenia

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in elderly patients. In an international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventional antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EPS symptoms was reduced in both groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean QT-c changes were not considered clinically relevant (Jeste et al, 2003).

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002b).

c) In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder. One hundred fifty patients were randomized to either olanzapine (10 to 20 milligrams per day (mg/d) (n=75) or risperidone (4 to 12 mg/d) (n=75) treatment for a period of 28 weeks. During the study, olanzapine- treated patients were significantly more likely to maintain a therapeutic response throughout the course of therapy than risperidone- treated patients (p=0.048). However, the proportion of patients who responded to treatment was not significantly different between groups. Overall, the incidence of side effects was similar between groups, but significantly more risperidone-treated patients required an anticholinergic to control treatment-emergent extrapyramidal effects than did those receiving olanzapine (45% versus 25%, p=0.016). Medication costs were signifi-

cantly higher for olanzapine-treated patients than those treated with risperidone ($2513 versus $1581 US), but this difference was offset by a 52% reduction in inpatient and outpatient service costs ($3516 vs $7291 US) (Edgell et al, 2000).
d) In an open-label study of patients with DSM-IV schizophrenia, olanzapine (n=21) was shown to be as effective as risperidone (n=21) as acute treatments. At 6 months, risperidone was more effective for treatment of psychotic symptoms. However, olanzapine was associated with less akathisia at the end of 6 months. At discharge the average doses of olanzapine and risperidone were 14.4 and 5.7 milligrams (mg) daily, respectively. The reduction of psychotic symptoms with risperidone was significantly greater than with olanazapine. The dose of drug was uncontrolled and adjusted by the treating psychiatrist based on the patient's response, tolerability of side effects, and manufacturer recommendations. Measures of effectiveness included the SANS, SAPS, Brief Psychiatric Rating Scale (BPRS), Global Assessment Scale (GAS) and quality of life measures. (Ho et al, 1999). Larger studies are needed comparing olanzapine and risperidone.
e) Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment of schizophrenic symptomology. In an international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with DSM-iv criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder, the olanzapine group had a significantly better overall response rate (greater than 40% decrease in the Positive and Negative syndrome Scale) and was significantly superior to risperidone in the treatment of negative symptomatology. Based on the Kaplan-Meier survival curves, a significantly greater number of the olanzapine patients maintained their response at 28 weeks compared to the risperidone group. Overall adverse reactions were significantly less with olanzapine, in particular extrapyramidal side effects, hyperprolactinemia and sexual dysfunction, with the exception of weight gain; suicide attempts occurred significantly less in the olanzapine group (Tran et al, 1997). The use of possibly unequivalent doses in this study has been subsequently criticized (Schooler, 1998; Gheuens & Grebb, 1998).

4.6.F.8) Adverse Effects
a) PANCREATITIS: The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of pancreatitis than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003b).
b) EXTRAPYRAMIDAL SYMPTOMS: Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine- and clozapine-treated patients. As compared with olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

4.6.G Paroxetine

4.6.G.1 Panic attack

a) In an 8-week, randomized, single-blind, comparative trial (n=56) of low-dose risperidone and paroxetine in the treatment of panic attacks, both treatments were effective in reducing the occurrence and severity of panic attacks but there was no difference in the efficacy of each to improve anxiety associated with panic disorders. Thirty-three (8 men, 25 women)

subjects were randomized to risperidone and 23 (8 men, 15 women) to paroxetine. The average age of the group was 40.36 +/- 12.37 years. Risperidone was initiated at 0.25 mg/day, adjusted as necessary for lack of response or sedation (maximum dose of 16 mg/day). Paroxetine was initiated at 30 mg/day, increased to a maximum of 60 mg/day if needed. The average risperidone dose was 0.53 mg (range 0.125 mg to 1 mg). All subjects in the paroxetine group received 30 mg/day except for one who required a dose of 40 mg. Subject assessments were conducted by a clinical rater blinded to medication status, using the 17-item Hamilton Depression Rating Scales (Ham-D-17), the Hamilton Anxiety Rating Scale (Ham-A), the Panic Disorder Severity Scale (PDSS), the Sheehan Panic Anxiety Scale-Patient (SPAS-P) and the Clinical Global Impressions Scale (CGI). Twenty subjects in the risperidone group and 9 in the paroxetine group completed all study visits. A significant decrease in CGI score was demonstrated in all subjects (p less than 0.001), but there was no significant difference between the groups. The CGI score improved from 4.4 +/- 0.6 at baseline to 2.84 +/- 1.02 at final assessment in the risperidone arm. Similarly, paroxetine resulted in a CGI score improvement from 3.81 +/- 1.33 to 2.67 +/- 0.71 at final assessment. All subjects, regardless of treatment, demonstrated a significant decrease in outcome scores for the PDSS total score, PDSS item 1, PDSS item 2, Ham-A and Ham-D. There was no statistical difference between treatment groups by the end of the study, and there was no significant change in SPAS-p scores over time (Prosser et al, 2009).

4.6.H Perphenazine

4.6.H.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.H.2 Schizophrenia

a) Risperidone and perphenazine were equally efficacious in a double-blind, multicenter, parallel-group study in which 107 chronic schizophrenics with acute exacerbation were enrolled (Hoyberg et al, 1993a). No statistically significant differences in clinical improvement (defined as a 20% reduction in total Positive and Negative Syndrome Scale score at endpoint) were found between the two treatment groups. Clinical Global Impression severity scores were also comparable. Patients with predominantly negative symptoms treated with risperidone had significantly lower Brief Psychiatric Rating Scale hostility scores compared to patients taking perphenazine.

4.6.I Quetiapine

4.6.I.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.I.2 Psychotic disorder

a) Quetiapine and risperidone were similarly efficacious in treating psychotic symptoms and had similar overall tolerability, but quetiapine treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing depression. In a 4- month, open-label study, patients with schizophrenia, schizoaffective disorder, or other psychotic disorders (including bipolar disorder, major depressive disorder and various forms of dementia) were randomized in a ratio of 3:1 to receive quetiapine (n=553) or risperidone (n=175). The starting dosage of quetiapine was 50 milligrams/day (mg/day), which was increased in 50- or 100- mg increments every 1 to 2 days, to a maximum of 800 mg/day, given in divided doses. Risperidone was started at 1 mg twice daily, with upward titration to a target dose of 3 mg twice daily by day 3. Dosages were individually titrated to maximize efficacy while minimizing adverse reactions (mean prescribed dose: quetiapine 253.9 mg, risperidone 4.4 mg). At the beginning of the study, approximately half of each group had EPS. There was a steady decline in the number of patients reporting EPS in both groups as the study progressed. The incidence of EPS in the quetiapine group was lower than in the risperidone group at one month (41.1 vs 47.3) but not at the end of the study (38.6 vs 39.2). The percentage of patients requiring a change of treatment due to EPS or requiring anti-EPS medication was lower in the quetiapine group than in the risperidone group (7% vs 20.5%). Approximately one third of patients in each group withdrew before completion of the study. A higher percentage withdrew from risperidone treatment for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from quetiapine treatment because of adverse effects (8.7% vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizziness, which all occurred significantly more often with quetiapine treatment (p less than 0.05). Occurrence of weight gain was low in both groups (Mullen et al, 2001).

4.6.J Ziprasidone

4.6.J.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

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Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999h.

Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999i.

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pression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral

Tablet coated

uel®, AstraZeneca

uel®, AstraZeneca

uel®, AstraZeneca

uel®, AstraZeneca

uel®, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia‡, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal

dosage was 3.8 mg daily. Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within therapeutic ranges of 0.6–1.4 mEq/L for lithium and 50–120 mcg/mL for valproate. Addition of risperidone to lithium or valproate was shown to be superior to continued monotherapy with lithium or valproate as assessed by reduction of Y-MRS total score.

In a second 3-week, placebo-controlled trial, inpatients and outpatients with bipolar mania receiving lithium, valproate (as divalproex), or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive risperidone or placebo in conjunction with their original therapy. Risperidone was given in a flexible dosage range of 1–6 mg daily, with an initial dosage of 2 mg daily; the mean modal dosage was 3.7 mg daily. Addition of risperidone to lithium, valproate, or carbamazepine therapy (with plasma drug concentrations maintained within therapeutic ranges of 0.6–1.4 mEq/L, 50–120 mcg/mL, or 4–12 mcg/mL, respectively) was not found to be superior to lithium, valproate, or carbamazepine given alone as assessed by reduction of the Y-MRS total score. A possible explanation for the failure of this trial was enzymatic induction of clearance of risperidone and its principal active metabolite, 9-hydroxyrisperidone, by carbamazepine in the subgroup of patients receiving combined therapy with these drugs, resulting in subtherapeutic plasma concentrations of risperidone and 9-hydroxyrisperidone.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combined therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The manufacturer states that efficacy of risperidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) in the treatment of acute manic episodes or for prophylactic use in patients with bipolar disorder.

■ **Autistic Disorder** Risperidone is used for the management of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

Short-term efficacy of risperidone in children and adolescents with autistic disorder has been demonstrated in 2 placebo-controlled trials of 8 weeks' duration in children and adolescents (aged 5–16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of the patients in these 2 trials were under 12 years of age and the majority weighed over 20 kg (weight range: 16–104.3 kg). The principal rating instruments used for assessing efficacy in these trials were the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I), which measures the emotional and behavioral symptoms of autism, including aggression toward others, deliberate self-injuriousness, temper tantrums, and rapidly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

In the first 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5 to 16 years received twice daily placebo or risperidone 0.5–3.5 mg daily on a weight-adjusted basis, starting at 0.25 mg daily or 0.5 mg daily if baseline weight was less than 20 kg or 20 kg or greater, respectively; dosage was then titrated according to clinical response. Risperidone (mean modal dosage of 1.9 mg/day; equivalent to 0.06 mg/kg daily) was found to substantially improve scores on the ABC-I subscale and the CGI-C scale compared with placebo in this study.

In the second 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5–12 years were given an initial risperidone dosage of 0.01 mg/kg daily, which was then titrated up to 0.02–0.06 mg/kg daily based on clinical response. Risperidone (mean modal dosage of 0.05 mg/kg daily; equivalent to 1.4 mg daily) improved scores on the ABC-I subscale compared with placebo.

The efficacy of risperidone for long-term use (i.e., longer than 8 weeks) in children and adolescents with autistic disorder has been demonstrated in an open-label extension of the first 8-week, placebo-controlled trial in which patients received risperidone for 4 or 6 months (depending on whether they received risperidone or placebo in the double-blind study). During the open-label treatment period, patients were maintained on a mean modal risperidone dosage of 1.8–2.1 mg daily (equivalent to 0.05–0.07 mg/kg daily).

Children and adolescents who maintained their positive response to risperidone (defined as at least a 25% improvement on the ABC-I subscale and a CGI-C rating of much improved or very much improved) during the 4–6 month open-label treatment period (average duration of therapy was 140 days) were randomized to receive either risperidone or placebo during an 8-week, double-blind withdrawal trial. A substantially lower relapse rate was observed in the risperidone group compared with the placebo group during the pre-planned interim analysis of data from this trial. Based on the interim analysis results, the study was terminated since a statistically significant effect on relapse prevention was demonstrated. Relapse was defined as at least a 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline for the randomized withdrawal phase). The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Although not curative, pharmacologic agents, such as risperidone, generally are used in children and adolescents with autistic disorder to reduce behavioral disturbances associated with autism and to help facilitate the child's or adolescent's adjustment and engagement in intensive, targeted educational interventions. In clinical studies, risperidone was not found to improve certain core symptoms of autism (e.g., language deficits, impaired social relatedness). However, the drug was more effective than placebo for improving scores on subscales for sensory motor behaviors, affectual reactions, and sensory responses in a controlled study. The possible risks, including clinically important weight gain, tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug, should be considered.

Risperidone also has been used for the treatment in a limited number of adults† with autistic disorder and other pervasive developmental disorders.

Dosage and Administration

■ **Administration** Risperidone is administered orally or by IM injection.

Oral Administration Risperidone is administered orally, either in a once-daily dose or in 2 equally divided doses daily. Because risperidone can cause orthostatic hypotension, twice-daily oral administration may be preferable during initiation of therapy and in patients who may be more susceptible to orthostatic hypotension, such as geriatric or debilitated patients. If once-daily dosing is being considered in geriatric or debilitated patients, it is recommended that the patient be titrated on a twice-daily regimen for 2–3 days at the target dose. Subsequent switching to the once-daily dosing regimen can be done thereafter. Some experts state that once-daily administration of risperidone may be sufficient in most patients receiving maintenance therapy because of the extended half-life of the drug's principal active metabolite (9-hydroxyrisperidone).

In children and adolescents receiving risperidone for the management of irritability associated with autistic disorder who experience persistent somnolence, administering the drug once daily at bedtime, twice-daily administration, or a reduction in dosage may be helpful.

Since food reportedly does not affect the rate or extent of GI absorption of risperidone, the drug can be administered without regard to meals. Compatibility tests show that risperidone oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; such testing also indicates that risperidone oral solution is *not* compatible in cola or tea.

Patients receiving risperidone orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid. Risperidone orally disintegrating tablets should not be divided or chewed.

IM Administration The commercially available risperidone powder for injection containing the drug in extended-release microspheres must be reconstituted prior to administration using the components of the dose pack supplied by the manufacturer. The dose pack should be allowed to reach room temperature before reconstituting the injection. Risperidone extended-release microspheres should be reconstituted using only the diluent in the prefilled syringe supplied by the manufacturer. The entire contents of the prefilled syringe should be injected into the vial, and the vial should be shaken vigorously while the plunger rod is held down with the thumb for at least 10 seconds to ensure a homogeneous suspension; the reconstituted suspension should appear uniform, thick, and milky. The manufacturer's prescribing information should be consulted for additional details on use of the components of the dose pack to reconstitute and administer risperidone injection. The manufacturer states that different dosage strengths of IM risperidone should not be combined in a single administration.

Following reconstitution, immediate use is recommended because the suspension will settle over time. If more than 2 minutes pass before administration, the vial should again be vigorously shaken to resuspend the drug. The contents of the vial must be used within 6 hours of reconstitution and should not be exposed to temperatures exceeding 25°C.

The entire contents of the vial should be administered by deep IM injection into the upper outer quadrant of the gluteal area every 2 weeks, alternating buttocks. The injection should *not* be administered IV.

■ **Dosage** ***Schizophrenia*** **Oral Dosage.** Risperidone has a bell-shaped dose-response curve, with therapeutic efficacy of oral dosages of 12–16 mg daily lower than that of dosages of 4–8 mg daily in adults. Because dosage information contained in the manufacturer's labeling principally is derived from early clinical studies of the drug in patients not typical of the general population of patients treated in the community (i.e., in hospitalized, chronically-ill schizophrenic patients accustomed to high-dose antipsychotic therapies), dosage of risperidone should be individualized according to the patient's response and tolerance. Clinicians also may consider consulting published protocols for specific dosage information, particularly in geriatric or younger patients, and in those experiencing their first psychotic episode.

The manufacturer's labeling states that the initial oral dosage of risperidone in adults generally is 1 mg twice daily, with dosage increase in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dosage

of 6–8 mg daily (administered once daily or in 2 equally divided doses). However, more recent evidence from open labeled studies and clinical experience with the drug indicates that an initial dosage of 1–2 mg daily, with dosage increases in increments of 0.5–1 mg daily titrated over 6–7 days, as tolerated, to a target dose of 4 mg daily may be more appropriate for the management of schizophrenia in most otherwise healthy adult patients. Because steady-state plasma concentrations of 9-hydroxyrisperidone (an active metabolite of risperidone) may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of at least 7 days. Lower initial dosages (e.g., 1 mg daily) and slower dosage titrations to an initial target dosage of 2 mg daily may be appropriate for younger patients and in those being treated for their first psychotic episode; dosage may then be titrated up to 4 mg daily depending on clinical response at the lower dosage and adverse neurologic effects. Such patients appear to benefit optimally from risperidone dosage of 1–3 mg daily. A substantial number of patients being treated for their first psychotic episode start to develop extrapyramidal symptoms once dosages are increased above 2 mg daily. Dosage reductions should be considered in any patient who develops extrapyramidal symptoms.

While antipsychotic efficacy has been established in clinical trials at oral dosages ranging from 4–16 mg daily, maximum efficacy of the drug was observed in most patients at risperidone dosages of 4–8 mg daily. In addition, the manufacturer and some clinicians state that dosages exceeding 6 mg daily, when given in 2 divided doses, did not result in further improvement but were associated with increases in some adverse effects, including extrapyramidal manifestations. Therefore, the manufacturer states that dosages exceeding 6 mg (in 2 divided doses) daily generally are not recommended and those exceeding 16 mg daily have not been evaluated for safety. In a single study of once-daily dosing, efficacy results generally were stronger for 8 mg than for 4 mg.

The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to risperidone or concomitant administration with other antipsychotic agents. While immediate discontinuance of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, gradual discontinuance of the drug may be appropriate for most patients. In all cases, the period of overlapping antipsychotic administration should be minimized. The first risperidone dose should be administered in place of the next scheduled parenteral antipsychotic dose in schizophrenic patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral risperidone therapy.

The optimum duration of oral risperidone therapy currently is not known, but maintenance therapy with risperidone 2–8 mg daily has been shown to be effective for up to 2 years. Patients should be reassessed periodically to determine the need for continued therapy with the drug. If risperidone therapy is reinitiated after a drug-free period, the manufacturer recommends that the appropriate recommended schedule of careful dosage titration be employed.

IM Dosage. For the management of schizophrenia, the recommended initial adult IM dosage of risperidone injection extended-release microspheres is 25 mg administered by deep IM injection in the gluteal area every 2 weeks. The manufacturer recommends that patients first receive oral risperidone to establish tolerability of the drug before the extended-release risperidone injection is used. To ensure that adequate plasma antipsychotic concentrations are maintained prior to the main release of risperidone from the injection site, therapy with oral risperidone or another oral antipsychotic agent (e.g., for patients being switched from other oral antipsychotic therapy to IM risperidone) should be given with the first IM injection of risperidone, and such oral therapy should be continued for 3 weeks, then discontinued. If risperidone injection is used in patients previously receiving other oral antipsychotic agents, the need for continuing any concomitant therapy for managing extrapyramidal manifestations should be periodically reevaluated.

Some patients not responding to the initial dosage of 25 mg every 2 weeks may benefit from increasing the IM dosage to 37.5 or 50 mg every 2 weeks. However, the dosage should not be increased more frequently than every 4 weeks, and clinical effects of the increased dosage should not be expected earlier than 3 weeks after the first injection of the higher dose. The maximum IM dosage should not exceed 50 mg every 2 weeks since higher dosages were associated with an increased incidence of adverse effects, but no additional clinical benefit was observed.

Although no controlled studies have been conducted to establish the optimum duration of IM risperidone therapy in patients with schizophrenia, oral risperidone has been shown to be effective in delaying time to relapse with longer term use. It is recommended that responding patients be continued on treatment with IM risperidone at the lowest dose needed. Patients should periodically be reassessed to determine the need for continued treatment.

If therapy with IM risperidone is reinitiated after a drug-free period, oral risperidone (or another oral antipsychotic agent) should again be administered for supplementation.

Bipolar Disorder For the management of acute manic and mixed episodes associated with bipolar disorder as monotherapy or as combined therapy in adults, an initial risperidone oral dosage of 2–3 mg given once daily was found to be effective in clinical trials. Dosage may be increased or decreased by 1 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. In these trials, the short-term (i.e., 3-week) antimanic efficacy of risperidone was demonstrated in a flexible dosage ranging from 1 to 6 mg daily. Safety of dosages exceeding 6 mg daily has not been established.

The optimum duration of risperidone therapy for bipolar disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone beyond 3 weeks. Therefore, the manufacturer states that clinicians who elect to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Autistic Disorder For the management of irritability associated with autistic disorder in children 5 years of age and older and adolescents, an initial risperidone oral dosage of 0.25 mg daily is recommended for patients weighing less than 20 kg and 0.5 mg daily is recommended for patients weighing 20 kg or more. The drug may be administered either once or twice daily.

Dosage should be individualized according to clinical response and tolerability of the patient. After a minimum of 4 days following initiation of therapy, the dosage may be increased to the recommended dosage of 0.5 mg daily for patients weighing less than 20 kg and 1 mg daily for patients weighing 20 kg or more; this dosage should then be maintained for a minimum of 14 days. In patients not responding adequately, increases in dosage may be considered at intervals of 2 weeks or longer in increments of 0.25 mg daily for patients weighing less than 20 kg or 0.5 mg daily for patients weighing 20 kg or more. Exercise caution with risperidone dosages in smaller children who weigh less than 15 kg. Safety and effectiveness in pediatric patients less than 5 years of age not established.

In clinical trials, 90% of patients who responded to risperidone therapy (based on at least 25% improvement in the Irritability subscale of the Aberrant Behavior Checklist [ABC-I]) received dosages from 0.5–2.5 mg daily. The maximum daily dosage in one of the pivotal trials, when the therapeutic effect reached a plateau, was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or more, and 3 mg in patients weighing more than 45 kg. Dosage data for children weighing less than 15 kg currently are lacking.

Once adequate clinical response has been achieved, consider a gradual reduction in dosage to achieve an optimal balance of efficacy and safety. Patients experiencing excessive somnolence may benefit from a once-daily dosage administered at bedtime or administering half the daily dosage twice daily, or a reduction in dosage.

The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Geriatric Patients and Others at Risk of Orthostatic Hypotension Like other α-adrenergic blocking agents, risperidone can induce orthostatic hypotension (e.g., manifested as dizziness, tachycardia, and occasionally syncope), particularly during initiation of therapy with the drug. The manufacturer and some clinicians state that the risk of this effect can be minimized by limiting the initial oral dosage of risperidone to 1 mg twice daily in otherwise healthy adults and to 0.5 mg once or twice daily in geriatric or debilitated patients, in patients with renal or hepatic impairment, and in those predisposed to, or at risk from, hypotension. Dosages in such patients should then be increased gradually at increments of not more than 0.5 mg twice daily as necessary and tolerated. Increases beyond a dosage level of 1.5 mg twice daily generally should occur at intervals of at least 7 days. However, other clinicians recommend initiating risperidone therapy at a dosage of 0.25 mg daily in geriatric patients and gradually increasing the dosage as tolerated. (See Cautions: Geriatric Precautions.) Most geriatric patients should not be maintained at an oral dosage exceeding 3 mg daily.

For geriatric patients with schizophrenia, the recommended IM risperidone dosage of the extended-release injection is 25 mg every 2 weeks. Oral risperidone (or another oral antipsychotic agent) should be given with the first risperidone extended-release injection and should be continued for 3 weeks to ensure that adequate antipsychotic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site.

Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning, slowly rising from a seated position). These patients should avoid sodium depletion or dehydration and circumstances that accentuate hypotension (e.g., alcohol intake, high ambient temperature). Monitoring of orthostatic vital signs should be considered.

Particular caution also is warranted in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) and in those for whom such reactions would pose a risk, and cautious dosage titration and careful monitoring are necessary in such patients. Dosage reduction should be considered in any patient in whom hypotension develops.

■ **Dosage in Renal and Hepatic Impairment** Because elimination of risperidone may be reduced and the risk of adverse effects, particularly hypotension, increased in patients with renal impairment, oral risperidone therapy should be initiated at a reduced dosage of 0.5 mg twice daily in adults and increased as necessary and tolerated at increments of 0.5 mg twice daily; increases beyond a dosage level of 1.5 mg twice daily should be made at intervals of at least 7 days. Likewise, this reduced oral dosage should be employed in

patients with hepatic impairment because of the risk of an increased free fraction of risperidone in such patients.

If IM risperidone is used for management of schizophrenia in adult patients with renal or hepatic impairment, the patient should be treated with titrated doses of oral risperidone prior to initiating treatment with the extended-release injection. The recommended starting oral risperidone dosage is 0.5 mg twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dosage of at least 2 mg daily of oral risperidone is well tolerated, an IM dosage of 25 mg of the extended-release injection can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Cautions

Although risperidone differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives. Not all adverse effects of the phenothiazines have been reported with risperidone, but the possibility that they may occur should be considered. Adverse effects of risperidone and the phenothiazines are numerous and may involve nearly all organ systems. Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal. In some patients, unexpected death associated with antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex. (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with schizophrenia who received the drug in 2 short-term (6–8 week) clinical studies and with an incidence of at least twice that of those who received placebo included nervous system (e.g., anxiety, dizziness, extrapyramidal symptoms, somnolence), GI (e.g., constipation, dyspepsia, nausea), dermatologic (e.g., rash), respiratory (e.g., rhinitis), and cardiovascular (e.g., tachycardia) effects. Approximately 9% of patients receiving risperidone in phase 2 or 3 studies discontinued treatment because of adverse effects compared with about 7% of those receiving placebo and 10% of those receiving an active control drug (haloperidol). Adverse effects commonly associated with discontinuance of therapy and considered to be possibly or probably related to risperidone include extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with bipolar mania who received the drug as monotherapy in the US placebo-controlled trial and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, dystonia, akathisia, parkinsonism, vision abnormalities) and GI (e.g., dyspepsia, nausea, increased salivation) effects. In the US placebo-controlled trial of risperidone in conjunction with mood stabilizers (lithium or valproate), the most common adverse effects associated with risperidone administration were somnolence, dizziness, parkinsonism, increased saliva, akathisia, abdominal pain, and urinary incontinence. In the US placebo-controlled trial of risperidone monotherapy, approximately 8% of patients receiving risperidone discontinued therapy because of adverse effects compared with about 6% of those receiving placebo. Adverse effects associated with discontinuance of therapy in this study and considered to be possibly, probably, or very likely related to risperidone included paroniria, somnolence, dizziness, extrapyramidal reaction, and involuntary muscle contractions; each of these occurred in 1 risperidone-treated patient (0.7%) but in none of those receiving placebo. In the US placebo-controlled trial of risperidone used in conjunction with mood stabilizers, there was no overall difference in the incidence of discontinuance because of adverse effects (4% for risperidone and 4% for placebo).

The most frequent adverse effects of oral risperidone reported in at least 5% of pediatric patients with autistic disorder who received the drug in 2 placebo-controlled trials and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, fatigue, tremor, dystonia, dizziness, parkinsonism, automatism, dyskinesia, confusion), GI (e.g., increased appetite, increased salivation, constipation, dry mouth), respiratory (e.g., upper respiratory tract infection), cardiovascular effects (e.g., tachycardia), and weight gain. Somnolence was the most frequent adverse effect in these trials, occurring in 67% of the risperidone-treated patients and in 23% of patients receiving placebo. Average weight gain over 8 weeks was 2.6 kg for the risperidone-treated patients compared with 0.9 kg for patients receiving placebo. Extrapyramidal symptoms occurred in approximately 28% of the risperidone-treated patients compared with 10% of those receiving placebo.

The most frequent adverse effects associated with use of risperidone extended-release IM injection reported in at least 5% of adult patients with schizophrenia in clinical trials and with an incidence of at least twice that of those receiving placebo included somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, and increased weight.

■ **Nervous System Effects** ***Tardive Dyskinesia*** Like other antipsychotic agents (e.g., phenothiazines), risperidone has been associated with tardive dyskinesias. Although it has been suggested that atypical antipsychotics appear to have a lower risk of tardive dyskinesia, whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is as yet unknown. In one open-label study, an annual incidence of tardive dyskinesia of 0.3% was reported in patients with schizophrenia who received approximately 8–9 mg of oral risperidone daily for at least 1 year. The prevalence of this syndrome appears to be highest among geriatric patients (particularly females). The risk of developing tardive dyskinesia and the likelihood that it will become irreversible also appear to increase with the duration of therapy and cumulative dose of antipsychotic agents administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Extrapyramidal Reactions Extrapyramidal reactions occurred in 17% of patients with schizophrenia receiving oral risperidone dosages of 10 mg daily or less and in 34% of patients receiving dosages of 16 mg daily in clinical studies. Although the incidence of extrapyramidal manifestations in patients receiving risperidone dosages of 10 mg daily or less was similar to that reported in patients receiving placebo, the incidence increased as the dosage of the drug increased, suggesting a dose-related effect. At recommended therapeutic dosages of risperidone (4–8 mg daily) for schizophrenia, the severity of extrapyramidal reactions appears to be comparable to placebo and clozapine 400 mg daily, and substantially less than that associated with haloperidol 10 or 20 mg daily. Similarly, the severity of parkinsonian symptoms, as assessed on the parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (ESRS), is also linearly related to risperidone dosages of 2–16 mg daily, with the incidence of parkinsonian symptoms at risperidone dosages of 6 mg daily or less comparable to that of placebo and substantially less than that seen with haloperidol dosages of 20 mg daily.

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents. NMS requires immediate discontinuance of the drug and intensive symptomatic and supportive care. For additional information on NMS, see Neuroleptic Malignant Syndrome under Nervous System Effects: Extrapyramidal Reactions in Cautions, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects Dose-related somnolence was a commonly reported adverse effect associated with risperidone treatment. Approximately 8% of adult patients with schizophrenia receiving 16 mg of oral risperidone daily and 1% of patients receiving placebo reported somnolence in studies utilizing direct questioning or a checklist to detect adverse events, respectively.

Insomnia, agitation, and anxiety have been reported in 20–26% of patients receiving risperidone. In addition, headache, dizziness, and aggressive reaction have been reported in 12–14, 4–7, and 1–3% of schizophrenia patients, respectively.

Adverse nervous system effects reported in 1% or more of patients with schizophrenia who received risperidone in clinical studies include increased sleep duration or dream activity, diminished sexual desire, fatigue, and nervousness. Impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia, dysarthria, vertigo, stupor, paraesthesia,malaise, seizure, and confusion also have been reported in 0.1–1% of patients. In addition, aphasia, cholinergic syndrome, choreoathetosis, coma, delirium, emotional lability, hypoesthesia, hypotonia, hyperreflexia, leg cramps, migraine, nightmares, tongue paralysis, torticollis, withdrawal syndrome, and yawning have been reported in fewer than 0.1% of patients. Mania also has been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Cardiovascular Effects** ***Orthostatic Hypotension*** Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period has been reported in patients receiving risperidone, probably reflecting the drug's α-adrenergic antagonistic properties. The risk of orthostatic hypotension and syncope may be minimized by limiting initial doses in geriatric patients and patients with renal or hepatic impairment. (See Dosage and Administration.) Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia). Clinically important hypotension has been observed with concomitant use of risperidone and antihypertensive drug therapy.

Other Cardiovascular Effects Pooled analysis of results of placebo-controlled studies indicates that risperidone therapy is not associated with statistically significant changes in ECG parameters (e.g., PR, QT, or QT_c intervals, heart rate). In pivotal clinical studies, however, tachycardia, which may be dose dependent, occurred in 3 or 5% of patients with schizophrenia receiving daily oral dosages of risperidone of 10 mg or less or 16 mg, respectively. In addition, palpitation, hypertension, hypotension, AV block, and myocardial infarction have occurred in 1% or more of patients receiving risperidone. Ventricular tachycardia, angina pectoris, atrial premature complexes (APCs, PACs), T-wave inversions, ventricular extrasystoles, ST depression, and myocarditis have occurred in fewer than 0.1% of patients receiving the drug in clinical trials. Atrial fibrillation, pulmonary embolism, cerebrovascular disorders (including stroke and transient ischemic attack) (see Cautions: Geriatric Precautions), and rarely, sudden death and/or cardiopulmonary arrest also have been reported

during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Endocrine and Metabolic Effects** Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., risperidone, clozapine, olanzapine, quetiapine).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., risperidone, quetiapine) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

Similar to other antipsychotic agents, risperidone causes elevated prolactin concentrations, which may persist during chronic use of the drug. Risperidone appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents. The clinical importance of elevated serum prolactin concentrations is as yet unknown for most patients receiving these drugs. Gynecomastia and breast pain in men have been reported in fewer than 0.1% of patients. In addition, galactorrhea, amenorrhea, and impotence have been reported with agents that increase serum prolactin concentrations, including risperidone.

Hyponatremia, weight gain or loss, increased serum creatine kinase (CK, creatine phosphokinase, CPK) concentrations, thirst, and diabetes mellitus have been reported in 0.1–1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, decreased serum iron concentrations, cachexia, dehydration, disorders in antidiuretic hormone, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, and hypoglycemia have been reported in fewer than 0.1% of patients. Precocious puberty and pituitary adenomas also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **GI Effects** Adverse GI effects that have been reported in 5–13% of patients with schizophrenia receiving oral risperidone in clinical studies include constipation, nausea, dyspepsia, and vomiting. Abdominal pain, increased salivation, and toothache also have been reported in 1–4% of patients receiving risperidone in clinical studies. In addition, anorexia and reduced salivation were reported in 1% or more of patients receiving risperidone in clinical trials. Flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, and gastritis have also been reported in 0.1–1% of patients. In addition, fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, lingual discoloration, cholelithiasis, lingual edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, and hematemesis have been reported in fewer than 0.1% of patients receiving the drug in clinical trials. Although a causal relationship to risperidone has not been established, intestinal obstruction has been reported during postmarketing surveillance.

■ **Respiratory Effects** Rhinitis has been reported in 8–10% of patients with schizophrenia receiving oral risperidone and was the most common adverse respiratory effect reported during clinical studies. In addition, cough, sinusitis, pharyngitis, upper respiratory infections, and dyspnea have been reported in 1–3% of patients receiving risperidone in clinical studies. Hyperventilation, bronchospasm, pneumonia, and stridor also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Asthma, increased sputum, and aspiration have been rarely reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, apnea also has been reported during postmarketing surveillance.

■ **Dermatologic Effects and Sensitivity Reactions** Rash and dry skin have been reported in about 2–5% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, adverse dermatologic effects that have been reported in 1% or more of patients receiving risperidone include seborrhea and increased pigmentation. Increased or decreased sweating, acne, alopecia, hyperkeratosis, pruritus, and skin exfoliation were reported in 0.1–1% of patients in clinical trials. Bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, and urticaria have been rarely reported.

Although a causal relationship has not been established, hypersensitivity reactions, including anaphylaxis, angioedema, and photosensitivity have been reported in patients receiving risperidone.

■ **Genitourinary Effects** Adverse genitourinary effects reported in 1% or more of patients with schizophrenia receiving oral risperidone include polyuria, polydipsia, menorrhagia, orgasmic dysfunction, and vaginal dryness. In addition, urinary incontinence, hematuria, dysuria, nonpuerperal lactation, amenorrhea, breast or perineal pain in females, leukorrhea, mastitis, dysmenorrhea, intermenstrual bleeding, and vaginal hemorrhage have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Urinary retention, cystitis, and renal insufficiency also have been reported in fewer than 0.1% of patients.

In male patients, erectile dysfunction and ejaculation failure were reported in up to 1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, rare cases of priapism have been reported. While a causal relationship to risperidone use has not been established, other drugs with α-adrenergic blocking effects have been reported to cause priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

■ **Musculoskeletal Effects** Back or chest pain and arthralgia have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, myalgia has been reported in 0.1–1% of patients. Arthrosis, synostosis, bursitis, arthritis, and skeletal pain also have occurred in fewer than 0.1% of patients.

■ **Hematologic Effects** Anemia, hypochromic anemia, epistaxis, and purpura have been reported in 0.1–1% of adult patients with schizophrenia and granulocytopenia has been reported in 0.1–1% of children and adolescents with autistic disorder receiving oral risperidone in clinical studies. Normocytic anemia, leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly, hemorrhage, superficial phlebitis, thrombophlebitis, and thrombocytopenia also have been reported in fewer than 0.1% of patients. In addition, thrombotic thrombocytopenic purpura occurred in at least one patient (a 28 year-old female patient) receiving risperidone in a large, open-labeled study. This patient experienced jaundice, fever, and bruising but eventually recovered after receiving plasmapheresis. The relationship of this adverse event to risperidone therapy is unknown.

■ **Hepatic Effects** Increased SGOT and increased SGPT have been reported in 0.1–1% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, and hepatocellular damage have been reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, jaundice also has been reported during postmarketing surveillance.

■ **Ocular and Otic Effects** Abnormal vision has been reported in 1–2% of patients with schizophrenia receiving oral risperidone in clinical studies. Abnormal accommodation and xerophthalmia also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. In addition, diplopia, ocular pain, blepharitis, photopsia, photophobia, abnormal lacrimation, tinnitus, hyperacusis, and decreased hearing have been reported in fewer than 0.1% of patients.

■ **Other Adverse Effects** Chest pain and fever have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. Although a causal relationship to the drug has not been established, pancreatitis and aggravated parkinsonian syndrome has been reported during postmarketing surveillance.

■ **Precautions and Contraindications** Risperidone shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone, the manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. (See Cautions: Endocrine and Metabolic Effects.) Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the antipsychotic; in other cases hyperglycemia resolved with discontinuance of the suspect drug. For further information on the management of diabetes risks in patients receiving atypical antipsychotics, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Because of the possibility of orthostatic hypotension, caution should be observed in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease (see Cautions: Geriatric Precautions), conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia), and patients receiving antihypertensive agents. Since patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies, clinicians should be aware that risperidone has not been evaluated or used to any appreciable extent in such patients. Patients receiving risperidone should be advised of the risk of orthostatic hypotension, especially during the period of initial dosage titration. (See Cautions: Cardiovascular Effects.)

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including risperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with more frequent falling, extrapyramidal adverse effects, and clinical features consistent with neuroleptic malignant syndrome. (For additional information on extrapyramidal adverse effects and neuroleptic malignant syndrome, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Plasma concentrations of risperidone and its principal active metabolite, 9-hydroxyrisperidone, are increased in patients with severe renal impairment (creatinine clearance less than 30 mL/minute per1.73 m^2), and an increased free fraction of risperidone occurs in patients with severe hepatic impairment. Therefore, lower initial dosages should be used in such patients. (See Dosage and Administration.)

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that risperidone 0.5-, 1-, 2-, 3-. or 4-mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®) which is metabolized in the GI tract to provide about 0.14, 0.28, or 0.-42, 0.63, or 0.84 mg of phenylalanine, respectively, following oral administration.

Because seizures have occurred in 0.3% of patients receiving risperidone in clinical studies, the drug should be administered with caution to patients with a history of seizures.

Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including risperidone. Because aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced dementia of the Alzheimer's type, risperidone and other antipsychotic drugs should be used with caution in patients at risk for aspiration pneumonia.

Because both hypothermia and hyperthermia have been associated with risperidone therapy, the drug should be administered with caution in patients who will be exposed to temperature extremes.

Because risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including driving automobiles, until they are reasonably certain that risperidone therapy does not adversely affect them.

Risperidone has an antiemetic effect in animals; this effect also may occur in humans, and may mask manifestations of overdosage with certain drugs or may obscure the cause of vomiting in various disorders such as intestinal obstruction, Reye's syndrome or brain tumor.

Patients should be advised to inform their clinician if they are taking, or plan to take, any prescription or nonprescription drugs, or have any concomitant illnesses (e.g., diabetes mellitus). Patients also should be advised to avoid alcohol while taking risperidone.

Risperidone is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** The manufacturer states that safety and effectiveness of risperidone in children with schizophrenia or acute mania associated with bipolar I disorder have not been established. However, efficacy and safety of the drug in the treatment of irritability associated with autistic disorder have been established in 2 placebo-controlled trials of 8 weeks' duration in 156 children and adolescents aged from 5–16 years. (See Uses: Autistic Disorder.) Additional safety information also was assessed from a long-term study in patients with autistic disorder and from short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight and who received similar risperidone dosages as patients treated for irritability associated with autistic disorder. Safety and effectiveness of risperidone in pediatric patients with autistic disorder younger than 5 years of age have not been established.

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 patients (0.1%) reportedly developed tardive dyskinesia, which resolved upon discontinuance of therapy. In addition, approximately 15% of children and adolescents receiving 0.5–2.5 mg daily dosages of risperidone developed withdrawal dyskinesia during the discontinuance phase of one long-term (6 month), open-label study.

In long-term, open-label trials in patients with autistic disorder or other psychiatric disorders, a mean body weight gain of 7.5 kg after 12 months of risperidone therapy was reported, which was higher than the normal expected weight gain (i.e., 3–3.5 kg per year adjusted for age, based on the Centers for Disease Control and Prevention normative data). The majority of the weight increase occurred within the first 6 months of drug exposure. Average percentiles at baseline and at 12 months were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index, respectively. When treating pediatric patients with risperidone, the manufacturer recommends that weight gain should be assessed against that expected with normal growth.

Somnolence frequently occurred in placebo-controlled trials in pediatric patients with autistic disorder. Most cases were mild to moderate in severity, occurred early during therapy (peak incidence during the first 2 weeks of therapy), and were transient (median duration of 16 days). Patients experiencing persistent somnolence may benefit from a change in dosage regimen.

Risperidone has been shown to elevate prolactin concentrations in children and adolescents as well as adults. In double-blind, placebo-controlled, 8-week trials in children and adolescents aged from 5–17 years, 49% of risperidone-treated patients had elevated prolactin concentrations compared with 2% of those receiving placebo.

In clinical trials conducted in 1885 children and adolescents with autistic disorder or other psychiatric disorders, galactorrhea and gynecomastia reportedly occurred in 0.8 and 2.3% of risperidone-treated patients, respectively.

The manufacturer states that the long-term effects of risperidone on growth and maturation have not been fully evaluated.

■ **Geriatric Precautions** Clinical studies of risperidone for the management of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. However, serious adverse effects, including an increased risk of death, have been reported in geriatric patients receiving risperidone or other atypical antipsychotic agents in clinical trials in patients with dementia-related psychosis. Risperidone is not approved for the treatment of dementia-related psychosis. (See Geriatric Considerations in Uses: Psychotic Disorders.)

Adverse cerebrovascular events (e.g., stroke, transient ischemic attack), some of which resulted in fatalities, have been reported in clinical studies of risperidone for the management of psychosis in geriatric patients (mean age 85 years; range 73–97) with dementia. Analysis of pooled data from 4 randomized, placebo-controlled studies indicates that adverse cerebrovascular events occurred in approximately 4% of geriatric patients with dementia of the Alzheimer's type, vascular dementia, or mixed dementia receiving risperidone compared with 2% of those receiving placebo. Although many of the patients who experienced adverse cerebrovascular events during the course of these studies had at least one risk factor for cerebrovascular events (e.g., arrhythmia, atherosclerosis, atrial fibrillation, diabetes, heart failure, hypertension, prior history of stroke or transient ischemic attack), the total number of such patients was too small to permit definitive conclusions about the relationship between known risk factors for cerebrovascular events and risperidone therapy. An increased risk of adverse cerebrovascular events has not been identified to date in clinical studies of risperidone for the management of schizophrenia.

An increased risk of death has been reported among geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., risperidone, aripiprazole, olanzapine, quetiapine) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

A higher incidence of mortality also was observed in geriatric patients with dementia-related psychosis receiving risperidone and furosemide concurrently in placebo-controlled trials when compared with that in patients receiving risperidone alone or placebo and furosemide concurrently. The increase in mortality in patients receiving risperidone and furosemide concurrently was observed in 2 out of 4 clinical trials. The pathological mechanism for this finding remains to be established and no consistent pattern for the cause of death was observed. An increased incidence of mortality in geriatric patients with dementia-related psychosis was observed with risperidone regardless of concurrent furosemide administration.

Risperidone dosage generally should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered. Although geriatric patients exhibit a greater tendency to orthostatic hypotension, the manufacturer states that its risk may be minimized by limiting the initial oral dosage to 0.5 mg twice daily followed by careful titration and close monitoring of orthostatic vital signs in patients for whom this is of concern. More recent evidence however, indicates that even lower initial dosages and slower dosage titration are better tolerated in these patients. Therefore, some clinicians recommend initiating oral risperidone therapy at 0.25 mg daily, and gradually increasing dosages, as tolerated, to a dosage of 2 mg daily in these patients. Higher oral dosages (e.g., 3 or 4 mg daily) may be required in some patients, but are usually associated with greater incidence of extrapyramidal reactions. Most geriatric patients should *not* be maintained at an oral risperidone dosage exceeding 3 mg daily. (See Geriatric Patients and Others at Risk of Orthostatic Hypotension under Dosage and Administration: Dosage.)

■ **Mutagenicity and Carcinogenicity** Risperidone did not exhibit mutagenic potential in in vitro chromosomal aberration studies in human lymphocytes or Chinese hamster cells, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or in microbial (Ames) test systems.

Statistically significant increases in pituitary gland adenomas and mammary gland adenocarcinomas were observed in female mice receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 18 months. In addition, statistically significant increases were observed in mammary gland adenocarcinomas in both male and female rats, and mammary gland neoplasms and endocrine pancreas adenomas in male rats receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 0.4, 1.5, and 6 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 25 months.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of prolactin-stimulating drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Since in vitro tests indicate that approximately

one-third of human breast cancers are prolactin-dependent, risperidone should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Reproductive studies in rats and rabbits using risperidone dosages of 0.4–6 times the maximum recommended human dosage on a mg/m² basis have not revealed evidence of fetal malformation. However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m² basis. In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m² basis. It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams. In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m² basis. Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown. Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy. Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. The effect of risperidone on labor and delivery in humans is unknown.

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m² basis. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dosage was not found in these studies in either rats or dogs.

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk. The manufacturer states that women receiving risperidone should avoid nursing.

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents. While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines). The exact mechanism of antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic ($5\text{-}HT_2$) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Risperidone

Oral		
Solution	1 mg/mL	**Risperdal®**, Janssen
Tablets	0.25 mg	**Risperdal®** (scored), Janssen
	0.5 mg	**Risperdal®** (scored), Janssen
	1 mg	**Risperdal®** (scored), Janssen
	2 mg	**Risperdal®** (scored), Janssen
	3 mg	**Risperdal®** (scored), Janssen
	4 mg	**Risperdal®** (scored), Janssen
Tablets, orally disintegrating	0.5 mg	**Risperdal® M-TAB®**, Janssen
	1 mg	**Risperdal® M-TAB®**, Janssen
	2 mg	**Risperdal® M-TAB®**, Janssen
	3 mg	**Risperdal® M-TAB®**, Janssen
	4 mg	**Risperdal® M-TAB®**, Janssen
Parenteral		
For injectable suspension, extended-release, for IM use	25 mg	**Risperdal® Consta®** (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	37.5 mg	**Risperdal® Consta®** (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	50 mg	**Risperdal® Consta®** (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** *Schizophrenia* Ziprasidone is used for the symptomatic management of schizophrenia. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7

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RISPERIDONE

0.0 Overview

1) Class
a) This drug is a member of the following class(es):
Antipsychotic
Benzisoxazole
2) Dosing Information
a) Adult
1) Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; van Schaick et al, 2003)
2) previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone long-acting injection to ensure that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
a) Bipolar I disorder
1) (oral, monotherapy or in combination with lithium or valproate) initial, 2 to 3 mg ORALLY once a day; maintenance, dosage adjustments should be made in increments of 1 mg/day at intervals of at least 24 hours; doses higher than 6 mg/day have not been evaluated in clinical trials (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)
2) (intramuscular, monotherapy or in combination with lithium or valproate) establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; initial, 25 mg IM every 2 weeks; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued (Prod Info

Exhibit 7

RISPERDAL(R)CONSTA(R) IM injection, 2010)

3) (intramuscular, monotherapy or in combination with lithium or valproate) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

b) Schizophrenia

1) (oral) initial, 2 mg/day ORALLY, administered either once or twice daily; increase as tolerated in increments of 1 to 2 mg/day (or slower) at intervals not less than 24 hours, to a recommended dose of 4 to 8 mg/day; doses above 6 mg/day for twice-daily dosing were not shown to be more efficacious than lower doses; the safety of doses above 16 mg/day has not been evaluated in clinical trials (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) (oral) maintenance, 2 mg/day to 8 mg/day (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) (oral) if risperidone is discontinued, restart with the initial titration schedule (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

4) (oral) when switching from other antipsychotic agents, minimize the period of overlapping administration (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

5) (oral) when switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

6) (intramuscular) establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; initial, 25 mg IM every 2 weeks; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

7) (intramuscular) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

b) Pediatric

1) safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients under 18 years of age (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) safety and effectiveness of oral risperidone in pediatric patients less than 13 years of age with schizophrenia have not been established (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) safety and effectiveness of oral risperidone in pediatric patients less than 10 years of age with bipolar mania has not been established (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

4) safety and effectiveness or oral risperidone in pediatric patients less than 5 years of age with autistic disorder have not been established (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

a) Autistic disorder - Irritability

1) dosing individualized according to the response and tolerability (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

2) (5 years and older; weight less than 20 kg) initial, 0.25 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 0.5 mg/day; maintenance, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days and may increase doses at 2-week intervals or longer, in increments of 0.25 mg per day to achieved sufficient clinical response; use with caution in children weighing less than 15 kg (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) (age 5 years and older; weight 20 kg or greater) initial, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 1 mg/da; maintenance, 1 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days; may increase doses at 2-week intervals or longer, in increments of 0.5 mg per day to achieved sufficient clinical response (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

4) in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

b) Bipolar I disorder

1) (10 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 2.5 mg/day (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

c) Schizophrenia

1) (13 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 3 mg/day (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) if risperidone is discontinued, restart with the initial titration schedule (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

4) when switching from other antipsychotic agents, minimize the period of overlapping administration (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

5) when switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info

RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) Contraindications

a) hypersensitivity to risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009), paliperidone (an active metabolite of risperidone) or to any product component

4) Serious Adverse Effects

a) Agranulocytosis

b) Diabetic ketoacidosis

c) Hypothermia

d) Leukopenia

e) Neuroleptic malignant syndrome

f) Neutropenia

g) Pancreatitis

h) Priapism

i) Seizure

j) Sudden cardiac death

k) Syncope

l) Tardive dyskinesia

m) Thrombocytopenia

n) Thrombotic thrombocytopenic purpura

5) Clinical Applications

a) FDA Approved Indications

1) Autistic disorder - Irritability

2) Bipolar I disorder

3) Schizophrenia

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Risperidone

C) Physicochemical Properties

1) Molecular Weight

a) 410.49 (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009; Prod Info

RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008)

2) Solubility

a) Risperidone is practically freely soluble in methylene chloride, soluble in methanol and 0.1 N hydrochloride, and insoluble in water (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008).

1.2 Storage and Stability

A) Preparation

1) Intramuscular route

a) Preparation

1) Risperidone long-acting injection must only be suspended in the diluent supplied by the manufacturer in the dose pack. Allow the drug and diluent to come to room temperature prior to reconstitution. After injecting the diluent into the vial, shake the vial vigorously for a minimum of 10 seconds. The suspension should appear uniform, thick, and milky in color. The particles will be visible in liquid, but no dry particle should remain. It should be used immediately after suspension and must be used within 6 hours of reconstitution. If two minutes pass before injection, resuspend by shaking vigorously, as settling will occur over time once the product is in suspension (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

b) Administration

1) Do NOT inject intravenously. Administer by deep intramuscular injection into the deltoid or gluteal muscles, alternating between the 2 arms or two buttocks. Use a 1-inch 21 gauge needle for deltoid injection and a 2-inch 20 gauge needle for gluteal injection. Do not combine different dosage strengths in a single administration (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) Oral route

a) Orally Disintegrating Tablets

1) Oral disintegrating tablets are supplied in blister packs and should not be opened until ready for use. Peel back foil to expose tablet; do NOT push the tablet through the foil backing because this could damage the tablet. Use dry hands to remove the tablet from the blister unit and immediately place the entire tablet on the tongue. The tablet should be consumed immediately once it is removed form the blister unit. Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Do not split or chew the tablet (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) Oral Solution

1) Calibrated dispensing-pipettes are provided with risperidone oral solution. The oral solution may be directly administered from the calibrated pipette, or can be mixed with water, coffee, orange juice, and low-fat milk. However, it is not compatible with cola or tea (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

B) Intramuscular route

1) The long-acting injection should be stored in the refrigerator between 36 and 46 degrees Fahrenheit (F) (2 and 8 degrees Celsius); or if refrigeration is not available, it may be stored at temperatures not exceeding 77 degrees F (25 degrees C) for no more than 7 days prior to administration; protect from light (Prod Info Risperdal(R) Consta(TM), 2003i).

C) Oral route

1) Solution

a) Store the oral solution at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); protect from light and freezing (Prod Info Risperdal(R), 2004).

2) Tablet

a) Tablets should be stored at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); protect from light and moisture (Prod Info Risperdal(R), 2004).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Intramuscular route

1.3.1.A.1 Bipolar I disorder

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be established with oral risperidone prior to initiation of treatment with the long-acting risperidone intramuscular injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly every 2 weeks. For patients not responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 weeks. Clinical effects from a dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher dose. The maximum dose should not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and should be reassessed periodically to determine the necessity of continued treatment. Risperidone long-acting injection should be administered by deep intramuscular injection into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administered by a health care professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection of long-acting risperidone and should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administration (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treatment in patients previously discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.3.1.A.2 Schizophrenia

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be

established with oral risperidone prior to initiation of treatment with the long-acting risperidone intramuscular injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly every 2 weeks. For patients not responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 weeks. Clinical effects from a dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher dose. The maximum dose should not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and should be reassessed periodically to determine the necessity of continued treatment. Risperidone long-acting injection should be administered by deep intramuscular injection into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administered by a health care professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection of long-acting risperidone and should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administration (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treatment in patients previously discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.3.1.A.3) Switching Antipsychotics

a) Previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone long-acting injection to ensure that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.3.1.B Oral route

1.3.1.B.1 Bipolar I disorder

a) Risperidone is approved for use as monotherapy or in combination with lithium or valproate in the treatment of bipolar mania. Risperidone should be administered once daily at an initial dose of 2 to 3 mg per day. If needed, dosage adjustments should be made at intervals of at least 24 hours in increments/decrements of 1 mg/day. In clinical trials, doses ranging from 1 to 6 mg/day were used; doses higher than 6 mg/day have not been studied (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) The effectiveness of risperidone for maintenance therapy beyond 3 weeks has not been evaluated. While, the continuation of treatment in a responding patient is generally desirable for maintenance of the initial response and for prevention of new manic episodes, there are no data from clinical trials to support the use of risperidone in long-term treatment (Prod Info RISPERDAL(R) oral solution, oral tablets,

2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

1.3.1.B.2 Schizophrenia

a) The recommended initial adult dose for the treatment of schizophrenia is risperidone 2 mg/day orally, administered either once or twice daily. Increase the dose as tolerated in increments of 1 to 2 mg/day at intervals not less than 24 hours, to a recommended dose of 4 to 8 mg/day. In some patients slower titration may be necessary. Efficacy has been demonstrated in a dose range of 4 to 16 mg/day, but doses above 6 mg/day for twice-daily dosing were not shown to be more efficacious than lower doses. Doses above 6 mg/day are associated with more adverse events including extrapyramidal symptoms. The safety of doses above 16 mg/day has not been evaluated in clinical trials (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
b) If risperidone is discontinued, restart with the initial titration schedule (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
c) When switching schizophrenic patients from other antipsychotic agents, minimize the period of overlapping administration. When switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
d) In a controlled, clinical trial, risperidone given at once-daily doses of 2 to 8 milligrams was effective in delaying relapse in patients who had been clinically stable for 4 weeks or longer. However, patients should be periodically reassessed to determine the need for maintenance treatment (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
e) The Consensus Study Group on Risperidone Dosing reports their empiric clinical experience has resulted in a lower-dose and slower-titration strategy for many patients. They target a goal of 2 to 4 milligrams (mg) daily during the first week of treatment. If no initial response occurs, the dose is increased to 6 to 8 mg/day during the second week of treatment. If there is no response at this dose during the next 2 weeks, then a higher dose may be warranted, usually increases of 2 mg/week up to a maximum daily dose of 16 mg/day are attempted. Any further dosage adjustments, if indicated, should be made at intervals of no less than 1 week (Borison et al, 1992).
f) In dose comparison studies chiefly utilizing chronic schizophrenic patients, the most consistently positive responses on all measures were seen for the 6 milligram (mg) dose group (Marder & Meibach, 1994a; Chouinard et al, 1993a; Marder, 1992) and for the 4 mg group in one study (Muller-Spahn, 1992a). In a review of 12 double-blind studies (n=2099), symptom improvement was maximal at 4 to 8 mg/day (Lemmens et al, 1999). There was no suggestion of increased benefit from larger doses. Another study utilizing only neuroleptic naive patients found a superior outcome in the 2 to 4 mg group versus a 5 to 8 mg dose group (Kopala et al, 1997).

1.3.1.B.3) Bioequivalence
a) Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; van Schaick et al, 2003).

1.3.2 Dosage in Renal Failure

A) Oral

1) The recommended initial dosage in patients with severe renal impairment is 0.5 mg twice daily. Doses may be increased by 0.5 mg twice daily. Increases in dosages above 1.5 mg twice daily should be done at intervals of at least 1 week. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

B) Intramuscular

1) Patients with renal impairment should receive titrated doses of oral risperidone prior to initiating treatment with the risperidone long-acting intramuscular injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral risperidone twice daily for one week; then the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dose of 2 mg is well tolerated, 25 mg of risperidone long-acting injection can be given intramuscularly every 2 weeks. Although the efficacy has not been confirmed in clinical trials, 12.5 mg of risperidone long-acting injection may be given to patients with renal impairment. Continue oral supplementation for 3 weeks following the first injection until the main release of risperidone from the injection site has begun. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.3.3 Dosage in Hepatic Insufficiency

A) Oral

1) The recommended initial dosage in patients with severe hepatic impairment is 0.5 mg twice daily. Doses may be increased by 0.5 mg twice daily. Increases in dosages above 1.5 mg twice daily should be done at intervals of at least 1 week. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

B) Intramuscular

1) Patients with hepatic impairment should receive titrated doses of oral risperidone prior to initiating treatment with the risperidone long-acting intramuscular (IM) injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral risperidone twice daily for one week; then the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dose of 2 mg is well tolerated, 25 mg of risperidone long-acting injection can be given IM every 2 weeks. Although the efficacy has not been confirmed in clinical trials, 12.5 mg of risperidone long-acting injection may be given to patients with hepatic impairment. Continue oral supplementation for 3 weeks following the first injection until the main release of risperidone from the injection site has begun. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.3.4 Dosage in Geriatric Patients

A) Oral

1) The recommended initial dosage in geriatric patients is 0.5 mg twice daily. Doses may be increased by 0.5 mg twice daily. Increases in dosages above 1.5 mg twice daily should be done at intervals of at least 1

week. Slower titration may be necessary in some patients If once-daily dosing is desired, initiate and titrate patient on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

B) Intramuscular

1) The recommended dosage of risperidone long-acting injection for elderly patients is 25 milligrams intramuscularly every 2 weeks. Oral risperidone or another antipsychotic medication should be administered with the initial injection of long-acting risperidone and should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.3.6 Dosage in Other Disease States

A) Debilitated Patients

1) Debilitated patients may have less ability to eliminate risperidone than normal patients. The recommended initial dosage in debilitated patients is 0.5 mg twice daily. Doses may be increased by 0.5 mg twice daily. Increases in dosages above 1.5 mg twice daily should be done at intervals of at least 1 week. Slower titration may be necessary in some patients. If once-daily dosing is desired, initiate and titrate patient on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

2) .

B) Hypotension Predisposition

1) The recommended initial dosage in patients with a predisposition to hypotension or for whom hypotension may pose a risk is 0.5 mg twice daily. Doses may be increased by 0.5 mg twice daily. Increases in dosages above 1.5 mg twice daily should be done at intervals of at least 1 week. Slower titration may be necessary in some patients (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

C) Concomitant Medications

1) (IM) For patients on CYP2D6 inhibitors (eg, fluoxetine, paroxetine), risperidone long-acting intramuscular injection may be initiated at doses of 12.5 milligrams (mg) or 25 mg. For patients already on 25 mg of long-acting risperidone injection and initiating fluoxetine or paroxetine, continue the 25 mg dose. However, if clinical judgement warrants, the dose of risperidone may be decreased to 12.5 mg or risperidone long-acting intramuscular injection may be discontinued. Although, the efficacy of 12.5 mg has not been confirmed in clinical trials (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) (Oral) For patients receiving CYP2D6 inhibitors (eg, fluoxetine, paroxetine), the plasma concentration of risperidone will increase. The oral risperidone dose should be titrated, especially during initiation or discontinuation of therapy (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) (IM) For patients on CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital), the dose of risperidone long-acting intramuscular injection will need to be titrated accordingly, especially during initiation or discontinuation of the CYP3A4 inducers. When CYP3A4 inducers are discontinued, continue with the 25 milligram (mg) dose. However, if clinical judgement warrants, the dose of risperidone

may be decreased to 12.5 mg or risperidone long-acting intramuscular injection may be discontinued. Although, the efficacy of 12.5 mg has not been confirmed in clinical trials (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

4) (Oral) For patients receiving CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital), the plasma concentration of risperidone will decrease. The oral risperidone dose should be titrated, especially during initiation or discontinuation of therapy (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

D) Poor Tolerability to Psychotropic Medications

1) Although the efficacy has not been confirmed in clinical trials, 12.5 milligrams intramuscularly may be given to patients with a history of poor tolerability to psychotropic medications (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Intramuscular route

1) The safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients under 18 years of age (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

1.4.1.B Oral route

1.4.1.B.1 Autistic disorder - Irritability

a) Dosing should be individualized according to the response and tolerability. Doses are administered once daily or half the total daily dose twice daily. In patients with persistent somnolence, a once-daily dose at bedtime or half the daily dose twice daily, or a reduction of the dose may be considered (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) For children age 5 years or older and weighing less than 20 kg, the recommended initial dose is 0.25 mg orally daily. Doses may be increased after a minimum of 4 days to 0.5 mg per day. Doses should be maintained for at least 14 days. They may be increased at 2-week intervals or longer, in increments of 0.25 mg per day if the patient has not achieved sufficient clinical response. Once adequate clinical response has been achieved and maintained, doses may be lowered gradually to obtain the optimal balance of efficacy and safety. Risperidone should be used with caution in children weighing less than 15 kg (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

c) For children age 5 years or older and weighing 20 kg or greater, the recommended initial dose is 0.5 mg orally daily. Doses may be increased after at least 4 days to 1 mg per day. Doses should be maintained for at least 14 days. They may be increased at 2-week intervals or longer, in increments of 0.5 mg per day if the patient has not achieved sufficient clinical response. Once adequate clinical response has

been achieved and maintained, doses may be lowered gradually to obtain the optimal balance of efficacy and safety (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) In clinical trials, a response (based on at least 25% improvement on ABC-I) was achieved in 90% of patients following doses of risperidone between 0.5 mg and 2.5 mg per day. In one of the pivotal trials, the maximum daily dose of risperidone was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or greater, or 3 mg in patients weighing greater than 45 kg, when the therapeutic effect reached plateau (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

1.4.1.B.2 Bipolar I disorder

a) For the short-term treatment of bipolar mania in adolescents age 10 years and older, initiate treatment at 0.5 mg orally once daily, given as a single daily dose either in the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day, as tolerated to a recommended daily dose of 2.5 mg/day. Efficacy has been demonstrated at doses between 0.5 and 6 mg/day, but no benefit was seen above 2.5 mg/day in pediatric patients. Higher doses are associated with more adverse events. Doses above 6 mg/day have not been studied. Data are unavailable to support use of risperidone beyond 3 weeks for the treatment of bipolar mania. Therefore, if therapy is required for extended periods, periodically reevaluate the long-term usefulness for the individual patient (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In patients with persistent somnolence, administering half the daily dose twice daily may be beneficial (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

1.4.1.B.3 Schizophrenia

a) In children 13 years of age and older, initiate treatment at 0.5 mg orally once daily, given as a single daily dose either in the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day, as tolerated to the recommended dose of 3 mg/day. If somnolence occurs, the daily dose may be divided into 2 equal doses. Data are unavailable to support use of risperidone beyond 8 weeks in adolescents with schizophrenia. Therefore, if therapy is required for extended periods, periodically reevaluate the long-term usefulness for the individual patient (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) When switching schizophrenic patients from other antipsychotic agents, minimize the period of overlapping administration. When switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) If risperidone is discontinued, restart with the initial titration schedule (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets,

2010).

1.4.1.B.4) The safety and effectiveness of oral risperidone have not been established (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010):
in pediatric patients less than 13 years of age with schizophrenia;
in pediatric patients less than 10 years of age with bipolar mania;
in pediatric patients less than 5 years of age with autistic disorder.

2.0 Pharmacokinetics

Onset and Duration
Drug Concentration Levels
ADME

2.1 Onset and Duration

A) Onset
1) Initial Response
a) Psychotic symptoms, oral: 1 to 2 weeks (Vanden Borre et al, 1993; Borison et al, 1992a; Mesotten et al, 1989a).
b) Psychotic symptoms, intramuscular: 3 weeks (Prod Info Risperdal(R) Consta(TM), 2003h).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug occurs (less than approximately 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003h).
B) Duration
1) Single Dose
a) Psychotic symptoms, intramuscular: 7 weeks (Prod Info Risperdal(R) Consta(TM), 2003h).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug occurs (less than approximately 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003h).
2) Multiple Dose
a) Psychotic symptoms, oral: 1 year (Addington et al, 1993; Carman & Wyatt-Knowles, 1993; Bressa et al, 1991; De Wilde & Dierick, 1991); (Mertens, 1991).
1) Clinical improvement in positive and negative symptoms has been observed for up to 7 months (Addington et al, 1993; Carman & Wyatt-Knowles, 1993; Bressa et al, 1991; De Wilde & Dierick, 1991); (Mertens, 1991).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Psychiatric disorders (dose, 6 mg/day): 50 to 150 nanomole/L (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) A therapeutic range has not been established. A dose of 6 mg/day produces a risperidone serum level of 50 to 150 nmol/L in 90% of patients (Olesen et al, 1998).

b) Plasma concentrations are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily) (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Nyberg et al, 1993a).

B) Peak Concentration

1) Oral, single-dose, 1 mg: 9 to 16 nanograms/mL (Huang et al, 1993)

a) In one study in healthy volunteers, peak plasma concentrations of the active moiety (risperidone plus 9-hydroxy-risperidone) ranging from 9 to 16 nanograms/mL were reported following oral administration of 1 mg of risperidone. However, no correlation between plasma concentrations and therapeutic effect has been definitively established. Although interindividual plasma concentrations vary considerably, plasma concentrations of risperidone, 9-hydroxy-risperidone, and the active moiety (risperidone plus 9-hydroxy-risperidone) are dose-proportional and linear over the therapeutic dosing range (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Manufacturer's comment, 6/95.; Borison, 1994a; Grant & Fitton, 1994; Chouinard et al, 1993b; Ereshefsky & Lacombe, 1993; Huang et al, 1993).

C) Time to Peak Concentration

1) Adult

a) Oral: 1 hr (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

1) Following oral administration of oral solution or tablet in adults, mean Tmax of risperidone occurred at approximately 1 hour. Tmax of the active metabolite, 9-hydroxyrisperidone, in extensive metabolizers (EM) occurred at about 3 hours and in poor metabolizers (PM) occurred at 17 hours. Steady-state concentrations of risperidone are reached in 1 day in EM and in approximately 5 days in PM. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5 to 6 days in EM (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

2) Pediatric

a) Oral: 2 hr (Thyssen et al, 2010)

1) Population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed that risperidone was rapidly absorbed following oral administration with a median Tmax of 2 hours for both children and adolescents (Thyssen et al, 2010).

2.3 ADME

2.3.1 Absorption

A) Bioavailability

1) Oral: 70% (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) The absolute oral bioavailability of risperidone is 70%; the relative oral bioavailability from a tablet

was 94% when compared to a solution. Population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed that bioavailability was decreased by 46.7% in the presence of a combined P-glycoprotein/CYP3A4 inducer (nifedipine and clotrimazole; n=7 of 780; p=0.005)(Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

B) Effects of Food

1) None (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) Food does not affect either the rate or extent of absorption, thus, risperidone may be administered regardless of food (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Adult

1) Risperidone: 90%; 9-hydroxyrisperidone: 77%(Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) In adults, the plasma protein binding of risperidone is 90%, and its major metabolite, 9-hydroxyrisperidone is 77%(Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

b) Pediatric

1) Risperidone: 85.3% (adolescents), 88.3% (children) (Thyssen et al, 2010)

2) 9-hydroxyrisperidone: 71.9 (adolescents) 75% (children) (Thyssen et al, 2010)

a) Population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed the mean plasma protein binding of risperidone was 85.3%, and its major metabolite, 9-hydroxyrisperidone was 71.9% in adolescents. In children, the mean plasma protein binding was 88.3% and 75%, respectively (Thyssen et al, 2010).

B) Distribution Kinetics

1) Volume of Distribution

a) 1 to 2 L/kg (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

1) Risperidone is rapidly distributed, with the volume of distribution of 1 to 2 L/kg. (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

2) Population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed steady state Vd of the active moiety (risperidone plus 9-hydroxy-risperidone) of 83.5 L for a typical child of 11 years old and weighs 39 kg, 150.2 L for an adolescent of 15 years old and 60 kg, and 182 L for an adult 33 years old and 70 kg (Thyssen et al, 2010)

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver: extensive (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Nyberg et al, 1993a)

a) Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP2D6 (debrisoquin hydroxylase) with a second minor pathway of N-dealkylation. Metabolism is sensitive to the debrisoquine hydroxylation type genetic polymorphism(Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Nyberg et al, 1993a).

B) Metabolites

1) 9-hydroxyrisperidone: active (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Nyberg et al, 1993a)

a) The main active metabolite, 9-hydroxyrisperidone, is approximately equi-effective to the parent compound, risperidone, in terms of receptor binding activity (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Nyberg et al, 1993a).

2.3.4 Excretion

A) Kidney

1) Renal Clearance (rate)

a) 0.96 L/hr (the active moiety, risperidone plus 9-hydroxy-risperidone)(Thyssen et al, 2010)

1) In a population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, the estimated renal clearance of the active moiety (risperidone plus 9-hydroxy-risperidone) was 0.96 L/hr for a typical patient weighing 62 kg, aged 18.1 years and had CrCl of 117.6 mL/min (median values in the overall population) (Thyssen et al, 2010).

2) Renal Excretion (%)

a) Adult

1) 70%(Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) Approximately 70% of risperidone and its metabolites are eliminated in the urine (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

b) Pediatric

1) Risperidone: 4.3% to 7.4% (Thyssen et al, 2010)

2) 9-hydroxyrisperidone: 23.9% to 26% (Thyssen et al, 2010)

a) Population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed that the dose excreted as risperidone and 9-hydroxyrisperidone was higher in adolescents (7.4% and 26%, respectively) than in children (4.3% and 23.9%, respectively) (Thyssen et al, 2010).

B) Feces

1) 14% (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) Approximately 14% of risperidone and its metabolites are eliminated in the feces (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

C) Total Body Clearance

1) Adult

a) 3.2 to 13.7 L/hr (Prod Info Risperdal(R) Consta(TM), 2003h)

1) The clearance of risperidone and risperidone plus 9-hydroxyrisperidone is 13.7 L/hr and 5 L/hr in extensive CYP2D6 metabolizers, and 3.3 L/hr and 3.2 L/hr in poor metabolizers, respectively (Prod Info Risperdal(R) Consta(TM), 2003h).

2) For a typical patient weighing 62 kg and aged 18.1 years with a median CrCl of 117.6 mL/min, population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed that apparent metabolic clearance was 4.26 L/hr. The estimated apparent total clearance of the active moiety (risperidone plus 9-hydroxyrisperidone) for an adult of 33 years old and weighs 70 kg was 5.04 L/hr, and 5.22 L/hr for a typical patient weighing 62 kg, aged 18.1 years, and CrCl of 117.6 mL/min (median values of the population) (Thyssen et al, 2010).

2) Pediatric

a) 18.1 L/hr (adolescents); 13.5 L/hr (children) (Thyssen et al, 2010)

1) Population pharmacokinetic analysis, which combined data from children, adolescents and adults from 9 independent clinical studies, showed that the total body clearance of risperidone was 18.1 L/hr in adolescents and 13.5 L/hr in children. The estimated apparent total clearance of the active moiety (risperidone plus 9-hydroxy-risperidone) for a typical child 11 years old and weighs 39 kg was 4.35 L/hr and 5.3 L/hr for an adolescent 15 years old and weighs 60 kg. The estimated total clearance of risperidone among immediate/poor metabolizers were 5.47 (children), 7.56 (adolescents), and 8.48 L/hr (adults). The corresponding estimates among extensive metabolizers were 20.8, 28.7, and 32.2 L/hr (Thyssen et al, 2010).

2.3.5 Elimination Half-life

A) Parent Compound

1) oral: 3 to 20 hours (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) The apparent half-life of risperidone was 3 hours in extensive metabolizers (EM) and 20 hours in poor metabolizers (PM). The pharmacokinetics of risperidone after single and multiple doses were similar in EM and PM with an overall mean elimination half-life of about 20 hours (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

2) intramuscular: 3 to 6 days (Prod Info Risperdal(R) Consta(TM), 2003h).

a) The half-life of intramuscular risperidone is related to the erosion of the microspheres and subsequent absorption of risperidone (Prod Info Risperdal(R) Consta(TM), 2003h).

B) Metabolites

1) 9-hydroxyrisperidone: 21 to 30 hr (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

a) The apparent half-life of 9-hydroxyrisperidone was 21 hours in extensive metabolizers (EM) and 30 hours in poor metabolizers (PM). The pharmacokinetics of 9-hydroxyrisperidone after single and mul-

tiple doses were similar in EM and PM with an overall mean elimination half-life of about 20 hours (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

3.0 Cautions

Contraindications
Precautions
Adverse Reactions
Teratogenicity/Effects in Pregnancy/Breastfeeding
Drug Interactions

3.0.A) Black Box WARNING

1) Intramuscular (Powder for Suspension, Extended Release)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Risperidone is not approved for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral (Tablet; Tablet, Disintegrating; Solution)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Risperidone is not approved for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

3.1 Contraindications

A) hypersensitivity to risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009), paliperidone (an active metabolite of risperidone) or to any product component

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
B) agranulocytosis, leukopenia and neutropenia have been reported; risk factors include history of low WBC, leukopenia or neutropenia; monitoring recommended (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
C) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
D) cerebrovascular adverse events (stroke, transient ischemic attack), including fatalities, have been reported in elderly patients with dementia-related psychosis (unapproved use) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
E) conditions that may contribute to elevated body temperature; may disrupt body temperature regulation (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
F) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
G) elderly patients; increased risk of tardive dyskinesia, especially among elderly women (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
H) elderly patients; increased risk of orthostatic hypotension, especially during the initial dose-titration period (oral) (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
I) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
J) hepatic impairment, severe; increased risperidone exposure and side effects have been reported; dosage adjustment necessary (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
K) hyperglycemia has been reported, some may lead to ketoacidosis, hyperosmolar coma, or death (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R)

M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
L) hyperprolactinemia; may result in galactorrhea, amenorrhea, gynecomastia, impotence, hypogonadism and decreased bone density; incidence of hyperprolactinemia appears to be higher with risperidone relative to other antipsychotic agents (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
M) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
N) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; immediately discontinue drug (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
O) Parkinson's disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
P) priapism has been reported; severe cases may require surgical intervention (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
Q) renal impairment, severe; increase in free fraction of risperidone and side effects have been reported; dosage adjustment necessary (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
R) seizure disorder, history, or conditions which lower seizure threshold (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
S) suicide risk; close monitoring of high-risk patients recommended (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)
T) tardive dyskinesia, potentially irreversible; discontinue treatment if appropriate (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

3.3 Adverse Reactions

3.3.1 Cardiovascular Effects

3.3.1.A Cardiac dysrhythmia

1) Incidence: up to 2% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)
2) The manufacturer reports that intergroup comparisons for pooled, placebo-controlled studies did not reveal statistically significant differences between oral risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals and heart rate. There was a mean increase in heart rate of 1 beat per minute when all risperidone doses were pooled from randomized, con-

trolled studies in several indications, as compared with no change for patients who received placebo. In short-term studies of patients with schizophrenia, higher doses of risperidone (8 to 16 mg/day) were associated with a higher mean increase in heart rate (4 to 6 beats per minute) as compared with placebo. Small decreases in mean heart rate were observed among all treatment groups in pooled data from placebo-controlled trials of adults with acute mania (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) In 3 double-blind, controlled trials of 4 to 8 weeks in duration in adult schizophrenia patients, increased heart rate was reported in less than 1% of patients who received risperidone 2 to 8 mg/day (n=366) and in 2% of patients who received greater than 8 to 16 mg/day (n=198) compared with 4% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

4) QRS prolongation and QTc prolongation, sometimes resulting in death, have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ak; Ravin & Levenson, 1997p; Gesell & Stephen, 1997h; Lo Vecchio et al, 1996h; Brown et al, 1993h).

5) A 40-year-old man experienced symptomatic bradyarrhythmia 1 day following an increase in his risperidone dose from 2 mg/day to 6 mg/day. The patient developed sinus bradycardia (38 beats per minute) and had several episodes of sinus pauses lasting 2 to 3 seconds. During this time, the QTc interval was 410 msec. Risperidone was discontinued and the symptoms resolved over the following 48 hours (Goyal & Goyal, 2003).

6) A 7-year-old boy developed sinus dysrhythmia and a QTc interval of 0.46 seconds after a single dose of risperidone 1 mg for attention deficit hyperactivity disorder (Gesell & Stephen, 1997h).

7) A 34-year-old woman with no history of cardiac disease developed fatal pulseless electrical activity following treatment with risperidone. On day 3, she developed postural hypotension and was then maintained on 2 mg twice daily. On day 5, she developed cardiac arrest and was treated for pulseless electrical activity with a prolonged QRS interval and an abnormal QTc interval of 480 msec. Despite resuscitative efforts, the patient expired (Ravin & Levenson, 1997p).

3.3.1.B Hypertension

1) Incidence: 3% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, hypertension was reported in 3% of patients receiving risperidone IM (n=154) as monotherapy compared with 1% in placebo (n=149) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.1.C Orthostatic hypotension

1) Incidence: oral, 1% to 2% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, orthostatic hypotension was reported in 2% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received

placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Orthostatic hypotension was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting risperidone IM for schizophrenia and bipolar disorder. Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope has also been reported, and may be more prominent during initial dosage titration (oral). Patients with cardiovascular disease, cerebrovascular disease, or conditions affecting hemodynamic response may be at a higher risk for occurrence of orthostatic hypotension (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

4) Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope (0.2% (6 of 2607) of patients in phase 2 and 3 studies receiving oral risperidone) has been reported. A dose reduction should be considered if hypotension occurs. Use risperidone cautiously in patients with known cardiovascular or cerebrovascular disease and conditions which may predispose patients to hypotension (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.1.D Palpitations

1) Incidence: oral, 2% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Palpitations were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, palpitations were reported in 2% of patients who received risperidone plus a mood stabilizer (n=127) compared with 0% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

4) During premarketing evaluation of oral risperidone, palpitations were reported. Data from a large study comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day) revealed a positive dose-related trend (p less than 0.05) for palpitations (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.1.E Peripheral edema

1) Incidence: adults, up to 3%; pediatrics, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In a 12-week, double-blind, placebo-controlled trial of adult schizophrenic patients, peripheral edema was reported in 2% and 3% of patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intra-

muscular therapy, respectively, compared with 1% with placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) During premarketing risperidone studies of various design types, peripheral edema was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

4) In a study of 110 elderly Chinese patients (age 65 or greater), 16% experienced peripheral edema. Leg-pitting edema was the primary complaint leading to discontinuation of treatment (Hwang et al, 2001).

5) A 27-year-old woman developed pitting edema in the legs and moderate periorbital and facial edema during the third week of risperidone (4 mg/day) treatment for schizophrenia. She experienced a 5-kg weight gain during this period. The patient had received diphenhydramine during the first 3 weeks for the management of mild dystonia and restlessness; this treatment was not continued after week 3. Resolution of edema occurred within 1 week when the dose of risperidone was reduced to 3 mg/day. No recurrence of edema was reported during an 8-month follow-up period (Tamam et al, 2002).

6) A 35-year-old man experienced edema with a 15-pound weight gain after 2.5 weeks of risperidone therapy. His other medications included divalproex sodium and clorazepate. Diuretic therapy with hydrochlorothiazide 25 mg/day and triamterene 50 mg/day resolved the edema within 1 week. The authors note that although edema is associated with divalproex, it did not occur until the risperidone was added. They suggested that both of these medications when used together may be more likely to cause edema by some unknown mechanism (Baldassano & Ghaemi, 1996).

3.3.1.F Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drugs and 186,600 nonusers of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using risperidone compared to those who were not using antipsychotic drugs (incidence-rate ratio, 2.91; 95% confidence interval (CI), 2.26 to 3.76; p less than 0.001). In participants being treated with atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) (Ray et al, 2009).

3.3.1.G Syncope

1) Incidence: oral, up to 1% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, up to 2%(Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In 3 double-blind, controlled trials of 4 to 8 weeks in duration in adult schizophrenia patients, syncope was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225). Syncope was reported in 0.2% (6/2607) of patients who received oral risperidone in phase 2 and 3 clinical trials (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info

RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) During a 12-week, double-blind, clinical trial, syncope was observed in 2% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 1% of patients receiving risperidone 50 mg long-acting IM injection (n=103), compared with 0% of patients receiving placebo (n=98). In multidose studies, syncope occurred in 0.8% (12/1499) of patients receiving long-acting injections (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.1.H Tachycardia

1) Incidence: oral, 1% to 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, controlled trials of adult patients with bipolar mania, tachycardia was reported in 1% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with less than 1% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, tachycardia was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) Tachycardia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting IM risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In two 8-week, double-blind, controlled trials in pediatric patients with irritability associated with autistic disorder, tachycardia was reported in 5% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 0% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.2 Dermatologic Effects

3.3.2.A Acne

1) Incidence: oral, 1% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 2% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, acne was reported in 1% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 0% of patients who

received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) During risperidone clinical trials, acne was reported in 2% of adult patients receiving intramuscular therapy (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.2.B Discoloration of skin

1) Incidence: oral: adults, less than 1%; pediatrics, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)
2) During risperidone clinical trials, skin discoloration was reported in less than 1% of adult patients receiving oral therapy and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) An adverse event analysis from a large study comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day) demonstrated a dose-related effect for reports of skin discoloration (p less than 0.05) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.2.C Dry skin

1) Incidence: oral, 1% to 3% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, up to 2% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, dry skin was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) In a 12-week, double-blind, placebo-controlled trial of adult schizophrenic patients, dry skin was reported in 2% and 0% of patients receiving risperidone 25 mg (n=99) and 50 mg (n=103) long-acting intramuscular therapy, respectively, compared with 0% in placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.2.D Injection site reaction

1) Incidence: IM, 1% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) During the 10th week of a 12-week clinical trial, injection site reaction (including redness, swelling, or induration) was observed in 1% of patients receiving risperidone 25 mg or 50 mg long-acting injection (n=202). Between the first and last injections, there was a decrease in the mean injection pain intensity scores (0=no pain to 100=unbearable pain) in the placebo group (16.7 to 12.6) and risperidone long-acting

injection groups (25 mg: 12 to 9; 50 mg: 18.2 to 11.8). In a separate study in which long-acting risperidone injection was given into the deltoid muscle every 2 weeks over 8 weeks period, only mild injection site events were observed in patients receiving doses of 37.5 mg or 50 mg at 2 hours after the injection. Serious injection site reactions have been reported in postmarketing surveillance (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.2.E Peeling of skin

1) A 37-year-old man with DSM-IV bipolar I disorder experienced rash and desquamation following oral risperidone treatment. The patient presented to an inpatient clinic as euphoric and irritable with rapid speech, and sleep and appetite disturbances. The patient's medical history consisted of several manic episodes since the age of 23. Treatment with oral risperidone solution 2 mg at bedtime was initiated, along with lithium (900 mg/day), diazepam (15 mg/day), zolpidem (10 mg at bedtime), and procyclidine hydrochloride (5 mg at bedtime). Facial flushing and rash under the patient's eyes were seen on day 3 of treatment. Risperidone and lithium were both increased to 4 mg/day and 1200 mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the entire face and neck, with desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to quetiapine 150 mg/day. Quetiapine was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two days following risperidone discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.F Rash

1) Incidence: oral, adults, 2% to 4%; pediatrics, up to 11% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adults

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, rash was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 4% of patients who received greater than 8 to 16 mg/day (n=198), compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) Rash was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

c) A 37-year-old man with DSM-IV bipolar I disorder experienced rash and desquamation following oral risperidone treatment. The patient presented to an inpatient clinic as euphoric and irritable with rapid speech and sleep and appetite disturbances. The patient's medical history consisted of several manic episodes since the age of 23. Treatment with oral risperidone solution 2 mg at bedtime was initiated, along with lithium (900 mg/day), diazepam (15 mg/day), zolpidem (10 mg at bedtime), and procyclidine hydrochloride (5 mg at bedtime). Facial flushing and rash under the patient's eyes were seen

on day 3 of treatment. Risperidone and lithium were both increased to 4 mg/day and 1200 mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the entire face and neck, with desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to quetiapine 150 mg/day. Quetiapine was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two days following risperidone discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, rash was reported in 0% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 7% of patients who received 3 to 6 mg/day (n=61), compared with 2% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, rash was reported in 11% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 8% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF DIABETES

3.3.3.B Diabetic ketoacidosis

1) Diabetic ketoacidosis in patients with impaired glucose metabolism has been reported during risperidone postmarketing surveillance (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) A 27-year-old schizophrenic man was hospitalized with fever and severe diabetic ketoacidosis (DKA) resulting in death following 2 months of risperidone treatment. The patient had no history of diabetes. On admission his serum glucose was 1297 mg/dL, ketone body and metabolic acidosis were positive, and his glycosylated hemoglobin was 13%. Risperidone was immediately discontinued. However, despite insulin treatment and fluid replacement, the patient died within 12 hours due to the rapid progression of DKA. The authors suggest risperidone-induced hyperglycemia resulting in fatal diabetic ketoacidosis (Lu & Yan, 2009).

3.3.3.C Excessive thirst

1) Incidence: oral: adults, less than 1%; pediatrics, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) During the double-blind, placebo-controlled trials for oral risperidone, less than 1% of adults and less than 5% of pediatric patients reported experiencing thirst (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) Risperidone was suspected of causing polydipsia in a 28-year-old man receiving the drug for treatment of schizophrenia (undifferentiated type). His schizophrenia had been refractory to various oral and injectable antipsychotics and electroconvulsive therapy. He was started on risperidone 8 mg/day (which improved his psychotic symptoms). Within 2 weeks, he started drinking water excessively, 4 to 5 L within a variable period of a few minutes to 8 hours. His polydipsia episodes initially occurred intermittently at 10- to 15-day intervals, but over time, became more frequent (ie, every 3 to 4 days, sometimes twice daily), especially after risperidone was increased to 16 mg/day. In addition to polydipsia, the patient experienced polyuria and, occasionally, nausea, vomiting, marked lassitude, slurring of speech, and drowsiness after an episode. Staring and unresponsiveness would sometimes precede an episode. Later risperidone was decreased to 8 mg/day; however, no decrease in frequency of polydipsia episodes occurred. Then risperidone was withdrawn. Polydipsia disappeared during the 2-week drug-free period. The patient was started on clozapine, and had no return of polydipsia. The authors noted that during the time the patient was drinking excessive amounts of water, he never developed hyponatremia or water intoxication. Diabetes mellitus or insipidus, as well as syndrome of inappropriate secretion of antidiuretic hormone (SIADH), had been ruled out, and he was taking no other medication linked to polydipsia (Kar et al, 2002).

3.3.3.D Hypercholesterolemia

1) Elevated blood cholesterol levels have been reported during postmarketing surveillance of risperidone (Prod Info RISPERDAL(R) oral tablets, solution, 2011; Prod Info RISPERDAL(R) CONSTA(R) IM long-acting injection, 2011).

3.3.3.E Hyperglycemia

1) Incidence: IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) Hyperglycemia, including cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving atypical antipsychotics, including risperidone. Hyperglycemia has resolved in some cases after discontinuation of the drug, while in other cases, continuation of antidiabetic treatment was required after drug discontinuation (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) Hyperglycemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder. One patient discontinued therapy due to hyperglycemia (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.3.F Hyperprolactinemia

1) Summary

a) Elevated prolactin levels associated with risperidone use appear to be dose-dependent and greater in females than males. Prolactin elevations are higher with risperidone use compared to elevations associated with other antipsychotic agents (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010) Risperidone is associated with increased prolactin which persist with chronic therapy (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Hellings et al, 2005; Kleinberg et al, 1999; Caracci & Ananthamoorthy, 1999) Male patients with primary hypothyroidism may be particularly sensitive to a neuroleptic-induced elevation of prolactin levels and close monitoring is suggested within the first 3 months of initiating risperidone therapy (Mabini et al, 2000)

2) Incidence: oral, adults, less than 1%; pediatrics, 49% to 87% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); intramuscular, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

3) Adult

a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010). Hyperprolactinemia was reported in less than 1% of adult patients in oral risperidone clinical trials (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-generation antipsychotics or risperidone at average doses of 4.2 to 5.2 mg/day. Compared with baseline, prolactin levels were significantly elevated (p less than 0.05) following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several clinical trials of patients with schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyperprolactinemia following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbances, sexual dysfunction, decreased bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al, 2009).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females on risperidone with females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prolactin was measured once each during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with mental retardation and pervasive developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and maintenance doses of risperidone were 0.92 mg/day (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day), respectively. For adults (mean age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/day (1 to 1.5 mg/day), respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 nanograms/mL for females. In children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/mL increased to 31 +/- 11.6 nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 26 weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increased to 93.3 +/- 54.2 nanograms/mL (p=0.001) in the acute

phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 33 weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanograms/mL vs 11.5 nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult males in the acute phase (128.1 vs 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/mL vs 26.8 nanograms/mL) (Hellings et al, 2005).

d) In a small study of 20 women, risperidone produced prolactin levels twice as high as in women receiving typical neuroleptic agents (Caracci & Ananthamoorthy, 1999). Another author reviewed the results of 4 clinical trials and found significant increases in prolactin levels with risperidone vs haloperidol. In women, risperidone increased prolactin levels significantly higher at all doses than in women receiving haloperidol 10 mg/day (p less than 0.001). Women receiving haloperidol 20 mg/day had similar prolactin levels to women receiving risperidone. In men, risperidone 4 to 6 mg/day produced significantly higher prolactin levels than haloperidol 10 mg/day (p=0.01) but not 20 mg/day. With doses of risperidone 6 mg/day and greater, prolactin levels were significantly greater than all haloperidol doses (p less than 0.01). Elevated prolactin levels are associated with amenorrhea, galactorrhea, hypogonadism, and osteoporosis. Amenorrhea or galactorrhea has been reported in 10% of female patients receiving risperidone (Kleinberg et al, 1999).

4) Pediatric

a) In double-blind clinical trials lasting 8 weeks in children and adolescents (5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, bipolar mania, or schizophrenia, elevated prolactin levels were reported in 49% patients receiving risperidone compared with 2% of patients receiving placebo (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In placebo-controlled clinical trials in adolescents (13 to 17 years) with schizophrenia and children and adolescents (10 to 17 years) with bipolar disorder, elevated prolactin levels were reported in 82% to 87% of patients receiving risperidone compared with 3% to 7% receiving placebo (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females on risperidone with females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prolactin was measured once each during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with mental retardation and pervasive developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and maintenance doses of risperidone were 0.92 mg/day (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day), respectively. For adults (mean age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/day (1 to 1.5 mg/day), respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 nanograms/mL for females. In children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/mL increased to 31 +/- 11.6 nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 26 weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increased to 93.3 +/- 54.2 nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenance phase after a minimum of 33 weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanograms/mL vs 11.5 nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females

compared with adult males in the acute phase (128.1 versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/mL versus 26.8 nanograms/mL) (Hellings et al, 2005).

5) Management

a) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotics that have the potential for inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding changes in libido or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejaculatory dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be considered (Bostwick et al, 2009).

3.3.3.G Hypertriglyceridemia

1) Elevated blood triglyceride levels have been reported during postmarketing surveillance of risperidone (Prod Info RISPERDAL(R) oral tablets, solution, 2011; Prod Info RISPERDAL(R) CONSTA(R) IM long-acting injection, 2011).

3.3.3.H Hypothermia

1) Hypothermia has been associated with the use of antipsychotic agents, including risperidone (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) A 37-year-old woman with psychosis in association with Prader-Willi syndrome suffered hypothermia with cellulitis and confusion while on risperidone therapy. Her rectal temperature was 30 degrees C. She had experienced 2 previous episodes of hypothermia, beginning 1 month after starting risperidone treatment. Withdrawal of risperidone resulted in normalization of temperature. She later had the same problem with olanzapine therapy. Hypothyroidism was excluded. The authors hypothesized that hypothermia may result from antipsychotic blockade of the serotonin 5-HT(2) receptor (Phan et al, 1998).

3.3.3.I Increased body temperature

1) Hyperthermia has been associated with the use of antipsychotic agents, including risperidone (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.3.J Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.K Weight decreased

1) Incidence: IM, 1% to 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) During a 12-week, double-blind, placebo-controlled trial of long-acting intramuscular risperidone, weight decrease was reported in 4% of adults receiving risperidone 25 mg (n=99), and in 1% receiving risperidone 50 mg IM injection (n=103) compared with 1% receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.3.L Weight increased

1) Summary
a) In adult clinical trials, up to 18% of patients receiving oral risperidone reported weight gains of at least 7% of body weight compared with 9% reported for placebo. Fixed-dose studies suggested weight gain was significantly dose-related. Weight gain was reported in up to 14% of adolescent and pediatric patients (5 to 16 years) receiving oral risperidone in clinical trials (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
2) Incidence: oral, 1% to 18%(Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)IM, 4% to 7% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
3) Adult
a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, weight increase was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and in 1% of patients who received greater than 8 to 16 mg/day (n=198), compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
b) Statistically significant weight gain of 7% or greater from baseline body weight was reported in 18% of patients receiving oral risperidone compared with 9% reported for placebo in a pooled analysis of 6- to 8-week placebo-controlled trials of adults with schizophrenia. An adverse event analysis from a large study comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day) demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
c) During a 12-week, clinical trial of schizophrenic patients, weight gain was reported in 5% and 4% of patients receiving risperidone 25 mg long-acting IM injection and risperidone 50 mg long-acting IM injection, respectively compared with 2% of patients who received placebo (n=98). In a 24-month, double-blind, placebo-controlled clinical trial of adult patients with bipolar I disorder, weight gain was reported in 5% of patients who received risperidone long-acting injection (n=154) compared with 1% of patients who received placebo (n=149). In a 52-week, double-blind, placebo-controlled trial in adults with bipolar disorder, weight gain was reported in 7% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 1% of patients who received placebo plus current

therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

4) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients (5 to 16 years) treated for irritability associated with autistic disorder, increased weight was reported in 5% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 0% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) Treatment-emergent weight gain (mean increase of 9 kg after 8 months of therapy) was reported in 14% of adolescents (n=103) in a long-term, open-label extension study of oral risperidone. Most increases were observed within the first 6 months of the study (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardation and autism showed significant weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a mean of 8.2 kg; adolescents (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

d) Risperidone-treated adolescents had significantly higher weight gains and increases in body mass index (BMI) than adolescents treated with conventional neuroleptic agents (p=0.0141 and p=0.0011, respectively). Adolescent inpatients living at a residential treatment center being treated with risperidone (n=18), conventional antipsychotics (n=23), or no antipsychotic medication (n=19) had their weight and BMI followed for 6 months. In the risperidone group, mean changes were a gain of 8.64 kg and 3.67 kg/m(2), for conventional antipsychotics changes were a gain of 3.03 kg and 0.31 kg/m(2), and for the no antipsychotic group changes were a loss of 1.04 kg and 1.01 kg/m(2). The average daily dose of risperidone was 2.83 mg, and gains did not correlate with dose (Kelly et al, 1998).

3.3.4 Gastrointestinal Effects

3.3.4.A Abdominal pain

1) Incidence: oral, 1% to 4% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, abdominal pain was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and in 1% of patients who received greater than 8 to 16 mg/day (n=198), compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) Abdominal pain was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.4.B Constipation

1) Incidence: oral, 8% to 21% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 5% to 7% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, constipation was reported in 8% of patients who received risperidone 2 to 8 mg/day (n=366) and in 9% of patients who received greater than 8 to 16 mg/day (n=198) compared with 6% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 12-week, double-blind, placebo-controlled trial of adult schizophrenic patients, constipation was reported in 5% and 7% of patients receiving risperidone 25 mg (n=99) and 50 mg (n=103) long-acting intramuscular therapy, respectively, compared with 1% in placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, constipation was reported in 21% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 8% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.C Decrease in appetite

1) Incidence: IM, 6% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, decreased appetite was reported in 6% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 1% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.4.D Diarrhea

1) Incidence: oral, 3% to 8% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3, double-blind, placebo-controlled trials of 4 to 8 weeks duration in adults with schizophrenia, diarrhea was reported in 2% of patients who received risperidone 2 to 8 m/day (n=366), and in 1% of patients who receive risperidone greater than 8 to 16 mg/day (n=198) compared with 1% of patients who received placebo (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, diarrhea was reported in 3% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 2% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, diarrhea was reported in 6% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 4% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) Diarrhea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, diarrhea was reported in 8% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and in 7% of patients who received 3 to 6 mg/day (n=61), compared with 2% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.E Drooling

1) Incidence: oral, 16% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, drooling was reported in 16% of patients who received oral risperidone 0.5 to 4 mg/day (n=76) compared with 5% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.F Excessive salivation

1) Incidence: oral, 1% to 10% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 1% to 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, salivary hypersecretion was reported in 2% of patients who received oral risperidone 2 to 8 mg/day (n=366) and in 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with less than 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In double-blind, controlled trials of adult patients with bipolar mania, salivary hypersecretion was

reported in 3% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 1% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, salivary hypersecretion was reported in 2% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 0% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, salivary hypersecretion was reported in 4% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 1% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

e) A 63-year-old woman developed sialorrhea while taking oral risperidone 6 mg per day for schizophrenia. The patient, having schizophrenia since age 20, had been previously treated with oral risperidone 2 mg to 4 mg daily without incident. After a relapse of her illness, her dose was increased to 6 mg per day; and within 24 hours she developed sialorrhea that wet her clothing, pillows, and other objects. Upon examination, she did not display any extrapyramidal symptoms such as tremor, swallowing difficulties, muscle rigidity, or dyskinesia. She took no concomitant medications. Her risperidone dose was gradually decreased to 4 mg daily; upon reaching that dose, sialorrhea resolved within 24 hours, and had not returned at follow-up 5 months later. The Naranjo probability scale rated risperidone the likely cause of the sialorrhea, with a score of 6 on a scale of 0 to 13. The authors suggested the reaction was dose-related, as it occurred only during the period of time she was treated with risperidone 6 mg per day (Liang et al, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, salivary hypersecretion occurred in 0% of patients who received risperidone 1 to 3 mg daily (n=55) and 10% of patients who received 4 to 6 mg daily (n=51), compared with 2% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, salivary hypersecretion was reported in 9% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 0% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.G Increased appetite

1) Incidence: oral, 4% to 47% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, increased appetite was reported in 4% of patients receiving long-acting risperidone IM injection plus current therapy

(n=72) compared with 0% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, increased appetite was reported in 4% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 7% of patients who received 3 to 6 mg/day (n=61) compared with 2% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, increased appetite was reported in 47% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 19% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.H Indigestion

1) Incidence: oral, 2% to 10% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 6% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of for 4 to 8 weeks duration in adult schizophrenia patients, dyspepsia was reported in 8% of patients who received risperidone 2 to 8 mg/day (n=366) and 6% of patients who received greater than 8 to 16 mg/day (n=198), compared with 5% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, dyspepsia was reported in 9% of patients who received risperidone plus a mood stabilizer (n=127) compared with 8% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In a 12-week, double-blind, placebo-controlled trial of adult schizophrenic patients, dyspepsia was reported in 6% and 6% of patients receiving risperidone 25 mg (n=99) and 50 mg (n=103) long-acting intramuscular therapy, respectively, compared with 0% in placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, dyspepsia was reported in 10% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 3% of patients who received 3 to 6 mg/day (n=61), compared with 2% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.I Nausea

1) Incidence: oral, 4% to 16% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 3% to 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, nausea was reported in 5% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 2% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, nausea was reported in 9% of patients who received risperidone 2 to 8 mg/day (n=366) and 4% of patients who received greater than 8 to 16 mg/day (n=198), compared with 4% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, nausea was reported in 6% of patients who received risperidone plus a mood stabilizer (n=127) compared with 4% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) In a 12-week, double-blind, placebo-controlled trial of adult schizophrenic patients, nausea was reported in 3% and 4% of patients receiving risperidone 25 mg (n=99) and 50 mg (n=103) of long-acting intramuscular therapy, respectively, compared with 5% in placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

e) Nausea was responsible for 1.4% of treatment discontinuation in schizophrenic adult trials in patients receiving oral risperidone 2 to 8 mg/day (n=366) compared with 0% in patients receiving risperidone 8 to 16 mg/day (n=198), or in placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, nausea was reported in 16% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 13% of patients who received 3 to 6 mg/day (n=61) compared with 7% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, nausea was reported in 8% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 6% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.J Pancreatitis

1) During postmarketing risperidone use, pancreatitis has been reported (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating

tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) Neuroleptic malignant syndrome and probable acute pancreatitis was described in a 45-year-old woman with disorganized schizophrenia treated with risperidone for 2 years. A month prior to transferring to a clinic within the hospital, the patient presented with muscular stiffness, increase in nonspeaking, oppositivity, food phobia, decreased voluntary bowel or urinary function, and a rise in body temperature. Laboratory findings showed hyperamylasemia, hyperlipasemia, myoglobinuria, and an increase in CPK plasma levels, suggesting rhabdomyolysis and probable acute pancreatitis. However, an abdominal computed tomography scan revealed nothing significant. In the following days, the patient's myoglobinuria and CPK slowly normalized, but both amylasemia 636 units/L (normal range, 5 units/L to 53 units/L) and lipasemia 1293 units/L (normal range 114 units/L to 286 units/L) levels increased to maximum despite any clinical or radiological evidence. Neurological exam revealed extrapyramidal stiffness, and the patient was laconic, negative, uncooperative, and seemed confused toward time and space. Risperidone was discontinued and lorazepam therapy was initiated, which produced a slow resolution to her muscular stiffness. Amylasemia and lipasemia levels gradually decreased and returned to normal within 20 days. Clozapine 12.5 mg/day (titrated over more than 30 days to 300 mg/day) was introduced, resulting in significant improvement in the patients psychopathological outcome. At her 18-month follow-up the patient maintained good clinical balance with no issues (Ghio et al, 2009).

3) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 16% of the cases were associated with the use of risperidone at a mean daily dose of 4 mg. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003c).

4) A 32-year-old man with chronic paranoid schizophrenia developed cholestatic hepatitis and pancreatitis 1 week after beginning risperidone 2 mg daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, jaundice, dark urine, and clay-colored stools. He had no history of abdominal trauma, alcohol, or drug abuse, and tests for autoimmune diseases, cytomegalovirus, hepatitis A, B, and C were all negative. Initial laboratory results were: amylase, 1617 international units/L; AST, 179 international units/L; ALT, 366 international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; CB, 1.9 mg/dL. One week after discontinuing risperidone, the patient improved clinically and his laboratory results were: amylase, 113 international units/L; AST, 26 international units/L; ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units/L; TB, 0.7 international units/L; CB, 0.5 international units/L (Cordeiro & Elkis, 2001).

5) A 32-year-old man was diagnosed with pancreatitis after he complained of diffuse abdominal pain, nausea, and constipation 3 weeks after starting risperidone therapy. His initial amylase level was 1087 international units/L. He had a mild leukocytosis, slight glycemic elevation, but no other changes in liver function tests. His risperidone was tapered off over 2 weeks. His amylase declined to 147 international units/L (Berent et al, 1997).

3.3.4.K Toothache

1) Incidence: IM, 1% to 3% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In a 12-week, double-blind, placebo-controlled trial of adult schizophrenic patients, toothache was reported in 1% and 3% of patients receiving risperidone 25 mg (n=99) and 50 mg (n=103) long-acting intramuscular therapy, respectively, compared with 0% in placebo (n=98) (Prod Info

RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.4.L Upper abdominal pain

1) Incidence: oral: adult, 1%; pediatric, 13% to 16% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, upper abdominal pain was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198), compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, upper abdominal pain was reported in 16% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 13% of patients who received 3 to 6 mg/day (n=61), compared with 5% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.M Vomiting

1) Incidence: oral, 10% to 25% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) Vomiting was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, vomiting was reported in 10% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 10% of patients who received 3 to 6 mg/day (n=61), compared with 5% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, vomiting was reported in 25% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 21% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.4.N Xerostomia

1) Incidence: oral, 4% to 15% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, up to 7% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, dry mouth was reported in 4% of patients who received oral risperidone 2 to 8 mg/day (n=366) and 0% of patients who received greater than 8 to 16 mg/day (n=198), compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, dry mouth was reported in 0% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 7% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder, dry mouth was reported in 15% of patients who received oral risperidone 0.5 to 4 mg/day (n=76), compared with 6% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.5 Hematologic Effects

3.3.5.A Agranulocytosis

1) Agranulocytosis has been reported during clinical and/or postmarketing use of risperidone. The potential risk factors include a history of low WBC and drug-induced leukopenia or neutropenia. These patients should have frequent monitoring of CBC during the first few months of treatment. Consider discontinuing therapy at the first sign of clinically significant decline in WBC if there are no other causative factors (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) A case report described agranulocytosis in a 40-year-old woman after 2 weeks of risperidone treatment. She had previously experienced agranulocytosis with other antipsychotic therapies: chlorpromazine with carbamazepine (WBC count, 2500/mm(3); neutrophil rate, 30%), haloperidol (WBC count, 2200/mm(3); neutrophil rate, 52%), and zuclopenthixol (WBC count, 2700/mm(3); neutrophil rate, 29%). With risperidone 4 mg/day, her WBC count was 2400/mm(3) and her neutrophil count was 32% (Finkel et al, 1998).

3.3.5.B Anemia

1) Incidence: oral, up to 1% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info

RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In 3, double-blind, controlled trials of 4 to 8-weeks duration in adult schizophrenia patients, anemia was reported in less than 1% of patients who received risperidone 2 to 8 mg/day (n=366) and in 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) The incidence of anemia was less than 2% in patients treated for schizophrenia, less than 2% in patients treated for bipolar disorder as monotherapy, and less than 4% in patients treated for bipolar disorder as adjunctive therapy during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.5.C Leukopenia

1) Leukopenia has been reported during clinical and/or postmarketing use of risperidone. The potential risk factors include a history of low WBC, and drug induced leukopenia and neutropenia. These patients should have frequent monitoring of CBC during the first few months of treatment. Consider discontinuing therapy at the first sign of clinically significant decline in WBC if there is no other causative factors (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) A case report described leukopenia in a 32-year-old man following treatment with risperidone and aripiprazole. The patient, who had a long history of paranoid schizophrenia, had been initiated on risperidone 2 mg/day a few years earlier. Although he reported no side effects and the results of his annual physical exam were normal, laboratory assessment showed a WBC and absolute neutrophil count (ANC) of 2.8 x 10(9) and 1.27 x 10(9), respectively. Risperidone-induced leukopenia was suspected and the patient agreed to reduce the risperidone dose to 1 mg/day. A few weeks later, a lab workup showed WBC count and ANC at 2.7 x 10(9) and 1.22 x 10(9), respectively. Subsequently, risperidone was discontinued and the patient was initiated on aripiprazole 10 mg daily. He was evaluated every 4 weeks and reported no adverse effects. Six months later, his WBC count and ANC were 2.4 x 10(9) and 0.85 x 10(9), respectively, and aripiprazole was discontinued. Two weeks later, he experienced paranoid delusions, irritable mood, and auditory hallucinations for which he was hospitalized. Upon admission, his WBC count and ANC were 6.4 x 10(9) and 1.29 x 10(9), respectively. He was discharged after being reinitiated on aripiprazole 10 mg/day. At a follow-up appointment, his WBC count and ANC were again low (2.9 x 10(9) and 1.29 x 10(9), respectively). It was decided to discontinue aripiprazole and treat the patient with paliperidone 6 mg and lithium 300 mg. Subsequent to the medication change, his WBC count and ANC increased to 3.3 x 10(9) and 1.42 x 10(9). A full hematologic workup was pending at the time of this publication (Qureshi & Rubin, 2008).

3) A 63-year-old man developed leukopenia and neutropenia 1 week after beginning risperidone 2 mg twice daily for schizophrenia. The reaction was confirmed upon rechallenge. He had experienced a similar reaction with clozapine (Dernovsek & Tavcar, 1997).

4) A case of leukopenia, possibly related to risperidone, was reported following 7 days of therapy (2 to 6 mg/day) for schizophrenia. The white count decreased from 5100/mm(3) to 3500/mm(3) over 7 days, and the neutrophil count decreased from 3430/mm(3) to 1820/mm(3). On day 9, the neutrophil count had further decreased to 980/mm(3). The patient also had influenza during this same time period which may

have confounded the circumstances (Meylan et al, 1995).

3.3.5.D Neutropenia

1) Neutropenia has been reported during clinical and postmarketing use of risperidone. The potential risk factors include a history of low WBC, and drug induced leukopenia and neutropenia. These patients should be evaluated for signs of infection, and frequent monitoring of CBC during the first few months of treatment is recommended. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm(3)) should discontinue risperidone and have their WBC followed at discontinuation of treatment until recovery (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.5.E Thrombocytopenia

1) Thrombocytopenia has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
2) A case report described thrombocytopenia in a 48-year-old man following risperidone use. The patient, who had no history of hematological disorders, presented to the emergency room with sudden right hemiplegia, aphasia, and disorientation. He had a history of hypertension but was not receiving medication for it. According to a brain CT scan, there was hemorrhaging in the left temporoparietal region. Upon admission, his platelet count was 160,000/microL and he was treated fairly conservatively. On day 3, he went into a coma due to brain edema and underwent emergency surgery. His postoperative regimen included carbamazepine 600 mg/day to prevent convulsions, nizatidine 300 mg/day to prevent gastric ulcer, and nifedipine 40 mg/day for hypertension. At 2 days post-operation, he experienced marked agitation, emotional lability, and sensory aphasia and would not remain on bedrest. A diagnosis of postoperative delirium was made for which the patient was initiated on risperidone 1 mg twice daily resulting in an improvement in symptoms. Two weeks later, his platelet count was 38,000/microL. Because thrombocytopenia was suspected and his delirium had improved, risperidone was discontinued. Four days after risperidone discontinuation, platelet count increased to 112,000/microL. He continued to receive carbamazepine and nifedipine until discharge, but nizatidine was discontinued 3 days after risperidone was discontinued. Upon discharge on postsurgery day 32, his platelet count was 158,000/microL with WBC and RBC counts within normal limits. Two months later, his platelet count was 176,000/microL (Semba & Okui, 2009).

3.3.5.F Thrombotic thrombocytopenic purpura

1) In a large, open, premarketing trial of approximately 1300 patients receiving oral risperidone therapy, a 28-year-old woman developed thrombotic thrombocytopenic purpura (TTP), which included symptoms of fever, jaundice, and bruising. The patient recovered following plasmapheresis. The relationship of the TTP to risperidone is not known (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info

RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.6 Hepatic Effects

3.3.6.A gamma-Glutamyltransferase deficiency

1) Reductions in plasma gamma-glutamyl transferase have been reported with risperidone therapy (Anon, 1991a; Mesotten et al, 1989).

3.3.6.B Increased liver function test

1) A 32-year-old male patient with chronic paranoid schizophrenia developed cholestatic hepatitis and pancreatitis 1 week after beginning risperidone 2 mg daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, jaundice, dark urine, and clay-colored stools. He had no history of abdominal trauma, alcohol, or drug abuse, and tests for autoimmune diseases, cytomegalovirus , hepatitis A, B, and C were all negative. Initial laboratory results were: amylase, 1617 international units/L; AST, 179 international units/L; ALT, 366 international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; and CB, 1.9 mg/dL. One week after discontinuing risperidone, the patient improved clinically and his laboratory results were: amylase, 113 international units/L; AST, 26 international units/L; ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units/L; TB, 0.7 international units/L; and CB, 0.5 international units/L (Cordeiro & Elkis, 2001).
2) Two patients developed moderate increases of liver function tests within the first 1 or 2 weeks of risperidone therapy. The levels nearly normalized spontaneously with only a slight decrease of 1 mg in one patient and an unchanged dose in the other. It has been suggested to check liver function tests in the early phase of risperidone treatment (Whitworth et al, 1999).
3) An 81-year-old man with paranoid delusions, Parkinson disease, dementia, and depression developed hepatotoxicity after only 2 doses of risperidone 0.5 mg. Other medications included aspirin, diltiazem, sublingual nitroglycerin, levothyroxine, and doxepin. Baseline liver functions tests had been normal before beginning risperidone. After 2 doses, he was noted to be jaundiced with aspartate aminotransferase (AST) 434 units/L, alanine aminotransferase (ALT) 101 units/L, total bilirubin 3.6 mg/dL, and alkaline phosphatase 244 units/L. Ultrasound showed mild splenomegaly and small gallstones. Two weeks after discontinuation of risperidone, liver function tests were normal (Phillips et al, 1998).

3.3.8 Musculoskeletal Effects

3.3.8.A Abnormal gait

1) Incidence: IM, 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, gait abnormality was reported in 4% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 0% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.8.B Arthralgia

1) Incidence: oral, 2% to 3% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In 3 double-blind, controlled trials of adult schizophrenia patients, arthralgia was reported in 2% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198) compared with less than 1% of patients who received placebo (n=225) for 4 to 8 weeks (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, arthralgia was reported in 4% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 3% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.8.C Decreased bone mineral density

1) In a small study, decreased bone mineral density was observed in female, premenopausal schizophrenia patients receiving risperidone (n=12; 3 to 6 mg/day for at least 24 months), but not in those receiving olanzapine (n=14; 15 to 20 mg/day for at least 24 months). Age-adjusted bone speed of sound was significantly lower in women treated with risperidone compared with patients taking olanzapine when determined at the radius and phalanx (p less than 0.05), but not the tibia. This effect is most likely due to persistent risperidone-induced hyperprolactinemia (Becker et al, 2003).

3.3.8.D Pain, In extremity

1) Incidence: oral, 1% to 2% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 2% to 6% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, pain in extremity was reported in 2% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198), compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, pain in the extremity was reported in 6% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 2% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.9 Neurologic Effects

3.3.9.A Akathisia

1) Incidence: oral, up to 10% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 4% to 11% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, controlled trials of adult patients with bipolar mania, akathisia (eg, akathisia and restlessness) was reported in 9% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 3% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, akathisia (eg, akathisia and restlessness) was reported in 10% of patients who received risperidone 2 to 8 mg/day (n=366) and 10% of patients who received greater than 8 to 16 mg/day (n=198) compared with 3% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, akathisia (eg, hyperkinesia and akathisia) was reported in 8% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 0% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) In a 12-week, placebo-controlled trial of adult schizophrenic patients, akathisia, including restlessness, was reported in 4% and 11% of patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 6% in placebo (n=98). Akathisia led to treatment discontinuation in 1% of patients who received risperidone long-acting IM injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

e) A 69-year-old woman suffered protracted akathisia after risperidone withdrawal. The akathisia and parkinsonism had originally started with haloperidol therapy, but due to lack of efficacy she was switched to risperidone 1.5 mg twice daily. The akathisia persisted for 4 months and risperidone was discontinued. Her restlessness became worse during the first week and did not respond to lorazepam. Five weeks later, propranolol therapy resulted in a gradual resolution of the akathisia (Rosebush et al, 1997).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, akathisia (eg, akathisia and restlessness) was reported in 9% of patients who received oral risperidone 1 to 3 mg/day (n=55) and 10% of patients who received 4 to 6 mg/day (n=51) compared with 4% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, akathisia (eg, akathisia and restlessness) was reported in 0% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and in 8% of patients who received 3 to 6 mg/day (n=61) compared with 2% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.B Cerebrovascular accident

1) Incidence: oral, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) Cerebrovascular accident and cerebrovascular disorder were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone. Cerebrovascular disorders, including cerebrovascular accident have been reported in postmarketing surveillance (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) In premarketing oral risperidone clinical trials, cerebrovascular disorder and cerebrovascular accident was reported in less than 1% of adults and in less than 5% of pediatric patients receiving risperidone therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
4) Cerebrovascular adverse events (stroke, transient ischemic attack) including fatalities occurred in elderly individuals (mean age 85 years of age; range, 73 to 97) who received risperidone for dementia-related psychosis. In placebo-controlled trials, the incidence of cerebrovascular events in patients treated with risperidone was significantly greater than placebo (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.C Chorea

1) In a case report, chorea and tardive dyskinesia were reported in a girl 13.5 years of age who received risperidone. Nine months after the initiation of risperidone and dose decrease, chorea-like movements were evident. Risperidone was discontinued. At month 12, movements were decreased and at month 16, the movement disorder was resolved (Carroll et al, 1999).

3.3.9.D Disturbance of attention

1) Incidence: IM, 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, disturbance in attention was reported in 4% of patients receiving long-acting risperidone intramuscularly plus current therapy (n=72) compared with 0% in placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.9.E Dizziness

1) Incidence: oral, 4% to 16% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 3% to 11%(Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) Adult

a) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, dizziness was reported in 6% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 5% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, dizziness was reported in 7% of patients who received risperidone 2 to 8 mg/day (n=366) and 4% of patients who received greater than 8 to 16 mg/day (n=198) compared with 2% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, dizziness was reported in 7% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 2% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) During a 12-week clinical trial in schizophrenic patients, dizziness was observed in 7% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 11% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 6% of patients receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, dizziness was reported in 3% of patients receiving long-acting risperidone intramuscularly (n=154) as monotherapy compared with 1% in placebo (n=149) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, dizziness was reported in 7% of patients who received oral risperidone 1 to 3 mg/day (n=55) and in 14% of patients who received 4 to 6 mg/day (n=51) compared with 2% of patients who received placebo (n=54). Dizziness was responsible for 2% of discontinuation of therapy in schizophrenic trials including pediatric patients treated with risperidone (n=106) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, dizziness was reported in 16% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and in 13% of patients who received 3 to 6 mg/day (n=61) compared with 5% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, dizziness was reported in 9% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 3% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.F Dyskinesia

1) Incidence: oral, 7% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 6% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, dyskinesia was reported in 7% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 3% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) In a 52-week, double-blind, placebo-controlled trial in patients with bipolar disorder, dyskinesia was reported in 6% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 3% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.9.G Dystonia

1) Incidence: oral, 2% to 6% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, monotherapy, controlled trials of adult patients with bipolar mania, dystonia (eg, dystonia, muscle spasm, oculogyration, torticollis) was reported in 5% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 1% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of adult schizophrenia patients, dystonia (eg, dystonia, muscle spasms, muscle contractions involuntary, muscle contracture, oculogyration, tongue paralysis) was reported in 3% of patients who received risperidone 2 to 8 mg/day (n=366) and 4% of patients who received greater than 8 to 16 mg/day (n=198), compared with 2% of patients who received placebo (n=225) for 4 to 8 weeks (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) Dystonia, which includes spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing, difficulty breathing, and/or protrusion of the tongue, was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder(Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

d) An 18-year-old female developed tardive "writer's dystonia" following treatment with risperidone for schizophrenia. The patient had began treatment with risperidone 4 mg/day and trihexyphenidyl 2 mg/day for 6 months following her diagnosis of schizophrenia. She was on no other medications and her medical history was unremarkable. The patient presented with a decline in handwriting, including cramping, aching, mild tremors, and coordination of her right hand that persisted for 5 months. Routine testing revealed nothing abnormal. A diagnosis of tardive writer's cramp was made. Risperidone was replaced with quetiapine 200 mg/day. Over the next 7 months, the patient had no other recurrence of dystonia or any other motor function issues. Based on the Naranjo score of 7, there was a probability relationship between risperidone and tardive writer's dystonia (Aggarwal et al, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, dystonia

(eg, dystonia and oculogyration) was reported in 2% of patients who received oral risperidone 1 to 3 mg/day (n=55) and 6% of patients who received 4 to 6 mg/day (n=51), compared with 0% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, dystonia (eg, dystonia, laryngospasm, and muscle spasm) was reported in 6% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 5% of patients who received 3 to 6 mg/day (n=61) compared with 0% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.H Electroencephalogram abnormal

1) Fifteen days after initiation of risperidone 2 mg per day, a 55-year-old man developed extrapyramidal symptoms, with EEG revealing bifrontal slow-wave abnormalities (De Leon et al, 1997).

3.3.9.I Extrapyramidal disease

1) Summary

a) Extrapyramidal symptoms were reported in 7% to 35% of adult patients receiving oral risperidone therapy. In clinical trials of risperidone, the incidence of extrapyramidal symptoms was found to be dose-related (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010). The overall incidence of extrapyramidal symptoms in patients treated with 25 mg long-acting risperidone injection was comparable to that of placebo but was higher in patients receiving 50 mg long-acting risperidone injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) Incidence: oral, 7% to 35% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) Adult

a) In a 12-week, double-blind, placebo-controlled trial comparing 3 doses of long-acting risperidone (25 mg, 50 mg, and 75 mg) with placebo in patients with schizophrenia, the overall incidence of extrapyramidal symptoms in patients treated with 25 mg long-acting risperidone IM injection was comparable to that of placebo, but was higher in patients receiving 50 mg long-acting risperidone IM injection (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

b) Extrapyramidal symptoms (EPS) were reported in 17%, 21%, 21%, and 35% of patients who received oral risperidone 2, 6, 10, and 16 mg/day, respectively, compared with 13% of patients who received placebo during an 8-week trial of adults with schizophrenia. Similarly, in another 8-week trial, EPS symptoms were reported in 7%, 12%, 17%, 18%, and 20% of patients who received oral risperidone 1, 4, 8, 12, and 16 mg/day, respectively (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) A 43-year-old man treated with risperidone 6 mg/day presented with episodic blepharospasms (Meige's disease) that occurred spontaneously or were brought on by stress, requiring him to discontinue driving. The more he tried to open his eyes the more tightly they closed (Ananth et al, 2000).

d) In a review of risperidone studies, factors associated with the development of extrapyramidal symptoms (EPS) included a dose-dependent increase in severity with higher doses, especially above 8 mg/day (p less than 0.001). Also, a higher baseline score on the extrapyramidal symptom rating scale (ESRS) was associated with a reduction in the severity of EPS (p less than 0.001). It has also been noted that worse scores on the ESRS scale correspond with an increased time since diagnosis, especially in the elderly (Lemmens et al, 1999).

e) A 79-year-old woman treated with risperidone 1 mg twice daily for behavior problems associated with dementia developed severe extrapyramidal symptoms when donepezil 10 mg daily was added to her regimen. Risperidone was discontinued and donepezil decreased to 5 mg. There was a complete resolution of symptoms. The authors hypothesize that extrapyramidal symptoms occurred due to an excess in central acetylcholine while dopamine receptors were blocked (Magnuson et al, 1998).

f) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidone caused few or no extrapyramidal symptoms. Mean changes in Extrapyramidal Symptom Rating Scale (ESRS) scores from baseline to worst score were significantly lower in each risperidone group than the haloperidol group (p less than 0.001). At 6 mg/day, the mean (ESRS) change score was not significantly different from that of the placebo group (Simpson & Lindenmayer, 1997a).

g) A 26-year-old man developed extrapyramidal symptoms the day after starting risperidone 4 mg. He described difficulty breathing, which his physician characterized as possible laryngospasm. This resolved after the medication was discontinued. Three weeks later, the patient requested that the risperidone be restarted. Risperidone 2 mg was restarted and after 2 days the patient reported painful and very distressing tongue movements. The risperidone was decreased to 1 mg and these symptoms subsided after 2 days (Brown, 1997).

h) A 55-year-old man with a left acoustic neurinoma (a manifestation of his neurofibromatosis) developed a severe extrapyramidal reaction to risperidone. Over a period of 10 years, he had experienced a gradual deterioration with periods of violence and paranoid ideation. He was started on risperidone 2 mg daily. Fifteen days later, he experienced multiple symptoms including rigidity, cogwheeling, and slowness. Risperidone was discontinued and he returned to baseline (De Leon et al, 1997).

i) Acute dystonia with an oculogyric crisis occurred in a 33-year-old man with paranoid schizophrenia during reinitiation of risperidone treatment after a period of noncompliance. Following a 2-month period of noncompliance, he restarted risperidone and was taking 3 mg twice daily by the third day of treatment; the next day he experienced intermittent retrocollis and tonic upward deviation of both eyes for 2 hours. The only other medication at the time of this dystonic reaction was clonazepam 3 mg at bedtime. He was treated with benztropine 2 mg IM and all signs resolved; a second dose was given when he complained of muscle tightening which resolved 30 minutes after treatment. He continued risperidone, clonazepam, and benztropine 1 mg twice daily for a week, after which he discontinued the benztropine. At a 1-month follow-up, there was no further indication of dystonia (Faulk et al, 1996). A similar reaction occurred in a 34-year-old schizophrenic man who was titrated in 3 days up to risperidone 3 mg twice daily after a noncompliant period in which he used crack cocaine. He experienced rigid extremities, mild torticollis, tongue protrusion, and laryngospasm and was cyanotic. He was treated with diphenhydramine 50 mg IV with complete resolution of all symptoms within 10 minutes. Risperidone dose was decreased to 1 mg twice daily and titrated more slowly without further side effects (Brody, 1996).

j) Acute dystonia occurred in a 17-year-old male with new-onset schizophrenia who had been administered risperidone 2 mg twice daily. After 3 doses, he experienced throat restriction, thickening of the

tongue, increased salivation, shortness of breath for 10 to 15 minutes, mild cogwheel rigidity, and stiffness. Risperidone was reduced to 2 mg at bedtime and benztropine 2 mg twice daily added. Benztropine 2 mg IM was given. Risperidone 2 mg at bedtime and benztropine 2 mg twice daily were given for the next 2 days. By day 5, he showed increased mental and autonomic instability; risperidone was reduced to 2 mg at bedtime, benztropine was reduced to 1 mg, and two doses of lorazepam 1 mg were given. All medications were then discontinued and all symptoms resolved on day 7 (Takhar & Manchanda, 1996).

4) Pediatric

a) A 12-year-old boy, with attention-deficit hyperactivity disorder and psychotic symptoms, developed extrapyramidal reactions following treatment with risperidone and several other drugs. On the day before a laser treatment to remove a birth mark, the boy started taking risperidone 1 mg twice daily in addition to sertraline 25 mg per day and methylphenidate 10 mg in the morning. His premedications for the procedure included morphine, ketorolac, and tropisetron. Eight hours after the procedure, he developed shortness of breath, stiffness, difficulty talking and moving, had slurred speech, and was unable to close his mouth. Twitching began in his hands, shoulders, neck, and head and progressed to jerking movements of his jaw and arms. He was treated with benztropine 0.02 mg/kg for these acute dystonic reactions and his symptoms gradually improved. His risperidone dose was decreased to 0.5 mg per day and ketorolac and tropisetron were eliminated from the premedication regimen (due to potential synergism for causing the extrapyramidal reactions). There was no recurrence of dystonic symptoms during the remaining 5 laser procedures (Teoh et al, 2002).

b) A 7-year-old boy developed hypertonicity of the extremities, confusion, lethargy, and limited tongue movement after a single dose of risperidone 1 mg for attention deficit hyperactivity disorder. Two doses of diphenhydramine did not improve the dystonia; the child recovered the following day (Gesell & Stephen, 1997h).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.J Headache

1) Incidence: IM, 15% to 21% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010); oral: pediatrics, 6% (Prod Info RISPERDAL(R) oral tablets, solution, 2011)

2) Headache occurred in 6% of pediatric patients treated with oral risperidone for irritability associated with autistic disorder (Prod Info RISPERDAL(R) oral tablets, solution, 2011).

3) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, headache was reported in 15% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 21% of patients receiving risperidone 50 mg long-acting IM injection (n=103), compared with 12% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.9.K Insomnia

1) Incidence: oral, up to 32% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, insomnia was reported in 32% of patients who received risperidone 2 to 8 mg/day (n=366) and 25% of patients who received greater than 8 to 16 mg/day (n=198) compared with 27% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) Insomnia and initial insomnia were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010). .

3.3.9.L Lethargy

1) Incidence: oral, 2% to 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)
2) Adult
a) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, lethargy was reported in 2% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 1% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
b) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, lethargy was reported in 2% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 1% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) Pediatric
a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, lethargy was reported in 5% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 3% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.M Paresthesia

1) Incidence: less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) Paresthesia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) Six patients (aged 37 to 65 years old) developed burning paresthesias while on risperidone therapy. The locations affected included the feet, lower body, back, face, arms, throat, and chest. The burning resolved with continued therapy in 2 cases, and the risperidone was discontinued in the other 4 cases (Heimberg & Yearian, 1996).

3.3.9.N Parkinsonism

1) Incidence: oral, 6% to 28% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 8% to 15% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, controlled trials of adult patients with bipolar mania, parkinsonism (eg, extrapyramidal disorder, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, bradykinesia, hypokinesia, , muscle rigidity and tightness) was reported in 25% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 9% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, parkinsonism (eg, extrapyramidal disorder, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson disease) was reported in 14% of patients who received risperidone 2 to 8 mg/day (n=366) and 17% of patients who received greater than 8 to 16 mg/day (n=198), compared with 8% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, parkinsonism (eg, extrapyramidal disorder, bradykinesia, and hypokinesia) was reported in 14% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 4% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) During a 12-week, double-blind, placebo-controlled trial, parkinsonism, which included extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia, was reported in 8% of adults who received risperidone 25 mg IM (n=99), and in 15% of adult who received risperidone 50 mg IM for schizophrenia compared with 9% of placebo (n=98). Parkinsonism, including muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia, was reported in 15% of patients who received adjunctive intramuscular risperidone for bipolar disorder (n=72) compared with 6% of patients who received placebo (n=67). Parkinsonism was one of the most common adverse effects reported in patients treated for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

e) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted hazard ratio (HR), 1.3; 95% confidence interval (CI), 1.04 to 1.58), and 60% less likely to occur in patients who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had

almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, parkinsonism (eg, extrapyramidal disorder, musculoskeletal stiffness, hypokinesia, and muscle rigidity) was reported in 16% of patients who received oral risperidone 1 to 3 mg/day (n=55) and 28% of patients who received 4 to 6 mg/day (n=51) compared with 11% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, parkinsonism (eg, extrapyramidal disorder, musculoskeletal stiffness, bradykinesia, and nuchal rigidity) was reported in 6% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 12% of patients who received 3 to 6 mg/day (n=61) compared with 3% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, parkinsonism (eg, extrapyramidal disorder, musculoskeletal stiffness, cogwheel rigidity, muscle tightness, and muscle rigidity) was reported in 11% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 1% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.O Reduced sensation of skin

1) Incidence: IM, 2% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, hypoesthesia was reported in 2% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 0% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.9.P Sedated

1) Incidence: oral: adult, 3% to 6%; pediatric, 8% to 29% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Adults

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, sedation was reported in 3% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198) compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, sedation was reported in 6% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 2% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, sedation was reported in 6% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 3% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, sedation was reported in 13% of patients who received oral risperidone 1 to 3 mg/day (n=55) and in 8% of patients who received 4 to 6 mg/day (n=51) compared with 2% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, sedation was reported in 20% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 23% of patients who received 3 to 6 mg/day (n=61) compared with 7% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, sedation was reported in 29% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 3% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.Q Seizure

1) Incidence: oral, 0.3% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 0.3% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) During premarketing trials, seizures occurred in 0.3% of patients receiving oral risperidone (9/2607) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010) and in 0.3% of patients receiving long-acting intramuscular risperidone (5/1499) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010). Two cases reported with oral therapy were associated with hyponatremia. Risperidone should be

used cautiously in patients with a history of seizures (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) A 64-year-old woman experienced a seizure 2 days after beginning risperidone therapy. She received two 1-mg doses and two 2-mg doses before having a 1-minute generalized tonic-clonic seizure with a 5-minute postictal confusion period. At the time of beginning risperidone therapy, she also received trimethoprim-sulfamethoxazole for a urinary tract infection and astemizole for scalp itch. Therapy with risperidone was restarted at 0.5 mg/day and increased to 0.5 mg twice daily with control of her psychotic symptoms and no further seizures (Lane et al, 1998).

3.3.9.R Somnolence

1) Incidence: oral, 3% to 49% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 5% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, somnolence was reported in 5% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 2% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, somnolence was reported in 7% of patients who received risperidone 2 to 8 mg/day (n=366) and 2% of patients who received greater than 8 to 16 mg/day (n=198), compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, somnolence was reported in 3% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 1% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) During risperidone multiple-dose clinical trials, somnolence was reported in 5% of adult patients receiving IM risperidone (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, somnolence was reported in 11% of patients who received oral risperidone 1 to 3 mg/day (n=55) and 4% of patients who received 4 to 6 mg/day (n=51) compared with 2% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, somnolence was reported in 22% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and in 30% of patients who received 3 to 6 mg/day (n=61) compared with 12% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated

with autistic disorder, somnolence was reported in 49% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 18% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.S Stuttering

1) A 48-year-old female developed stuttering following treatment with risperidone for the onset of psychosis (probable paranoid schizophrenia). The patient had no history of drug or alcohol abuse and radiologic (CT of the head and EEG) and laboratory studies were unremarkable. On the eleventh day of risperidone treatment (4 mg), the patient developed speech repetition and pausing which produced an excess of physical tension; this had not occurred with the lower dose. Risperidone was increased to 6 mg/night resulting in improvement in the patient's psychosis. After discharge, the patient was started on procyclidine 5 mg twice daily due to extrapyramidal side effects; however, the stuttering persisted. Risperidone was decreased to 4 mg/night, but only a small reduction in stuttering was observed. Based on the Naranjo probability assessment (score of 8), probable causality was determined (Yadav, 2010).
2) A 32-year-old Korean patient with a prior history of stuttering demonstrated a recurrence of stuttering with risperidone 1 mg on day 5 of hospitalization. The dosage was increased to 8 mg daily on day 25 and the stuttering was more pronounced. Due to his auditory hallucinations and idea of reference, the dosage was maintained. On day 48, the stuttering was lessened (Lee et al, 2001).

3.3.9.T Tardive dyskinesia

1) Summary
a) Potentially irreversible tardive dyskinesia may develop in patients receiving antipsychotic drugs and may be positively correlated to the duration of treatment and the cumulative dose of antipsychotic; however, though less common, the syndrome can develop after brief treatment periods at low doses. Antipsychotics may mask the underlying process by suppressing the signs and symptoms of the syndrome. The prevalence of the syndrome appears to be highest among the elderly, especially elderly women; however, it is impossible to rely upon prevalence to estimate which patients are likely to develop the syndrome. The syndrome may remit partially or completely upon discontinuation of the antipsychotic medication (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010; Carroll et al, 1999; Saran, 1998; Sakkas et al, 1998; Campbell, 1999; Gwinn & Caviness, 1997; Meco et al, 1997).
2) Incidence: oral, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
3) Tardive dyskinesia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder. Tardive dyskinesia led to treatment discontinuation in one patient who received risperidone long-acting IM injection for adjunctive treatment of

bipolar I disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

4) During premarketing risperidone studies of various design types, tardive dyskinesia was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

5) Tardive dyskinesia was reported in 0.1% (2 of 1885) of children and adolescents who received oral risperidone in clinical trials. Symptoms resolved following risperidone discontinuation (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

6) The use of long-acting risperidone in schizophrenic patients has been associated with a low incidence of emergent tardive dyskinesia, as well as improvement in existing dyskinesia. In an open label trial (n=725), patients with stable schizophrenia or schizoaffective disorder received long-acting risperidone in 25 mg, 50 mg, or 75 mg intramuscular doses every 2 weeks for up to 50 weeks. Dyskinesia was assessed via the Extrapyramidal Symptom Rating Scale (ESRS) at months 1, 2, 3, 6, 9, and 12; tardive dyskinesia was defined as either 2 or more "mild" scores or 1 or more "moderate" scores on the ESRS dyskinesia 7-item subscale over at least a 4-week period. Of the 662 patients for whom ESRS data were available, 530 (80.1%) had no dyskinesia and 132 (19.2%) has existing dyskinesia at study enrollment. Emergent tardive dyskinesia was observed in 0.94% (5/530) of patients without dyskinesia at baseline. This represents an annualized rate of 1.19% when adjusted for study drug exposure or when assessed by Kaplan-Meier survival analysis (95% confidence interval (CI), 0.15 to 2.24). The incidence of tardive dyskinesia was similar among all doses, with no observation of a dose-dependent effect. For patients with dyskinesia existing at baseline, mean ESRS scores were significantly improved from baseline to endpoint (6.9 vs 4.6, respectively; p less than 0.001) (Gharabawi et al, 2005).

7) Case Reports

a) Tardive dyskinesia (TD) was reported in a 24-year-old male following risperidone treatment for Tourette syndrome (TS). At age 15, the patient developed repetitive twisting movements of his head and neck. Nine years following the onset of symptoms, he was diagnosed with TS. He experienced motor and phonic tics, along with obsessional thoughts. Sertraline (50 mg/day) and haloperidol (0.5 mg/day) was initiated. No follow-up was available. The patient returned for treatment with identical symptoms, so risperidone (1 mg/day) and fluoxetine (40 mg/day) were initiated and maintained. His tics were mild, but the patient developed oromandibular dyskinetic movements of the lower jaw after 4 months of treatment. Treatment with risperidone was discontinued and vitamin E with clonazepam was initiated. The patient experienced a significant improvement in dyskinetic symptoms within about 45 days, yet the patient's TS significantly worsened, causing severe distress (Thomas et al, 2009).

b) Tardive dyskinesia (TD) was reported in a 44-year-old female following risperidone treatment for undifferentiated schizophrenia. The patient suffered for 4 years with delusions, hallucinations, alogia, and had minimal contact with reality. Following her first psychotic episode, she was hospitalized and risperidone 4 mg/day was initiated. Symptoms improved, but without complete resolution. Upon discharge, the patient maintained her risperidone dose without issue for approximately 4 years. Her risperidone dose was increased to 6 mg/day following a worsening of positive psychotic symptoms. Within 2 weeks, she experienced partial remission of delusions and significant reduction of aggression, hostility and auditory hallucinations. However, the patient reported abnormal movements of the jaw, lips, mouth, tongue, and lower extremities 4 months following the increased risperidone dose. With no

family history of movement disorders and normal testing results, the patient was diagnosed with neuroleptic-induced TD. Risperidone was switched to aripiprazole 15 mg/day, and was gradually discontinued. Her severity of TD started to subside within 2 weeks, and she remained on aripiprazole with no reoccurrence of TD or other involuntary movements or psychotic symptoms (Caykoylu et al, 2009).

c) In a substudy (n=21) of a randomized double-blind, placebo-controlled trial, a 51-year-old female developed tardive dyskinesia, manifested by involuntary tongue movements during maintenance. For the substudy, the mean risperidone dose was 2 mg per day for the first 10 weeks (acute) and 1.36 mg per day (maintenance). During the acute phase, prolactin level was 239.5 nanograms/mL and during maintenance after 41 weeks from initial risperidone dose, prolactin was 199.6 nanograms/mL. Prolactin remained elevated at 85.3 nanograms/mL after 5.1 years (Hellings et al, 2005).

d) In case reports, risperidone has caused tardive dyskinesias with doses as low as 1 mg daily (Saran, 1998) and with a course of therapy as short as 8 months (Sakkas et al, 1998). In patients with a history of tardive dyskinesias, risperidone has worsened their dyskinesia or made it reappear within 1 week of therapy (Sherr & Thaker, 1998). Several more cases of tardive dyskinesia due to risperidone have been reported in the literature (Campbell, 1999).

e) A 69-year-old man with a long history of bipolar disorder developed involuntary oral-buccal-lingual dyskinesias and parkinsonism while treated with risperidone. A few months after being treated with valproic acid, lorazepam, bupropion, trihexyphenidyl, and risperidone 3 mg twice daily, he developed involuntary mouth movements, tremor, slowness, and difficulty with gait. At 10 months, the risperidone and trihexyphenidyl were discontinued. Three weeks later the movements and parkinsonism persisted. At seven weeks, there was no rigidity present but the dyskinesia persisted. The patient was then lost to follow-up. The authors believe that the tardive dyskinesia and parkinsonism was induced by risperidone and that the bupropion may have contributed. However, since the parkinsonism improved after discontinuation of risperidone, they believe that the risperidone was mostly responsible for these extrapyramidal effects (Gwinn & Caviness, 1997).

3.3.9.U Transient ischemic attack

1) Cerebrovascular adverse events (stroke, transient ischemic attack) including fatalities occurred in elderly individuals (mean age 85 years of age; range, 73 to 97) who received risperidone for dementia-related psychosis. In placebo-controlled trials, the incidence of cerebrovascular events in patients treated with risperidone was significantly greater than placebo (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.9.V Tremor

1) Incidence: oral, 2% to 12% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R) oral tablets, 2007); IM, 3% to 24% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, tremor (eg, tremor and parkinsonian rest tremor) was reported in 6% of patients who received oral risperidone 1 to 6

mg/day (n=448) compared with 3% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, tremor (eg, tremor and parkinsonian rest tremor) was reported in 2% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198) compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, tremor was reported in 6% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 2% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

d) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, tremor was reported in 0% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 3% of patients receiving risperidone 50 mg long-acting IM injection (n=103), compared with 0% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, tremor was reported in 24% of patients receiving long-acting risperidone intramuscularly plus current therapy (n=72) compared with 16% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, tremor was reported in 11% of patients who received oral risperidone 1 to 3 mg/day (n=55) and 10% of patients who received 4 to 6 mg/day (n=51), compared with 6% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, tremor was reported in 12% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 1% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.10 Ophthalmic Effects

3.3.10.A Abnormal vision

1) Incidence: IM, 2% to 3% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) An adverse event analysis from a large study comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day) demonstrated a dose-related effect for reports of abnormal vision (p less than 0.05) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, blurred vision was reported in 2% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 3% of pa-

tients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.10.B Blurred vision

1) Incidence: oral, 1% to 7% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, blurred vision was reported in 3% of patients who received risperidone 2 to 8 mg/day (n=366) and in 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, blurred vision was reported in 2% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 1% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, blurred vision was reported in 4% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 7% of patients who received 3 to 6 mg/day (n=61) compared with 0% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.11 Otic Effects

3.3.11.A Otalgia

1) Incidence: oral, up to 1% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, ear pain was reported in less than 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.12 Psychiatric Effects

3.3.12.A Agitation

1) Incidence: oral, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info

RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Agitation was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder. In the trials for the treatment of schizophrenia, agitation led to treatment discontinuation in 3% of patients (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) During risperidone clinical trials, agitation was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

4) Agitation and aggressive reaction occurred in 1% or more (and were at least as frequent among) risperidone-treated patients (dosage: 10 mg/day or less) than among placebo-treated patients (Diaz, 1996).

3.3.12.B Anxiety

1) Incidence: oral, up to 16% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, anxiety was reported in 16% of patients who received risperidone 2 to 8 mg/day (n=366) and 11% of patients who received greater than 8 to 16 mg/day (n=198) compared with 11% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, anxiety was reported in 3% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 2% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) Anxiety was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder. In the 12-week, double-blind, placebo-controlled trial for schizophrenia, anxiety led to treatment discontinuation in 1% of patients (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 6-week, double-blind, placebo-controlled trial in pediatric patients with schizophrenia, anxiety was reported in 7% of patients who received oral risperidone 1 to 3 mg/day (n=55) and 6% of patients who received 4 to 6 mg/day (n=51), compared with 0% of patients who received placebo (n=54) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010). Anxiety was responsible for 1% of discontinuation of therapy in schizophrenic trials including pediatric patients treated with risperidone (n=106) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, anxiety was reported in 0% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 8% of patients who received 3 to 6 mg/day (n=61), compared with 3% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.12.C Catatonia

1) A 61-year-old schizophrenic woman developed catatonia after beginning risperidone 2 mg daily. The woman had a history of frontal lobotomy 36 years previously. She had been receiving fluphenazine decanoate 25 mg intramuscularly every 2 weeks. Two weeks after her last dose, she began risperidone which was increased to 5 mg. Catatonic symptoms worsened and she was taken off risperidone and placed on clozapine. Her catatonia subsided within 5 days (Bahro et al, 1999).

3.3.12.D Delirium

1) Three cases of possible risperidone-induced delirium were reported in patients aged 71, 83, and 83 years. All were hospitalized patients being treated for major depression with psychotic features. In each case, the mania abated after risperidone was discontinued. The authors acknowledge that the delirium may have been multifactorial in etiology; however, risperidone use appeared to be a risk factor (Ravona-Springer et al, 1998).
2) An 85-year-old woman with schizophreniform disorder was treated with risperidone 1 mg daily and then increased to 1 mg twice daily after 4 days with resultant delirium. The woman was restless, disoriented, and hallucinating. Risperidone was discontinued and she recovered after 18 hours (Tavcar & Dernovsek, 1998).

3.3.12.E Mania

1) Mania has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
2) A review of the literature identified 16 cases of mania related to risperidone therapy. Patients were treated with 2.5 to 9 mg daily for schizoaffective, bipolar type, mixed (n=2); schizoaffective, bipolar type, depressed (n=4); schizophrenia (n=5); schizoaffective, depressed (n=2); recurrent depression, psychotic (n=1); and bipolar type I, manic (n=2). The onset of development of manic symptoms ranged from 2 to 40 days. Five of 16 patients were receiving no other medications and in 6 cases it wasn't determined if there were concomitant medications. Two patients received valproate, 1 lithium, and 1 haloperidol concomitantly, which makes causality difficult to assess. In 2 cases, risperidone was continued and manic symptoms resolved without treatment. On 7 occasions, risperidone was discontinued and in the remaining 6 instances, risperidone was either continued with antimanic medications or reduced in dosage, or both. Remission of symptoms generally occurred within 2 to 14 days, although there was one case where it took 60 days for manic symptoms to resolve (Aubry et al, 2000).

3) Four cases of mania developing after beginning risperidone therapy were presented. Two patients were treated for schizophrenia with risperidone 5 mg and 6 mg while 1 patient was treated for schizoaffective disorder with risperidone 2 mg. Sexual disinhibition was one of the most predominant symptoms. In 1 patient, only risperidone discontinuation was needed to resolve the mania. In another schizophrenic patient, carbamazepine, benzodiazepines, and neuroleptics were required for control. In the schizoaffective patient, valproic acid was needed (Zolezzi & Badr, 1999).
4) Mania occurred in a 50-year-old man with chronic schizophrenia and mild mental retardation. He had been tapered off of haloperidol and risperidone was started and titrated to 9 mg/day within 12 days. Forty days later he exhibited manic behavior. Risperidone was reduced to 6 mg/day and clonazepam 2 mg was initiated. A week later the patient was hospitalized and, over a 32-day period, he was treated with lithium, valproic acid, and haloperidol until the mania resolved (Diaz, 1996).
5) Three cases of mania developing within days of starting risperidone therapy were reported. The patient's diagnoses included one with schizoaffective disorder, one with schizophrenia, and one with bipolar I disorder. Risperidone was discontinued in the first patient and decreased in the last 2 patients with resolution of symptoms (Schnierow & Graeber, 1996).

3.3.12.F Nocturnal sleep-related eating disorder

1) Risperidone-induced sleep-related eating disorder was observed in a 68-year-old man following the administration of risperidone for the treatment of vascular dementia. The patient's psychotic symptoms resolved after his daily dose of risperidone was increased from 1 mg to 2 mg; however, he began experiencing sleep disturbances almost nightly, including episodes during which he would consume large quantities of food while asleep. These episodes persisted for 2 months and then quickly resolved when the dosage was reduced to 1 mg/day (Lu & Shen, 2004).

3.3.12.G Obsessive-compulsive disorder

1) A schizophrenic man developed obsessive imagery after being treated with risperidone 4 mg/day for 18 months. He was also receiving valproate, trihexyphenidyl, and zuclopenthixol. He repeatedly saw the image of a person's face as he went about his activities. This disappeared after the dosage of risperidone was decreased to 3 mg/day (Mahendran, 1999).
2) A 26-year-old woman with schizophrenia developed obsessive-compulsive symptoms after 2 weeks of risperidone therapy. She was receiving risperidone 4 mg daily when she experienced excessive thoughts about playing mah-jongg. Risperidone was reduced to 2 mg without success. Clomipramine 25 mg was added and the ruminations disappeared. The clomipramine was eventually withdrawn after 4 weeks and she was maintained on risperidone 1 mg daily (Mahendran, 1998).

3.3.13 Renal Effects

3.3.13.A Hemorrhagic cystitis

1) An 11-year-old boy with significant behavioral problems developed hemorrhagic cystitis 1 week after

beginning risperidone therapy. Other medications included fluoxetine, valproic acid, benztropine, haloperidol, clonidine, trazodone, and nasal desmopressin. He presented with acute onset of dysuria and increased frequency with gross hematuria. There were no signs of viral illness and urine cultures were negative. Ultrasonography showed a thickened bladder wall and mild hydronephrosis. Symptoms were not relieved with oxybutynin and trimethoprim-sulfamethoxazole. Risperidone was withdrawn and symptoms resolved within a week. At a 1-month follow-up, the patient was asymptomatic and ultrasonography showed a normal thin-walled bladder (Hudson & Cain, 1998).

3.3.13.B Urinary incontinence

1) Incidence: oral, 2% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, urinary incontinence was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) Urinary incontinence was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

c) There was a temporal correlation with risperidone therapy and urinary incontinence in 2 case reports. Both patients developed urinary incontinence with risperidone 4 mg daily. Upon discontinuation of risperidone, urinary incontinence resolved (Agarwal, 2000).

3.3.13.C Urinary tract infectious disease

1) Incidence: oral, 1% to 3% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, urinary tract infection was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198), compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, urinary tract infection was reported in 2% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 1% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.14 Reproductive Effects

3.3.14.A Abnormal ejaculation

1) Incidence: oral, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) Ejaculation disorder was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder. Retrograde ejaculation and ejaculation failure have also been reported (incidence unknown) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) During risperidone clinical trials, ejaculation disorder was reported in less than 1% of adult patients receiving oral therapy and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
4) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less than 0.05) for ejaculatory dysfunction among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
5) Two cases of probable retrograde ejaculation were attributed to risperidone treatment. A 36-year-old African American man and a 30-year-old Caucasian man being treated with risperidone 6 mg and 3 mg per day, respectively, were poorly compliant with treatment. It was later determined that their poor compliance was due to concern over an absence of semen with ejaculation (Compton, 2002).
6) The absence of ejaculation was reported in 2 male patients treated with risperidone. In one patient, ejaculation dysfunction disappeared spontaneously after 4 weeks of risperidone treatment. In the other patient, absence of ejaculation was still present 8 weeks after the initiation of risperidone (Raga, 1999).
7) A 38-year-old man experienced ejaculatory dysfunction and dysuria one week after starting risperidone. He had no past history of genitourinary problems. On day 12 of treatment, risperidone was discontinued, with symptoms resolving 2 days later. The patient underwent rechallenge with risperidone and symptoms recurred in 2 days (Madhusoodanan & Brenner, 1996).

3.3.14.B Absence of ejaculation

1) Incidence: oral, up to 1% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)
2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, ejaculation failure was reported in less than 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198), compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.14.C Amenorrhea

1) Incidence: oral, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, amenorrhea was reported in 4% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 1% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010). During risperidone clinical trials, amenorrhea was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) Five psychiatric patients developed amenorrhea with elevated serum prolactin levels on risperidone 1 to 8 mg/day. In 4 cases, menstruation resumed upon discontinuation; menstruation resumed in case 5 after tapering risperidone (Kim et al, 1999).

3.3.14.D Erectile dysfunction

1) Incidence: IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) Erectile dysfunction was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) An adverse event analysis from a large study comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day) demonstrated a dose-related effect for reports of erectile dysfunction (p less than 0.05) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.14.E Priapism

1) A 31-year-old man developed priapism following therapy with risperidone for the treatment of chronic, paranoid-type schizophrenia (10 years). His medical history included obesity, hypercholesterolemia, keloid on neck, and tonsillectomy (age 6 years). His only medication consisted of risperidone 2 mg in the morning and 3 mg at bedtime. The patient presented to the emergency room following 10 days of persistent and painful penile erection. He was not sexually active and had no history of penile, genital, or pelvic trauma. Since laboratory tests returned within normal limits, a diagnosis of priapism was made, and an irrigation of normal saline and an injection of phenylephrine was initiated. However, on day 2, his symptoms worsened and he was admitted to the operating room to have a shunt placed between the corpora cavernosa and corpora spongiosa. The priapism completely resolved within hours of shunt placement. Even though risperidone was an effective treatment for this patient, it was discontinued and replaced with aripiprazole with no further incidence at his 2-month follow-up (Sharma & Fleisher, 2009).

2) An African American man developed priapism on 2 occasions after receiving risperidone and again after receiving ziprasidone for the treatment of schizophrenia. Following risperidone treatment (4 mg twice daily), the man developed an erection lasting 13 hours, which resolved upon irrigation of the corpora with phenylephrine 200 mcg. Following discontinuation of risperidone, the patient developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 mg twice daily. This erection lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the ziprasidone was discontinued and the priapism quickly resolved (Reeves & Mack, 2002).

3) A 47-year-old African American man developed priapism after taking risperidone 2 mg twice daily for 2 years. He had experienced prolonged painful erections multiple times in the past few weeks. Physical and laboratory examinations revealed no abnormalities apart from the erect penis. Penile irrigation with normal saline and phenylephrine injection caused detumescence. Risperidone was discontinued. No other antipsychotic treatment was started. One month later, he reported spontaneous, partial rigid erection (Ankem et al, 2002).

4) A 26-year-old Hispanic man had a 5-day episode of persistent erection, dysuria, and urinary incontinence. His medications, which he had been receiving for 1 year, included risperidone 3 mg/day and divalproex sodium 1500 mg/day for the treatment of intermittent mood and psychotic symptoms. His erection persisted despite 2 corpora cavernosa irrigations with phenylephrine. Corpora cavernosa venous blood gas analysis was consistent with a diagnosis of low-flow priapism. A cavernosal glandular shunt and a corpora cavernosum/corpus spongiosum shunt were performed. As there have not been any previously reported instances of priapism associated with divalproex use, the authors assumed that risperidone was the likely cause of the condition (Bourgeois and Mundh, 2003).

3.3.15 Respiratory Effects

3.3.15.A Cough

1) Incidence: oral, adults, 2%; pediatrics, 24% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 2% to 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, cough was reported in 2% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 0% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, cough was reported in 4% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 2% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 3% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, cough was reported in 4% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 1% of patients receiving placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, cough was reported in 24% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 18% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.15.B Dyspnea

1) Incidence: oral, 1% to 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
2) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, dyspnea was reported in 1% of patients who received risperidone 2 to 8 mg/day (n=366) and 2% of patients who received greater than 8 to 16 mg/day (n=198) compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).
3) Dyspnea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.15.C Epistaxis

1) Incidence: oral: pediatrics, 6% (Prod Info RISPERDAL(R) oral tablets, solution, 2011)
2) Epistaxis occurred in 6% of pediatric patients being treated with oral risperidone for irritability associated with autistic disorder (Prod Info RISPERDAL(R) oral tablets, solution, 2011).

3.3.15.D Nasal congestion

1) Incidence: oral: pediatric, 13% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)
2) Pediatric
a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, nasal congestion was reported in 13% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 5% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.15.E Nasopharyngitis

1) Incidence: oral: pediatric, 21% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, nasopharyngitis was reported in 21% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 10% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.15.F Pain in throat

1) Incidence: oral: adult, 5%; pediatric, 3% to 10% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

2) Adult

a) In two 3-week, double-blind, placebo-controlled adjuvant therapy studies of adults with bipolar mania, pharyngolaryngeal pain was reported in 5% of patients who received oral risperidone plus a mood stabilizer (n=127) compared with 2% of patients who received placebo plus a mood stabilizer (n=126) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, pharyngolaryngeal pain was reported in 10% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 3% of patients who received 3 to 6 mg/day (n=61), compared with 5% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.15.G Pharyngitis

1) Incidence: oral, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) During the double-blind, placebo-controlled trials for oral risperidone, less than 1% of adults and less than 5% of pediatric patients reported pharyngitis (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3) Pharyngitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.15.H Pulmonary embolism

1) A case report described 3 episodes of pulmonary embolism in a 25-year-old man after treatment with olanzapine and with risperidone for early-onset schizoaffective disorder. His physical health was generally good and there was no personal or family history of VTE. He was not overweight nor had his weight or

physical activity level changed under neuroleptic medication. Smoking a pack of cigarettes per day was his only known cardiovascular risk factor. His antipsychotic therapy included olanzapine 20 mg/day, paroxetine 20 mg/day and oral valproate 2000 mg/day for his psychotic symptoms. After 12 weeks of treatment, the patient presented with a complaint of sudden back pain radiating to the left front part of his thorax. Over the next few hours, he became short of breath and experienced an episode of hemoptysis. A CT scan revealed bilateral pulmonary embolism. Ultrasound of the lower extremities showed no signs of DVT. His coagulopathy workup did not demonstrate any abnormalities. Olanzapine was discontinued and oral warfarin treatment with a target INR of 2.5 (range of 2 to 3) was initiated and maintained for 6 months. Twelve weeks after olanzapine was discontinued, he was initiated on risperidone 3 mg/day for a recurrence of psychotic symptoms. After 3 weeks of risperidone treatment, the patient presented with chest pain, cough, dyspnea, and hemoptysis. Multiple peripheral pulmonary emboli were observed on a chest spiral CT scan. Concomitant DVT in lower extremities was ruled out. Nonadherence to warfarin treatment (evidenced by low INR) appeared to be the cause of this second episode of pulmonary embolism. Therefore, warfarin was reinitiated under close supervision to confirm adherence. Sixteen weeks later, the patient presented with thoracic pain and dyspnea. Spiral chest CT scan and Doppler ultrasound of the lower limbs indicated bilateral pulmonary embolism with no DVT in the lower limbs. Because antipsychotic agents appeared to be the causal factor of the pulmonary emboli, the patient was administered anticoagulant therapy and amisulpride 400 mg/day which resulted in improvement in his condition. Paroxetine 20 mg/day and valproate 2000 mg/day therapy was continued after being maintained throughout the 3 episodes of pulmonary embolism (Borras et al, 2008).

3.3.15.I Rhinitis

1) Incidence: oral, 13% (Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) Rhinitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, rhinitis was reported in 13% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 10% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.15.J Sinusitis

1) Incidence: IM, less than 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Sinusitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patients during premarketing trials of various design types in patients receiving long-acting intramuscular

risperidone for schizophrenia and bipolar disorder (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.3.15.K Upper respiratory infection

1) Incidence: oral, 2% to 8% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 2% and 6% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adult

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration in adult schizophrenia patients, upper respiratory tract infection was reported in 2% of patients who received risperidone 2 to 8 mg/day (n=366) and 3% of patients who received greater than 8 to 16 mg/day (n=198) compared with 1% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, upper respiratory tract infection was reported in 2% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 0% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 1% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, upper respiratory tract infection was reported in 6% of patients receiving long-acting risperidone IM injection plus current therapy (n=72) compared with 3% in placebo plus current therapy (n=67) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, upper respiratory tract infection was reported in 8% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 3% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.16 Other

3.3.16.A Angioedema

1) Angioedema has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

2) A 63-year-old woman, who had been hospitalized for 36 years with paranoid schizophrenia, developed periorbital and orbital edema on 3 occasions when risperidone was added to her continuing therapy. In all instances, the edema disappeared within a few days of discontinuation of risperidone. The first time, risperidone 2 mg daily, titrated to 6 mg/day over 2 weeks, was added to her stable regimen of fluphenazine, biperiden, and bromazepam. Periorbital edema occurred after 1 month and faded 1 week after discontinuation of risperidone, with all other medications maintained. A year later, risperidone 6 mg/day was again introduced, along with her current therapy of promethazine, biperiden, clonazepam, and nitrazepam; after

45 days moderate periorbital and orbital edema appeared. Discontinuation of promethazine did not alter the edema. Discontinuation of risperidone resulted in disappearance of the edema within 3 days. Five months later, risperidone was reintroduced at 3 mg/day. After 3 weeks, angioedema occurred, affecting the lips, face, neck, and tongue, making breathing difficult. She was given intensive antiallergenic therapy and risperidone was discontinued. The edema diminished in a few hours and resolved completely in 4 days (Plesnicar et al, 2001).

3.3.16.B Death

1) Sudden death has been reported in postmarketing use of oral risperidone (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

2) In a 5-year, retrospective, cohort study among demented elderly male veterans, antipsychotic exposure was associated with a short-term increase in mortality compared with those who did not have antipsychotic exposure. The analysis included subjects with dementia, aged 65 years or older, and had an antipsychotic prescription dispensed concurrently or after a dementia diagnosis. Four cohorts of patients exposed to haloperidol (n=2217), olanzapine (n=3384), risperidone (n=8249), and quetiapine (n=4277) were identified. Control subjects were those with a diagnosis of dementia but did not receive an antipsychotic prescription, matched according to date of dementia diagnosis and time elapsed from diagnosis to the initiation of antipsychotic therapy. Within the first 30 days of therapy, there was a significant increase in mortality risk among subjects receiving risperidone at doses above 1 mg (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.1 to 2.2, p=0.01). Subjects receiving olanzapine at doses above 2.5 mg had a HR of 1.5 (95% CI, 1.1 to 2, p=0.01), and those receiving haloperidol at doses above 1 mg had a HR of 3.2 (95% CI, 2.2 to 4.5, p less than 0.001). Greater mortality was not seen in quetiapine recipients receiving any prescribed doses (HR, 0.8; 95% CI, 0.6 to 1.1; p=0.14). None of the antipsychotics were associated with greater mortality beyond the first 30 days of therapy (Rossom et al, 2010).

3) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical vs no antipsychotic use and conventional vs atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community vs long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups.

Some important limitations to the study included unknown or unmeasured confounders that may influence the results; and cause of death could not be examined (Gill et al, 2007).

4) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional vs atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

5) The findings of one meta-analysis suggested that there may be a small increased risk of death associated with the use of atypical antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly patients (weighted mean age, 81.2 years) with dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving atypical antipsychotics compared with placebo was 1.54 (95% confidence interval (CI), 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dropout rate was observed between antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found by meta-analysis (Schneider et al, 2005).

6) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: relative risk (RR), 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3 to 1.63), in a

nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies that specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.C Drug withdrawal

1) A 38-year-old man with longstanding schizophrenia unresponsive to conventional therapy received an unsuccessful trial of risperidone which resulted in mania when the drug was withdrawn. He had been increased to risperidone 2 mg twice daily which resulted in tachycardia, tremor, and akathisia. After a taper, his hallucinations and delusions reoccurred but with manic symptoms for the first time. Risperidone 1 mg twice daily was reinitiated with resolution of his psychotic symptoms and his mania (Lane & Chang, 1998a).

3.3.16.D Drug withdrawal syndrome in newborn

1) Neonatal drug withdrawal syndrome has been reported during postmarketing surveillance of risperidone (Prod Info RISPERDAL(R) oral tablets, solution, 2011; Prod Info RISPERDAL(R) CONSTA(R) IM long-acting injection, 2011).

3.3.16.E Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.F Fatigue

1) Incidence: oral, adults, 1% to 3%; pediatrics, 18% to 42% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010); IM, 3% to 9% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) Adults

a) In 3 double-blind, controlled trials of 4 to 8 weeks duration adult schizophrenia patients, fatigue was reported in 3% of patients who received risperidone 2 to 8 mg/day (n=366) and 1% of patients who received greater than 8 to 16 mg/day (n=198), compared with 0% of patients who received placebo (n=225) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In double-blind, controlled, monotherapy trials of adult patients with bipolar mania, fatigue was reported in 2% of patients who received oral risperidone 1 to 6 mg/day (n=448) compared with 1% of patients who received placebo (n=424) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

c) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, fatigue, which

includes asthenia, was reported in 3% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 9% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) In a 3-week, double-blind, placebo-controlled trial of pediatric patients with bipolar mania, fatigue was reported in 18% of patients who received oral risperidone 0.5 to 2.5 mg/day (n=50) and 30% of patients who received 3 to 6 mg/day (n=61) compared with 3% of patients who received placebo (n=58) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

b) In two 8-week, double-blind, controlled trials of pediatric patients treated for irritability associated with autistic disorder, fatigue was reported in 42% of patients who received risperidone 0.5 to 4 mg/day (n=76) compared with 13% of patients who received placebo (n=80) (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

3.3.16.G Fever

1) Incidence: IM, 1% to 2% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010); oral: pediatrics, 6% (Prod Info RISPERDAL(R) oral tablets, solution, 2011)

2) Adult

a) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, pyrexia was reported in 2% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 1% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3) Pediatric

a) Pyrexia occurred in 6% of pediatric patients treated with oral risperidone for irritability associated with autistic disorder (Prod Info RISPERDAL(R) oral tablets, solution, 2011).

3.3.16.H Neuroleptic malignant syndrome

1) Summary

a) Neuroleptic malignant syndrome (NMS), with hyperpyrexia, muscle rigidity, autonomic instability, altered mental status, and elevated CPK levels, myoglobinuria, and acute renal failure cannot be excluded as a side effect of risperidone therapy. If neuroleptic malignant syndrome does occur, all antipsychotic medications and other drugs not essential to concurrent therapy should be discontinued, intensive symptomatic and medical monitoring should be initiated, and treatment of any concomitant serious medical problems should occur. Careful consideration of reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences have been reported (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010). Neuroleptic malignant syndrome has been reported in patients receiving long-acting risperidone injection

(Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010). During premarketing risperidone studies of various design types, neuroleptic malignant syndrome was reported in less than 1% of adult patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

2) Incidence: oral: adults, less than 1%; pediatrics, less than 5% (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010)

3) Adult

a) Neuroleptic malignant syndrome and probable acute pancreatitis was described in a 45-year-old woman with disorganized schizophrenia treated with risperidone for 2 years. A month prior to transferring to a clinic within the hospital, the patient presented with muscular stiffness, increase in non-speaking , oppositivity, food phobia, decreased voluntary bowel or urinary function, and a rise in body temperature. Laboratory findings showed hyperamylasemia, hyperlipasemia, myoglobinuria, and an increase in CPK plasma levels, suggesting rhabdomyolysis and probable acute pancreatitis. However, an abdominal CT revealed nothing significant. In the following days, the patient's myoglobinuria and CPK slowly normalized , but both amylasemia 636 units/L (normal range, 5 units/L to 53 units/L) and lipasemia 1293 units/L (normal range 114 units/L to 286 units/L) levels increased to maximum despite any clinical or radiological evidence. Neurological exam revealed extrapyramidal stiffness, and the patient was laconic, negative, uncooperative, and seemed confused toward time and space. Risperidone was discontinued and lorazepam therapy was initiated, which produced a slow resolution to her muscular stiffness. Amylasemia and lipasemia levels gradually decreased and returned to normal within 20 days. Clozapine 12.5 mg/day (titrated over more than 30 days to 300 mg/day) was introduced, resulting in significant improvement in the patient's psychopathological outcome. At her 18-month follow-up the patient maintained good clinical balance with no issues (Ghio et al, 2009).

b) A 27-year-old man developed neuromuscular malignant syndrome 21 months after being treated with risperidone 6 to 8 mg daily (Lee et al, 2000).

c) A 47-year-old man developed neuroleptic malignant syndrome after the administration of risperidone during a benzodiazepine (diazepam) withdrawal period. Symptoms abated over the next 9 days after discontinuation of risperidone and treatment with dantrolene, bromocriptine, and diazepam (Bobolakis, 2000).

d) A 73-year-old woman developed neuroleptic malignant syndrome while on monotherapy with risperidone 0.5 mg twice daily for multiinfarct dementia. Symptoms resolved after discontinuation (Gleason & Conigliaro, 1997).

e) Two cases of neuroleptic malignant syndrome (NMS) were reported in which each patient developed NMS symptoms 4 days after beginning risperidone 6 mg/day. The drug was discontinued and both patients were treated with medical support; the symptoms resolved in 7 and 10 days, respectively. One of these patients was restarted on risperidone 1 mg/day; NMS symptoms returned within 24 to 36 hours. The drug was again discontinued and the symptoms resolved within 72 hours (Tarsy, 1996; Meterissian, 1996). Five previously reported cases of risperidone-associated NMS had histories of extrapyramidal side effects related to the use of various antipsychotic drugs; 2 of the patients had experienced a previous episode of NMS (Meterissian, 1996).

4) Pediatric

a) Neuroleptic malignant syndrome (NMS) was reported in a 13-year-old boy following risperidone treatment for Joubert syndrome (JS). The patient was admitted for agitation, fever, diaphoresis, and extremity spasms, including his neck. His medication consisted of risperidone 0.5 mg/day and clonazepam 0.1 mg/kg/day for subsequent dystonia. Due to fever, rigidity, and autonomic instability, and elevated CPK levels (1200 units/L), he was diagnosed with risperidone-associated NMS. Risperidone was discontinued with institution of intravenous hydration, biperidene lactate, cold compresses, and paracetamol treatment. His agitation, sweating, dystonia, rigidity, and CPK (390 units/L) improved, and he was discharged with normalized biochemical results on the fourth day (Vurucu et al, 2009).

3.3.16.I Opioid withdrawal

1) Two patients receiving stable doses of opioids experienced withdrawal symptoms 3 days after beginning risperidone. Symptoms subsided over 2 days following discontinuation of risperidone (Wines & Weiss, 1999d).

3.3.16.J Pain, General

1) Incidence: IM, 1% to 4% (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

2) During a 12-week, double-blind, placebo-controlled trial of schizophrenic patients, generalized pain was reported in 4% of patients receiving risperidone 25 mg long-acting IM injection (n=99) and in 1% of patients receiving risperidone 50 mg long-acting IM injection (n=103) compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There are no adequate and well-controlled studies of risperidone use during pregnancy. However, third trimester antipsychotic drug exposure, including risperidone, has been associated with extrapyramidal

and/or withdrawal symptoms in neonates. Therefore, risperidone should be used during pregnancy only if the maternal benefit justifies the fetal risk. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during risperidone therapy and for at least 12 weeks after the last injection of intramuscular risperidone (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008).

5) Literature Reports

a) One case report described a 40-year-old woman who was treated with a varying dose of risperidone throughout pregnancy and postpartum. The mother received 1 mg/day of risperidone during the first 8 months of pregnancy and an increased dose of 2 mg/day for the last month of pregnancy due to psychological distress. Maternal use of risperidone during pregnancy did not result in physical or neurologic abnormalities, and the infant showed no signs or symptoms of withdrawal (Weggelaar et al, 2011).

b) There are no adequate and well-controlled studies of risperidone use in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

c) A prospective, observational study of 54 women (mean age, 30.7 years) recruited from the Emory Women's Mental Health program exposed to antipsychotic medication during pregnant showed permeability of the placental barrier. Outcomes were determined by maternal and umbilical cord blood samples taken at delivery and through data collected from maternal reports and medical records. Placental passage showed a significant difference between antipsychotic medications, olanzapine 72.1% (95% confidence interval (CI), 46.8% to 97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3% to 90.7%), risperidone 49.2% (95% CI, 13.6% to 84.8%), and quetiapine 24.1% (95% CI, 18.7% to 29.5%), showing the lowest placental passage. In the risperidone group, there were no reports of preterm labor or infants requiring neonatal intensive care admission. Of the 6 infants with maternal risperidone exposure, 1 infant weighed less than 2500 g (Newport et al, 2007).

d) A review of pooled data from the Benefit Risk Management Worldwide Safety database found no increase in risk of spontaneous abortions, structural malformations, or fetal teratogenic risk from in utero exposure to risperidone. The voluntary reports (516 prospective and 197 retrospective) of drug exposure during pregnancy identified 713 pregnancies in women with psychiatric illnesses who received risperidone during pregnancy. Of the 68 prospective pregnancies reported with known outcome, organ malformations (3.8%) and spontaneous abortions (16.9%) were documented (non-medically induced abortions excluded). Third-trimester exposure to risperidone was associated with drug withdrawal, or possible withdrawal-emergent syndrome (WES) in 13 retrospectively reported cases. The study lacked information on long-term neurodevelopmental outcomes in the neonate and developing child. In addition, many of the reports were confounded by concomitant medications, several of which are known teratogens (Coppola et al, 2007).

e) A case report described 2 successive, normal pregnancies in a 23-year-old woman receiving risperidone therapy. The woman had an unplanned yet uneventful pregnancy 6 months after starting risperidone 3 mg/day for treatment of schizophrenia. She had spontaneous labor at 39 weeks gestation and delivered a healthy baby girl weighing 3.2 kg. There were no postnatal complications. Subsequently, her risperidone

dose was decreased to 2 mg/day due to mental stability. Nine months later, she became pregnant again and was maintained on the 2 mg/day dose of risperidone without prenatal complications. Following spontaneous labor at 39 weeks, she delivered a healthy baby boy weighing 3 kg. Both of the infants were breast-fed for 6 months. The children did not show any signs of neurodevelopmental delays or behavioral problems at 36 and 18 months of age, respectively (Mendhekar & Lohia, 2008).

f) A case report described a normal pregnancy and healthy baby born to a middle-aged woman with schizophrenia who was treated with risperidone prior to and throughout her pregnancy. Successfully maintained for 7 years on risperidone, her dose was gradually decreased from 3 mg/day to 1 mg/day at 6 months' gestation, then to 0.5 mg/day a few days prior to delivery. The baby was delivered at term and remained healthy over the first 3 months of life (Rodriguez-Salgado, 2008).

g) One case report of agenesis of the corpus callosum in an infant exposed in utero to risperidone has been reported; a causal relationship to risperidone has not been established. In postmarketing surveillance, following use of risperidone in the last trimester of pregnancy, reversible extrapyramidal symptoms have been observed in the neonate (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) As both risperidone and its active 9-hydroxy metabolite are excreted into breast milk, women should be advised to not breastfeed during treatment with risperidone and for at least 12 weeks after the last injection of intramuscular risperidone (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). It is estimated that a nursing infant would receive 0.84% of the maternal dose as risperidone and an additional 3.46% from 9-hydroxyrisperidone (as risperidone equivalents). Although this amount is not likely to result in sedation or extrapyramidal side effects in a full-term or older infant, the possibility of more serious adverse effects, such as neuroleptic malignant syndrome, should not be overlooked (Hill et al, 2000).

3) Literature Reports

a) One case report described a 40-year-old woman who was treated with a varying dose of risperidone throughout pregnancy and postpartum. She was advised not to breastfeed her infant. At a maternal dose of 1 mg/day, the mother consented to provide 7 serial serum samples and 6 breast milk samples over a 24-hour period in addition to 1 infant serum sample 6 hours after dosing, so that risperidone and 9-hydroxyrisperidone levels could be measured. The milk to plasma ratio calculated from the AUC for 9-hydroxyrisperidone was 0.88. The milk to plasma ratio for risperidone could not be calculated because all milk levels were below the assay detection level (Weggelaar et al, 2011).

b) One case report described a 21-year-old woman who was treated postpartum with risperidone. She was advised not to breastfeed her infant. After a gradual increase in maternal dose to 6 mg/day, she agreed to provide serial samples (over 24 hours) of plasma and breast milk so that risperidone and 9-hydroxyrisperidone could be measured. The milk to plasma ratios calculated from the AUCs were 0.42 and 0.24 for risperidone and the active metabolite, respectively (Hill et al, 2000).

4) Drug Levels in Breastmilk

a) Parent Drug
1) Milk to Maternal Plasma Ratio
a) 0.42 (Hill et al, 2000)
b) Active Metabolites
1) 9-hydroxyrisperidone (Prod Info Risperdal(R), 1999)
a) Milk to Maternal Plasma Ratio
1) 0.24 (Hill et al, 2000)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of acecainide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of acecainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as acecainide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule,

2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.C Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concurrent use of amiodarone and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of amiodarone and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demon-

strated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as amiodarone and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D Amisulpride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of amisulpride with other drugs that potentiallly prolong the QTc interval, such as risperidone, should be approached with caution (Prod Info Solian(R), 1999q; Prod Info Risperdal(R), 2002b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as amisulpride and risperidone, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999y; Ravin & Levenson, 1997i; Gesell & Stephen, 1997d; Lo Vecchio et al, 1996d; Brown et al, 1993d).

3.5.1.E Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of

the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.F Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.G Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as aprindine, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H Arsenic Trioxide

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999ab), haloperidol (O'Brien et al, 1999r), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999aj), sertindole (Agelink et al, 2001z), quetiapine (Owens, 2001af), sultopride (Lande et al, 1992ac), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.I Asenapine

1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with antipsychotic drugs known for QT prolongation (eg, haloperidol, risperidone, or quetiapine) should be avoided . In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient (Prod Info SAPHRIS(R) sublingual tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as antipsychotic agents (haloperidol, risperidone, or quetiapine), should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info SAPHRIS(R) sublingual tablets, 2009). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.J Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999f), quetiapine (Owens, 2001j), risperidone (Duenas-Laita et al, 1999m; Prod Info Risperdal(R) risperidone, 2002), sertindole (Agelink et al, 2001h), sultopride (Lande et al, 1992g), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993b; Wilt et al, 1993a). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

3.5.1.K Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular

tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as azimilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.L Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002; Agelink et al, 2001; Owens, 2001; Prod Info Orap(R), 1999a; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997).

3.5.1.M Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of bretylium and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bretylium and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as bretylium and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.N Bupropion

1) Interaction Effect: increased plasma levels of risperidone
2) Summary: It is recommended that risperidone, an antipsychotic metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and risperidone should be approached with caution and should be initiated at the lower end of the dose range of risperidone. If bupropion is added to the treatment regimen of a patient already receiving risperidone, consider decreasing the dose of risperidone.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated risperidone metabolism

3.5.1.O Carbamazepine

1) Interaction Effect: increased risperidone clearance
2) Summary: The manufacturer reports that carbamazepine may increase risperidone clearance with chronic combined use. Patients should be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. Eleven subjects received risperidone titrated to 6 mg/day orally for 3 weeks, followed by coadministration of carbamazepine for an additional 3 weeks. Plasma concentrations of risperidone and 9-hydroxyrisperidone were decreased by 50%. The plasma concentrations of carbamazepine were unaffected (Prod Info Risperdal(R) Consta(TM), 2003a). One published case report describes a patient who had risperidone levels which were less than expected during carbamazepine therapy, along with decreased risperidone efficacy. The risperidone level dramatically increased when carbamazepine was discontinued (de Leon & Bork, 1997a). Carbamazepine is an inducer of cytochrome P450 3A (CYP3A) enzymes, while risperidone is primarily metabolized by CYP2D6. Whether carbamazepine is also inducing CYP2D6 or whether risperidone may be partly metabolized by CYP3A is uncertain (Lane & Chang, 1998; de Leon & Bork,

1998). The marked decrease in risperidone levels caused by carbamazepine may result in decreased therapeutic efficacy. When risperidone is used in combination with carbamazepine larger doses of risperidone may be required to achieve or maintain a desired antipsychotic effect (Spina et al, 2000a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of carbamazepine during the first 4-8 weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by carbamazepine

8) Literature Reports

a) Carbamazepine was reported to induce the metabolism of risperidone in a 22-year-old male with chronic schizophrenia, resulting in low risperidone levels and lack of effectiveness. The patient was started on carbamazepine 600 mg daily and risperidone 4 mg daily. The plasma concentration of 9-hydroxyrisperidone was less than half the expected concentration when the dose of risperidone was doubled to 8 mg daily. After achieving a therapeutic plasma concentration of 9-hydroxyrisperidone (19 mcg/L), the dose of carbamazepine was tapered and stopped. Plasma levels of 9-hydroxyrisperidone increased to 49 mcg/L, necessitating a decrease in the dose of risperidone (de Leon & Bork, 1997).

b) Plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was added or increased when it was discontinued. One study evaluated the pharmacokinetic interactions between risperidone and carbamazepine. Thirty-four patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder participated in the study. All patients were stabilized on risperidone alone or in combination with carbamazepine for at least four weeks. Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in patients treated with risperidone alone and patients comedicated with carbamazepine. The plasma concentrations of both 9-OH risperidone and the sum of risperidone and 9-OH risperidone (active moiety) differed significantly among groups. In five patients evaluated with and without comedication, the plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was added or increased when it was discontinued. The results demonstrate that in patients receiving risperidone alone, the concentration of the active moiety (risperidone plus its active metabolite 9-OH risperidone) was reduced by approximately 70% when carbamazepine was given concomitantly (Spina et al, 2000).

c) The concomitant use of carbamazepine and risperidone leads to a marked decrease in the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone through stimulation of an inducible cytochrome as well as the influence of the cytochrome P450 2D6 genotype. A 50-year-old male with chronic schizophrenia and deficient CYP2D6 activity was given carbamazepine with his existing risperidone therapy. Carbamazepine 800 mg/day for 5 days was added to his medication regimens as a mood stabilizer. After 4 weeks of carbamazepine treatment, the patient exhibited psychotic symptoms including hallucinations, paranoid delusions, ideas of reference, and mild excitement. Plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone, had decreased from 22 and 30 ng/mL, respectively. Carbamazepine concentration was 8.2 mcg/mL. The risperidone dose was in-

creased to 9 mg/day, carbamazepine was discontinued, and lorazepam 5 mg/day was added. Psychotic symptoms improved over the following 3 weeks and concentrations of risperidone and 9-hydroxyrisperidone increased to 40 and 57 ng/mL, respectively. A resultant decrease in the plasma concentrations of risperidone and 9-hydroxyrisperidone suggest that the CYP2D6 genotype may influence susceptibility to a clinically important interaction with risperidone and carbamazepine (Spina et al, 2001).

d) Eleven schizophrenic patients in a drug interaction study received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. The plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. At the initiation of therapy with carbamazepine, patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone may need to be adjusted. A dose increase or additional risperidone may need to be considered. If carbamazepine is discontinued, the dosage of risperidone should be re-evaluated and, if necessary, decreased. A lower dose of risperidone may be required between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003).

3.5.1.P Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic dose (Young et al, 1986). Even though no formal drug interaction studies have been done, the administration of drugs known to prolong the QTc interval, such as antipsychotics and chloral hydrate is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999i), quetiapine (Owens, 2001n), risperidone (Duenas-Laita et al, 1999s), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992k), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998d). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997a).

b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993c; Wilt et al, 1993b). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration

of haloperidol.

3.5.1.Q Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999e), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as chloroquine is not recommended.
7) Probable Mechanism: additive effect on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999j; Ravin & Levenson, 1997d).

3.5.1.R Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999v), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992n), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.S Cimetidine

1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and cimetidine resulted in a 64% increase in the bioavailability of risperidone. The AUC of the active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007). Use caution if these agents are used concomitantly. Monitor patients for increased risperidone adverse events (sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with cimetidine and risperidone has resulted in a 64% increased bioavailability of risperidone. The AUC of the active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007). Caution is advised if these agents are used concomitantly. Consider monitoring for increased risperidone adverse events, including sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth.
7) Probable Mechanism: unknown

3.5.1.T Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Owens, 2001b; Prod Info Orap(R), 1999c). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999b).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999d; Ravin & Levenson, 1997b).

3.5.1.U Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999t), haloperidol (O'Brien et al, 1999o), quetiapine (Owens, 2001v), risperidone (Duenas-Laita et al, 1999ab), sertindole (Agelink et al, 2001r), sultopride (Lande et al, 1992s), and zotepine (Sweetman, 2004). Even though no formal drug interaction studies have been done, concomitant use of clarithromycin and antipsychotic agents may cause additive effects on the QT interval and is not recommended (Prod Info Biaxin(R), 2002).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT interval, such as antipsychotics, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) A 32-year-old male with schizoaffective disorder and metabolic syndrome experienced a significant increase in plasma concentration following administration of quetiapine. The patient, hospitalized for acute psychotic symptoms was treated with 50 mg quetiapine daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg clarithromycin along with his evening dose of quetiapine 400 mg. The following morning, 750 mg sultamicillin, 500 mg clarithromycin, and the morning 300-mg quetiapine dose were given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 microgram/L (normal range, 70 to 170 microgram/L). The patient developed severe impaired consciousness and respiratory depression. Quetiapine overdose was suspected and treatment was discontinued. Plasma levels were continually measured over the course of a week until complete recovery was achieved (Schulz-Du Bois et al, 2008).

b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993e; Wilt et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(R) risperidone, 2002a).

3.5.1.V Clozapine

1) Interaction Effect: decreased risperidone clearance

2) Summary: The manufacturer reports that clozapine may decrease risperidone clearance with chronic combined use (Prod Info Risperdal(R) Consta(TM), 2003b).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects of risperidone when these drugs are given concurrently.
7) Probable Mechanism: unknown

3.5.1.W Darunavir

1) Interaction Effect: increased risperidone plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir, a CYP2D6 inhibitor, and risperidone, a CYP2D6 substrate, may result in increased plasma concentrations of risperidone, possibly due to inhibition of CYP2D6-mediated risperidone metabolism by darunavir/ritonavir. As this may result in risperidone adverse effects, a lower dose of risperidone should be considered with concomitant use is necessary (Prod Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted darunavir and risperidone may increase risperidone plasma concentrations. Consider using a lower risperidone dose when these agents are coadministered (Prod Info PREZISTA(R) film coated oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated risperidone metabolism by darunavir/ritonavir

3.5.1.X Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of risperidone
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with risperidone should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and risperidone. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to risperidone
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20

milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.Y Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included

prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.Z Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.AA Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AB Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of dofetilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dofetilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as dofetilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AC Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001a), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of dolasetron and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Anzemet(R), 1997a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of dolasetron and agents that prolong the QT interval, such as antipsychotics, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, and QTc intervals compared to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. Increases in PR and QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron to fast sodium channels. The cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in heart rate, or both (Prod Info Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).

b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993; Wilt et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(R) risperidone, 1999).

3.5.1.AD Doxepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of

a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.AE Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999w), haloperidol (O'Brien et al, 1999p), quetiapine (Owens, 2001y), risperidone (Duenas-Laita et al, 1999ad), sertindole (Agelink et al, 2001u), sultopride (Lande et al, 1992v), and zotepine (Sweetman, 2003). Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including antipsychotics is not recommended (Prod Info Inapsine(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AF Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as encainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AG Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001v; Owens, 2001z; Prod Info Haldol(R), 1998f; Lande et al, 1992y). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including enflurane (Owens, 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval, such as antispychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999af; Ravin & Levenson, 1997m).

3.5.1.AH Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999l), haloperidol (O'Brien et al, 1999j), risperidone (Duenas-Laita et al, 1999t), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992l), and zotepine (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if erythromycin and antipsychotics are used concomitantly. Monitor QT interval at baseline and periodically during treatment.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AI Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as flecainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Prod Info Tambocor(R), 1998; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of flecainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AJ Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999). Haloperidol (Prod Info Haldol(R), 1998b), risperidone (Prod Info Risperdal(R) risperidone, 2000), amisulpride (Prod Info Solian(R), 1999j), sertindole (Brown & Levin, 1998c); sultopride (Lande et al, 1992j), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if fluconazole and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AK Fluoxetine

1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as sedation, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by fluoxetine. One study demonstrated increased risperidone levels in patients treated concurrently with fluoxetine and risperidone. The risperidone dose should be reevaluated if fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010; Spina et al, 2002). Monitoring the patient for side effects indicative of increased risperidone plasma levels may be necessary (Spina et al, 2002). . If coadministration of fluoxetine and intramuscular risperidone is necessary, a lower risperidone dose 2 to 4 weeks prior to fluoxetine initiation may be considered. Patients receiving the standard risperidone injection dose of 25 mg may continue that dose when fluoxetine is initiated, unless clinical judgement necessitates the initiation of a lower risperidone dose of 12.5 mg. When risperidone injection is initiated in patients already on fluoxetine, a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects. Reevaluate the dose of risperidone when concomitant fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010; Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010). Carefully monitor patients for increased plasma risperidone levels and side effects (drowsiness, sedation, extrapyramidal symptoms, and cardiotoxicity) when fluoxetine is coadministered with risperidone (Spina et al, 2002). If coadministration of fluoxetine and intramuscular risperidone is necessary, a lower risperidone dose 2 to 4 weeks prior to fluoxetine initiation may be considered. Patients receiving the standard risperidone injection dose of 25 mg may continue that dose when fluoxetine is initiated, unless clinical judgement necessitates the initiation of a lower risperidone dose of 12.5 mg. When risperidone injection is initiated in patients already on fluoxetine, a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) 2.5- to 2.8-fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosage of risperidone should be reevaluated when fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R), RISPERDAL(R) oral tablets, solution, 2010).
b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily

by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In an open, 4-week, pharmacokinetic study including 9 patients with schizophrenia or schizoaffective disorder, depressive type, risperidone concentrations increased when fluoxetine was coadministered with risperidone. Patients were stabilized on a fixed dose of risperidone 4 to 6 mg/day for at least four weeks and received adjunctive fluoxetine therapy 20 mg/day for the management of concomitant depression. Mean plasma risperidone concentrations increased from 12 ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0.01) at week 2, and 56 ng/mL (p less than 0.01) at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant increase at 4 weeks compared with baseline. After 4 weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75% (range: 9% to 204%, p less than 0.01) compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increased significantly. Two patients experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The authors suggest that monitoring plasma risperidone levels may be warranted in patients receiving concomitant fluoxetine and risperidone treatment (Spina et al, 2002).

3.5.1.AL Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999m), haloperidol (O'Brien et al, 1999k), quetiapine (Owens, 2001o), risperidone (Duenas-Laita et al, 1999u), sertindole (Agelink et al, 2001m), sultopride (Lande et al, 1992m), and zotepine (Sweetman, 2003). Because antipsychotics may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and antipsychotics is not recommended (Prod Info Foscavir(R), 1998; Ravin & Levenson, 1997h).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AM Gemifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interval, such as antipsychotics, have not been performed, gemifloxacin should be used cautiously in patients receiving antipsychotic medications (Prod Info Factive(R), 2003).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AN Ginkgo Biloba

1) Interaction Effect: increased risk of risperidone adverse effects
2) Summary: Concomitant use of risperidone and ginkgo biloba may have precipitated priapism in one case report. Ginkgo biloba inhibits the cytochrome P450 isoforms 3A4 and 2C9, both of which are responsible for risperidone metabolism. Increased serum concentrations of risperidone may lead to an increased risk of side effects, including priapism, as in this case report (Lin et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution patients taking risperidone to discuss the use of nonprescription medicines, herbs, and dietary supplements with their doctor or pharmacist. If a patient presents with symptoms consistent with excessive risperidone, inquire about the use of nonprescription medicines, herbs, and dietary supplements. It is recommended to avoid ginkgo in patients taking risperidone (Lin et al, 2007).
7) Probable Mechanism: unknown
8) Literature Reports
a) Priapism occurred in a 26-year-old patient treated with risperidone 3 mg/day for 3 years who began ginkgo biloba 2 weeks prior to emergency department admission. He reported no other recent trauma, illness, or use of drugs or medications, and had not had any other adverse effects related to risperidone therapy. He was treating occasional tinnitus with ginkgo biloba 160 mg/day (Lin et al, 2007).

3.5.1.AO Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001w; Owens, 2001ae; Prod Info Solian(R), 1999aa; Prod Info Haldol(R), 1998i; Lande et al, 1992ab). The concurrent administration of halofantrine with antipsychotics is not recommended (Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

3.5.1.AP Haloperidol

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999q; Ravin & Levenson, 1997g; Gesell & Stephen, 1997c) and in overdose situations (Lo Vecchio et al, 1996c; Brown et al, 1993c). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and risperidone are used concomitantly. Screen patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999p; Ravin & Levenson, 1997f; Gesell & Stephen, 1997b) and in overdose situations (Lo Vecchio et al, 1996b; Brown et al, 1993b).

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).

3.5.1.AQ Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001t; Owens, 2001x; Prod Info Solian(R), 1999v; Prod Info Haldol(R), 1998e; Lande et al, 1992u). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with

other drugs which may also prolong the QTc interval, including halothane (Owens, 2001x).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval, such as antispychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ac; Ravin & Levenson, 1997k).

3.5.1.AR Hydromorphone

1) Interaction Effect: an increase in CNS or respiratory depression
2) Summary: The concomitant use of hydromorphone and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including respiratory depression, hypotension, profound sedation, and coma. When administering hydromorphone and an antipsychotic together, dose reduction of one or both of the medications should be considered (Prod Info EXALGO(R) extended release oral tablets, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of hydromorphone and other CNS depressants, such as antipsychotics, may result in respiratory depression, hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered (Prod Info EXALGO(R) extended release oral tablets, 2010).
7) Probable Mechanism: additive effects

3.5.1.AS Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AT Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as ibutilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AU Imipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.AV Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001y; Owens, 2001ac; Prod Info Solian(R), 1999z; Prod Info Haldol(R), 1998h; Lande et al, 1992aa). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (Owens, 2001ac).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ah; Ravin & Levenson, 1997n).

3.5.1.AW Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes, and its use with other drugs known to cause QT prolongation is not recommended (Prod Info DynaCirc(R), 2000). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999x), haloperidol (O'Brien et al, 1999q), quetiapine (Owens, 2001aa), risperidone (Duenas-Laita et al, 1999ag), sertindole (Agelink et al, 2001w), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AX Itraconazole

1) Interaction Effect: increased risperidone concentrations
2) Summary: In an open-label study, coadministration of itraconazole and risperidone in 19 schizophrenic patients resulted in increased serum concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone. It has been postulated that in addition to cytochrome P450 2D6 enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. Inhibition of risperidone's CYP3A-mediated metabolism by itraconazole, a potent CYP3A inhibitor, may result in increased serum risperidone concentrations and may potentially affect clinical symptoms and side effects of risperidone (Jung et al, 2005). If these two agents are coadministered, consider monitoring patients for clinical symptoms of risperidone efficacy and potentially, increased risperidone side effects (hypotension, sedation, extrapyramidal side effects, arrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of itraconazole and risperidone can result in increased serum concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone. If these two agents are coadministered, consider monitoring patients for clinical symptoms of risperidone efficacy and potentially, increased risperidone side effects (hypotension, sedation, extrapyramidal side effects, arrhythmias).
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated risperidone metabolism
8) Literature Reports
a) Concurrent administration of itraconazole with risperidone resulted in increased serum risperidone concentrations. Schizophrenic patients (n=19, mean age 41.4 years) who were being treated with 2 to 8 milligrams (mg) of risperidone per day (dosed at 8 am and 8 pm) for at least 2 months were administered itraconazole 200 mg per day (dosed at 8 pm) for 1 week and then withdrawn. Results of this open-label study indicated that the dose-normalized, steady-state plasma concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone, were significantly increased by 82% and 70%, respectively (p

less than 0.01). Upon itraconazole discontinuation, both concentrations returned to the levels prior to itraconazole administration. Scores on the Brief Psychiatric Rating scale, signifying improvement in clinical symptoms, decreased by 6% (p=0.017). However, there was no increase in adverse effects as evaluated by the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating scale. It has been postulated that in addition to cytochrome P450 2D6 enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. The proposed mechanism for this interaction is inhibition of risperidone's CYP3A-mediated metabolism by itraconazole, a potent CYP3A inhibitor (Jung et al, 2005).

3.5.1.AY Lamotrigine

1) Interaction Effect: increased risperidone plasma concentrations and risk of adverse effects
2) Summary: Increased risperidone plasma concentrations, with signs of toxicity, developed in a patient administered lamotrigine in addition to a stable dose-regimen of risperidone and clozapine (Bienentreu & Kronmuller, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware of the increased risk of risperidone adverse effects in patients receiving lamotrigine together with risperidone. When concomitant lamotrigine is initiated, discontinued, or the dose of lamotrigine is changed, re-evaluate the dose of risperidone.
7) Probable Mechanism: unknown
8) Literature Reports
a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient receiving lamotrigine in addition to a stable dose-regimen of risperidone and clozapine. The patient, a 26-year-old woman diagnosed with schizophrenia, had sustained only a partial response to her established regimen of clozapine 550 milligrams (mg) daily and risperidone 8 mg daily. Baseline plasma concentrations of risperidone and clozapine were 55-70 nanograms/milliliter (ng/mL) and 800-1100 ng/mL, respectively. Lamotrigine was initiated, with the dose incrementally titrated up to 200 mg daily. Clozapine and risperidone plasma concentrations increased to 1300 ng/mL and 263 ng/mL, respectively; no symptoms of intoxication were observed. Lamotrigine was further titrated up to a dose of 225 mg daily, after which risperidone plasma concentration increased to 412 ng/mL, accompanied by symptoms of dizziness and tiredness. The risperidone dose was reduced to 2 mg daily and completely withdrawn shortly thereafter (Bienentreu & Kronmuller, 2005).

3.5.1.AZ Levodopa

1) Interaction Effect: loss of levodopa efficacy
2) Summary: Because risperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is expected to antagonize the effects of levodopa (Prod Info Stalevo(TM), 2003; Prod Info Risperdal(R) Consta(TM), 2003g).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of risperidone in patients with parkinsonism should be avoided. If concurrent use cannot be avoided, monitor the patient for loss of levodopa therapeutic efficacy.
7) Probable Mechanism: pharmacologic antagonism

3.5.1.BA Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as risperidone that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with risperidone as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: additive cardiac effects

3.5.1.BB Levorphanol

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients
2) Summary: A patient stabilized on levorphanol 14 mg daily for neck pain experienced opioid cravings and cramps following three days of risperidone therapy. Discontinuing risperidone resolved her symptoms of withdrawal. Possible mechanisms for this effect include risperidone accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorption or secretion of the opioid, altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risperidone is concurrently prescribed.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 31-year-old female with a lengthy history of drug dependency, including opioids, was being treated with fluoxetine 40 mg daily for depression and levorphanol 14 mg daily for chronic severe neck pain. Because of recurring nightmares and flashbacks, risperidone 0.5 mg daily was initiated and increased to 1.5 mg daily within two days. While her dissociative symptoms improved, she complained of cramps, gooseflesh, and opioid cravings. Risperidone was decreased to 1 mg daily but her dissociative symptoms worsened. Her risperidone was again increased to 2 mg daily, but she experienced an increase in her

withdrawal symptoms which persisted for days. Risperidone therapy was eventually discontinued (Wines & Weiss, 1999).

3.5.1.BC Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999i), haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001l), risperidone (Duenas-Laita et al, 1999r), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Linezolid

1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: In a review of post-marketing data, 1 case of serotonin toxicity was reported with the concurrent use of linezolid and risperidone, which was coadministered with other serotonergic agents (Lawrence et al, 2006) . Risperidone, in combination with other serotonergic agents, has been associated with the serotonin syndrome (Springuel & McMorran, 2003). There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents (Wigen & Goetz, 2002; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). Although coadministration of linezolid and serotonergic agents did not result in serotonin syndrome in phase 1, 2, or 3 clinical trials, linezolid is a reversible, non-selective MAOI and can potentially interact with serotonergic agents, precipitating the serotonin syndrome. If concurrent use of linezolid and a serotonergic agent is clinically warranted, monitor patients closely for signs and symptoms of serotonin syndrome. Consider discontinuing either one or both agents if these symptoms occur, keeping in mind that discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Serotonin toxicity has been reported in 1 individual with the concurrent use of linezolid and risperidone, which was coadministered with other serotonergic agents (Lawrence et al, 2006).

If concurrent use of linezolid and risperidone, particularly with additional serotonergic agents, is clinically necessary, monitor patients closely for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005). Keep in mind that discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) In a review of post-marketing data, one case of serotonin toxicity was reported in the concurrent use of linezolid and risperidone, which was coadministered with other serotonergic agents. A review was conducted of post-marketing adverse events reported to the US Food and Drug Administration's Adverse Event Reporting System (AERS) database between November 1997 and September 2003 regarding serotonin toxicity with linezolid use. A serotonin toxicity case was defined as having: (a) linezolid as the primary suspect drug, (b) concomitant administration of 1 or more secondary suspect drug with CNS serotonergic activity, and (c) serotonin toxicity, as defined by the modified Hunter Serotonin Toxicity Criteria or by the reporter of the adverse event. A total of 29 cases were identified (age range 17 to 83 years), where linezolid was used concomitantly with 1 drug (n=20), with 2 drugs (n=6), and with 3 or more drugs (n=3). While SSRIs were the most common class of drugs received concomitantly with linezolid (n=26), other drug classes included tricyclic antidepressants (n=6), and atypical antidepressants (n=4). Additionally, drugs used concurrently included carbidopa-levodopa (n=2), dextromethorphan (n=1), lithium (n=1), metoclopramide (n=1), risperidone (n=1), and tramadol (n=1). Symptoms of serotonin toxicity included tremor, fever, seizure, clonus, sweating, agitation, akathesia, rigors, twitching, and muscle rigidity. Intervention including hospitalization was required in 13 patients, and 3 deaths were reported with concurrent SSRI use. For the 1 case identified with the concurrent use linezolid and risperidone, additional coadministered serotonergic drugs included bupropion, sertraline and trazodone (Lawrence et al, 2006).

3.5.1.BE Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage

2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment

decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related to

combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BF Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as lorcainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lorcainide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BG Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, caution is advised if mefloquine is used with other drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999). Mef-

loquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al, 1996). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998d), quetiapine (Owens, 2001w), risperidone (Prod Info Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999u), sertindole (Agelink et al, 2001s); sultopride (Lande et al, 1992t), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if mefloquine and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BH Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999g), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BI Methadone

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients
2) Summary: A patient stabilized on methadone 50 mg daily experienced aches, nasal congestion, and irritability within three days of starting risperidone therapy. Discontinuing risperidone resolved his symptoms of withdrawal. Possible mechanisms for this effect include risperidone accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorption or secretion of the opioid, altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if

risperidone is concurrently prescribed.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 26-year-old male with a long history of chemical dependency was receiving a methadone maintenance dose of 50 mg daily when he was hospitalized for an exacerbation of paranoia and agitation. Risperidone 0.5 mg twice daily was initiated, and within three days the patient complained of feeling "dope sick", with symptoms of aches, nasal congestion, and irritability. These symptoms worsened as risperidone was increased to 2 mg daily and dissipated when risperidone was discontinued. His paranoia was successfully treated with chlorpromazine with no further signs of opioid withdrawal (Wines & Weiss, 1999b).

3.5.1.BJ Metoclopramide

1) Interaction Effect: an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome
2) Summary: Concomitant use of metoclopramide with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as tardive dyskinesia or neuroleptic malignant syndrome, and is contraindicated (Prod Info REGLAN(R) oral tablets, 2009). If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions. Injection of diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of metoclopramide with antipsychotic agents is contraindicated (Prod Info REGLAN(R) oral tablets, 2009). If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome. Injection of diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).
7) Probable Mechanism: unknown

3.5.1.BK Midodrine

1) Interaction Effect: an increased risk of acute dystonia
2) Summary: A case report described development of acute dystonia in a 33-year-old female following concomitant administration of midodrine and risperidone (Takahashi, 2000). Patients receiving this combination may need to be monitored for increased risperidone adverse events, including signs and symptoms of acute dystonia.
3) Severity: moderate

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if midodrine and risperidone are prescribed concurrently. Monitor for signs and symptoms of acute dystonia or other risperidone adverse events.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 33-year-old female developed acute dystonia after addition of midodrine to treat orthostatic hypotension secondary to risperidone therapy. The patient had a 12-year history of catatonic schizophrenia, which was adequately controlled with a stable dose of risperidone 6 mg/day. Two days after addition of midodrine 4 mg/day to treat complaints of orthostatic hypotension, the patient exhibited manifestations of acute dystonia, including tongue protrusion, retrocollis, and oculogyric crisis. Intramuscular injection of anticholinergics immediately resolved all symptoms. Midodrine was discontinued and risperidone 6 mg/day monotherapy was continued. After two weeks without dystonic symptoms, midodrine 4 mg/day was added again to therapy to treat continuing complaints of orthostatic hypotension. A similar acute dystonic reaction recurred one day later and was successfully treated with one intramuscular injection of an anticholinergic. Again, midodrine was discontinued and the patient remained on risperidone 6 mg/day without dystonic symptoms. Two weeks later, the risperidone dose was decreased to 3 mg/day due to persistent orthostatic hypotension, and the patient was free of catatonic and dystonic symptoms at a 3-month follow-up. Increased risperidone-associated central noradrenergic activity due to the peripheral alpha-1 receptor activity of midodrine was a postulated mechanism for this interaction (Takahashi, 2000).

3.5.1.BL Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant use of milnacipran and an antipsychotic may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of serotonin syndrome develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated (Prod Info SAVELLA(R) oral tablets, 2010).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in hypertension and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of serotonin syndrome develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment (Prod Info SAVELLA(R) oral tablets, 2010).
7) Probable Mechanism: additive serotonergic effect

3.5.1.BM Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.BN Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including octreotide, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999o), haloperidol (O'Brien et al, 1999m), risperidone (Duenas-Laita et al, 1999w), sertindole (Agelink et al, 2001o), quetiapine (Owens, 2001q), sultopride (Lande et al, 1992o), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BO Paroxetine

1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of paroxetine (potent CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by paroxetine. Two studies demonstrated increased risperidone levels resulting in a greater frequency of extrapyramidal symptoms in patients treated concurrently with paroxetine and risperidone (Saito et al, 2005; Spina et al, 2001a). One of these studies showed an association between paroxetine dose increases and greater risperidone plasma concentrations (Spina et al, 2001a). In a case report, serotonin syndrome was observed in a patient who had already been receiving risperidone and was initiated on paroxetine (Hamilton & Malone, 2000). Monitoring the patient for increased risperidone plasma levels side effects may be necessary. The risperidone dose should be reevaluated if paroxetine is initiated or discontinued. Concomitant use of a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2001a). If coadministration of paroxetine and intramuscular risperidone is necessary, a lower risperidone dose 2 to 4 weeks prior to paroxetine initiation may be considered. Patients receiving the standard risperidone injection dose of 25 mg may continue that dose when paroxetine is initiated, unless clinical judgement necessitates the initiation of a lower risperidone dose of 12.5 mg. When risperidone injection is initiated in patients already on paroxetine, a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of paroxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Saito et al, 2005; Spina et al, 2001a; Hamilton & Malone, 2000). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when paroxetine is coadministered with risperidone. Reevaluate the dose of risperidone when concomitant paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008). Coadministering a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Saito et al, 2005). If coadministration of paroxetine and intramuscular risperidone is necessary, a lower risperidone dose 2 to 4 weeks prior to paroxetine initiation may be considered. Patients receiving the standard risperidone injection dose of 25 mg may continue that dose when paroxetine is initiated, unless clinical judgement necessitates the initiation of a lower risperidone dose of 12.5 mg. When risperidone injection is initiated in patients already on paroxetine, a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Paroxetine (a potent CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concen-

tration of risperidone (a CYP2D6 substrate) by 3- to 9- fold. Paroxetine also lowered the concentration of 9-hydroxyrisperidone by about 10%. In postmarketing surveillance of risperidone, torsade de pointes has been reported with combined overdose of risperidone and paroxetine. The dosage of risperidone should be reevaluated when paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

b) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizophrenia and negative symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receiving risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared with baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine dose; increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by 4.2-fold (95% CI, 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 to 26.8) with 40 mg. Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal symptoms scores were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine with risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

c) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the duration of the study. A significant elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant paroxetine treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministration. Total plasma levels of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The occurrence of extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharmacodynamic effect of paroxetine (Spina et al, 2001a).

d) Serotonin syndrome occurred in a patient using concomitant paroxetine and risperidone, an antipsychotic agent with potent serotonin antagonism and dopamine blocking activity . A 53-year-old male with a 7-month history of psychotic depression was being treated with risperidone 3 mg/day and paroxetine 20 mg/day for 10 weeks before presentation. Nine weeks into therapy, the patient showed de-

creased motivation and bilateral jerking movements of the mouth and legs. The patient discontinued his medication during the week before his admission. Upon presentation he was apathetic, confused, disorganized, and talked to himself. The doses of paroxetine and risperidone were doubled to 40 mg/day and 6 mg/day, respectively. Within 2 hours of taking his medication, he experienced bilateral jerking movements, ataxia, tremor, and shivering. He presented to the emergency room with involuntary jerking movements and lethargy. His mental status exam was notable for depression with psychomotor agitation, difficulty being aroused, and auditory hallucinations. Differential diagnosis included recurrent psychotic depression, neuroleptic malignant syndrome (NMS), drug overdose, and serotonin syndrome. Nortriptyline 100 mg at bedtime, haloperidol 10 mg twice daily and diphenhydramine 50 mg at night were initiated at discharge. The patient returned to baseline 9 months after discharge and is without symptoms of depression or psychosis (Hamilton & Malone, 2000).

3.5.1.BP Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including pentamidine, is not recommended (Agelink et al, 2001p; Owens, 2001r; Prod Info Haldol(R), 2001a; Prod Info Solian(R), 1999p; Duenas-Laita et al, 1999x; Duenas-Laita et al, 1999x; Prod Info Nipolept(R), 1996a; Metzger & Friedman, 1993d; Lande et al, 1992p).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BQ Phenobarbital

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyrisperidone
2) Summary: Concomitant use of phenobarbital may reduce plasma concentrations of risperidone. Patients should be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of phenobarbital therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003d).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenobarbital during the first 4-8 weeks of therapy; higher risperidone doses may be needed. Patients may be placed

on a lower dose of risperidone between 2 to 4 weeks before the discontinuation of phenobarbital therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients currently maintained on the lowest available dose (25 mg) risperidone, it is recommended to continue with that dose unless an interruption of treatment is necessary.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by phenobarbital

3.5.1.BR Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.BS Phenytoin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyrisperidone
2) Summary: Concomitant use of phenytoin may reduce plasma concentrations of risperidone. Upon initiation of therapy with phenytoin, patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone may need to be adjusted. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of phenytoin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenytoin higher risperidone doses may be needed. Monitor patients during the first 4-8 weeks of coadministration with phenytoin and risperidone; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinuation of phenytoin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients currently maintained on the lowest available dose (25 mg) risperidone, it is recommended to continue with that dose unless an interruption of treatment is necessary.
7) Probable Mechanism: induction of risperidone metabolism through cytochrome P450 enzymes by phenytoin

3.5.1.BT Pimozide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration of pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R) pimozide, 1999). Risperidone has been reported to prolong the QTc interval (Prod Info Risperdal(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as pimozide and risperidone, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999e).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking

risperidone therapeutically (Duenas-Laita et al, 1999n; Ravin & Levenson, 1997e; Gesell & Stephen, 1997a; Lo Vecchio et al, 1996a; Brown et al, 1993a).

3.5.1.BU Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BV Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BW Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998c), quetiapine (Owens, 2001s), risperidone (Prod Info Risperdal(R) risperidone, 2000a), amisulpride (Prod Info Solian(R), 1999r), sertindole (Brown & Levin, 1998e); sultopride (Lande et al, 1992q), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if probucol and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BX Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999h; O'Brien et al, 1999g; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001k; Duenas-Laita et al, 1999o; Agelink et al, 2001i; Lande et al, 1992h; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BY Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999v), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992n), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BZ Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such as propafenone, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001m; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of propafenone and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CA Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall

& Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.CB Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Risperidone can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes, and its use with other agents that may prolong the QT interval, such as quetiapine, is not recommended (Prod Info Risperdal(R), 2002c; Owens, 2001u). Coadministration of risperidone 3 mg twice daily with quetiapine 300 mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Because of the potential additive effects on the QT interval, the concurrent administration of quetiapine and risperidone is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999aa; Ravin & Levenson, 1997j; Gesell & Stephen, 1997e; Lo Vecchio et al, 1996e; Brown et al, 1993e).

3.5.1.CC Ranitidine

1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and ranitidine resulted in a 26% increase in the bioavailability of risperidone. The AUC of the active metabolite, 9-hydroxyrisperidone, and risperidone combined was increased by 20% (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009). Use caution if these agents are used concomitantly. Monitor patients for increased risperidone adverse events (sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with ranitidine and risperidone has resulted in increased risperidone bioavailability (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009). Caution is advised if these agents are used concomitantly. Consider monitoring for increased risperidone adverse events, including sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth.
7) Probable Mechanism: unknown

3.5.1.CD Rifampin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyrisperidone
2) Summary: Concomitant use of rifampin may reduce plasma concentrations of risperidone (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). Patients should be closely monitored if concomitant use is required. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of rifampin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of rifampin during the first 4 to 8 weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone 2 to 4 weeks before the discontinuation of rifampin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients currently maintained on the lowest available dose of risperidone long-acting injection (25 mg), it is recommended to continue with that dose unless an interruption of treatment is necessary (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2008).
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by rifampin

3.5.1.CE Ritonavir

1) Interaction Effect: increased risperidone serum concentrations and potential toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of risperidone, resulting in risperidone toxicity (Jover et al, 2002a; Kelly et al, 2002a)A risperdal dose decrease may be required when coadministered with ritonavir (Prod Info NORVIR(R), 2005).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable

6) Clinical Management: Monitor patients for signs and symptoms of neuroleptic toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias). Reduce doses of risperidone as required.
7) Probable Mechanism: decreased risperidone metabolism
8) Literature Reports
a) Increases in risperidone serum concentration occurred in a patient taking concomitant ritonavir. A 48-year-old man previously diagnosed with acquired immunodeficiency syndrome (AIDS) was admitted to a psychiatric hospital for manic symptoms. His current medications included zidovudine 250 mg twice daily, didanosine 300 mg once daily, indinavir 400 mg twice daily, and ritonavir 200 mg twice daily. He was given risperidone 3 mg twice daily upon admission. After receiving two doses of risperidone he became ataxic, progressively drowsy and disoriented. He then became lethargic and comatose. Physical exam revealed a Glasgow coma score of 7/15 points with miotic pupils. Laboratory tests were normal. A toxic or metabolic etiology was suspected to be the cause of the coma and all medication was discontinued. Twenty-four hours later, his neurologic status returned to baseline and progressively the manic symptoms reappeared. The author suggests that an interaction between risperidone, indinavir and ritonavir may have caused a reversible toxic coma (Jover et al, 2002).
b) Extrapyramidal symptoms (EPS) occurred in a patient initiated on ritonavir and indinavir while taking risperidone for a tic disorder. A 35-year-old white male with AIDS received risperidone 2 mg twice daily for treatment of Tourette's-like tic disorder. The patient had an 8 month history of hand tremor, twitching and jerky involuntary movements of the face, shoulders, arms, and legs. His current medications were dapsone, pyrimethamine, azithromycin, and hydroxyzine. Risperidone was initiated at 1 mg twice daily for 2 weeks and then increased to 2 mg twice daily. Indinavir 800 mg twice daily and ritonavir 200 mg twice daily was initiated at the same time the risperidone dosage was increased. One week later he experienced significantly impaired swallowing, speaking, and breathing, and worsening of his existing tremors. Ritonavir and indinavir were discontinued. One month later the patient agreed to try indinavir/ritonavir therapy again. At the same time he increased the risperidone dose to 3 mg twice daily. Symptoms worsened over the next 3 days. All laboratory parameters were unremarkable and vital signs were stable. Risperidone was discontinued and clonazepam initiated. Three days later the patients symptoms improved. Caution is warranted when risperidone is prescribed with ritonavir/indinavir (Kelly et al, 2002).

3.5.1.CF Ropinirole

1) Interaction Effect: diminished effectiveness of ropinirole
2) Summary: Theoretically, risperidone may oppose the dopaminergic effect of dopamine agonists, such as ropinirole (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info REQUIP(R) oral tablets, 2006). If concurrent use of ropinirole and a dopamine antagonist is clinically warranted, monitor patients closely for loss of ropinirole efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concurrent use of risperidone and ropinirole as this may result in reduced effectiveness of ropinirole due to the antagonistic dopaminergic effect of risperidone (Prod Info REQUIP(R) oral tablets, 2006). If concurrent use of ropinirole and a dopamine antagonist is

clinically warranted, monitor patients closely for signs and symptoms of diminished effectiveness of ropinirole, such as worsening of extrapyramidal movements, rigidity, tremor, or gait disturbances.
7) Probable Mechanism: pharmacological antagonism

3.5.1.CG Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sematilide and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as sematilide and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CH Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sertindole with other drugs that potentiallly prolong the QTc interval, such as risperidone, should be approached with caution (Brown & Levin, 1998a; Prod Info Risperdal(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risperidone and sertindole, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999c; Ravin & Levenson, 1997a; Gesell & Stephen, 1997; Lo Vecchio et al, 1996; Brown et al, 1993).
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16

mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001b).

c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).

3.5.1.CI Simvastatin

1) Interaction Effect: increased simvastatin serum concentrations with an increased risk of myopathy or rhabdomyolysis

2) Summary: Concomitant use of risperidone and simvastatin may increase the bioavailability of simvastatin. Risperidone and simvastation are both metabolized by cytochrome P450-3A4 (CYP3A4). Although risperidone is predominantly metabolized by CYP2D6, individuals having a slow metabolizer phenotype due to possession of a CYP2D6 polymorphic genotype may convert to CYP3A4 as the primary isoform for risperidone metabolism. As a result, risperidone may competitively inhibit simvastatin metabolism, thereby increasing the risk of myopathy and rhabdomyolysis. In a case report, a patient developed rhabdomyolysis complicated by acute compartment syndrome after receiving simvastatin concomitantly with risperidone (Webber et al, 2004).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of risperidone with simvastatin is not recommended. If concurrent therapy is required, monitor patient for signs and symptoms of myopathy or rhabdomyolysis (muscle pain, tenderness, or weakness). Monitor creatine kinase (CK) levels and discontinue use if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

7) Probable Mechanism: competitive inhibition of cytochrome P450-3A4-mediated simvastatin metabolism

8) Literature Reports

a) Rhabdomyolysis occurred in a 22-year-old man after simvastatin 10 milligrams (mg) daily was added to a stable treatment regimen comprising clonazepam 2 mg and risperidone 4 mg daily. Approximately 5 days after beginning simvastatin treatment, the patient presented with right ankle and heel pain. Over the next 24 hours, the pain advanced proximally and increased in severity, with the extremity showing signs of warmth, erythema, rash, and pronounced tenseness of the distal muscle compartments. Serum creatine kinase (CK), aspartate and alanine aminotransferase concentrations were 12, 408 units/liter (L), 296 International Units (IU)/L, and 97 IU/L, respectively. CK concentrations peaked at 25, 498 units/L. Simvastatin was withdrawn and the patient required emergent decompression fasciotomies due to acute compartment syndrome of the right lower extremity. Risperidone and clonazepam were continued without incident (Webber et al, 2004).

3.5.1.CJ Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sotalol and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sotalol and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as sotalol and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CK Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the co-administration of antipsychotics and other drugs known to prolong the QTc interval, including spiramycin, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999c), quetiapine (Owens, 2001g), risperidone (Duenas-Laita et al, 1999i), sertindole (Agelink et al, 2001e), sultopride (Lande et al, 1992d), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CL Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999n), quetiapine (Owens, 2001t), risperidone (Duenas-Laita et al, 1999z), sertindole (Agelink et al, 2001q), sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CM Sultopride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sultopride with other drugs that potentiallly prolong the QTc interval, such as risperidone, should be approached with caution (Lande et al, 1992x; Montaz et al, 1992a; Harry, 1997b; Prod Info Risperdal(R), 2002d).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risperidone and sultopride, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ae; Ravin & Levenson, 1997l; Gesell & Stephen, 1997f; Lo Vecchio et al, 1996f; Brown et al, 1993f).
b) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992w; Montaz et al, 1992; Harry, 1997a).

3.5.1.CN Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of tedisamil and risperidone is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tedisamil and risperidone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including risperidone (Duenas-Laita et al, 1999). Concomitant use of Class III antiarrhythmic agents such as tedisamil and risperidone may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CO Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Agelink et al, 2001c; Owens, 2001c; Prod Info Haldol(R), 1998a; Lande et al, 1992a). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of telithromycin and an antipsychotic is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999e; Ravin & Levenson, 1997c).

3.5.1.CP Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002b; Owens, 2001ad; Prod Info Orap(R), 1999g). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999f).

3.5.1.CQ Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyramidal disorders
2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, risperidone) should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008) In addition to QT prolongation, tetrabenazine may also cause adverse reactions such as neuroleptic malignant syndrome and extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic drugs (eg, risperidone) (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with risperidone or other neuroleptic drugs may increase tetrabenazine adverse reactions, such as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neuroleptic malignant syndrome and extrapyramidal disorders may be enhanced when given with a dopamine agonist such as risperidone (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.CR Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001d), pal-

iperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992b), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CS Tramadol

1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.CT Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999v), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992n), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.

7) Probable Mechanism: additive QT prolongation

3.5.1.CU Trimethoprim

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999n), quetiapine (Owens, 2001t), risperidone (Duenas-Laita et al, 1999z), sertindole (Agelink et al, 2001q), sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Trimipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999f), haloperidol (O'Brien et al, 1999e), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001g), quetiapine (Owens, 2001i), sultopride (Lande et al, 1992f), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.CW Valproic Acid

1) Interaction Effect: increased plasma valproic acid concentrations

2) Summary: The addition of risperidone to valproic acid produces a significant increase in the peak plasma concentration (Cmax) of valproic acid (Prod Info Risperdal(R) Consta(TM), 2003f) as well as marked increases in ammonia levels (Carlson et al, 2007). The high protein capacity of risperidone could lead to a competition for protein-binding with the high protein-binding capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (van Wattum, 2001). However, Valproic acid can be added safely to a treatment regimen consisting of risperidone (Spina et al, 2000c). Monitoring of ammonia levels may be warranted in patients who exhibited new or increased manic behavior when taking valproic acid and risperidone, especially in patients vulnerable to valproic acid-induced hyperammonemia, including the young, on valproate polytherapy, severely handicapped, or suffering from malnutrition, protein load, and decreased free serum carnitine (Carlson et al, 2007). In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperidone concentrations does not appear to be warranted.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for increased ammonia levels and plasma valproic acid concentrations with the addition of risperidone to drug therapy or changes in risperidone dose.

7) Probable Mechanism: unknown

8) Literature Reports

a) In 2 case reports of 11 year-old boys, there were marked exacerbations in manic behavior and a 2 to 4-fold increase in serum ammonia levels when risperidone and valproic acid were concomitantly administered. The first patient, who had a history of Asperger's disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, and manic symptoms, was admitted for increasing aggressive behavior. Chlorpromazine was added as needed and risperidone was added to replace his aripiprazole. Following the initiation of valproic acid 250 mg twice daily, the patient experienced a qualitative exacerbation of manic behavior. The risperidone dosage was eventually adjusted to 2 mg/day and valproic acid to 625 mg/day. The patient's valproate level ranged from 87 to 90 and ammonia level was 213. When valproic acid was discontinued, and the ammonia level fell to 55, his manic behavior stopped. The second patient, with a history of absence epilepsy and ADHD, was on stable doses of valproic acid. Because of his psychotic symptoms, risperidone was started and increased to 1.125 mg/day over 5 weeks. The patients exhibited markedly pronounced manic behavior and had a serum ammonia level of 113, despite a normal valproic acid level of 71. Upon discontinuation of risperidone and valproic acid, the ammonia level normalized to 55 and the manic behavior resolved. One month later when the patient was rechallenged with risperidone (in the absence of valproic acid), there was no return of either mania or hyperammonemia (Carlson et al, 2007).

b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic acid. Steady state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in patients treated with risperidone alone or in patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or bipolar

disorder, were stabilized with risperidone alone or in combination with valproic acid. The results demonstrate that valproic acid given at doses up to 1200-1500 mg/day had clinically insignificant effects on plasma concentrations of risperidone and its active metabolite. Valproic acid can be added safely to a treatment regimen consisting of risperidone. In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperidone concentrations does not appear to be warranted (Spina et al, 2000b).

c) The combination of valproic acid and risperidone led to significantly increased levels of valproic acid in one case . A 10-year-old male suffered from mood swings and increasingly aggressive behavior. Valproic acid treatment was initiated and titrated up to 1750 mg/day. Valproate serum levels were in the therapeutic range. After 10 days of treatment, risperidone 2 mg/day was added, which was increased to 3 mg/day on day 4. On day 5 after risperidone was started, the patients symptoms improved but valproic acid levels were above the therapeutic range at 191 mg/L. Valproic acid was decreased to 1000 mg/day and the level normalized to 108 mg/L within 3 days and subsequently stabilized. The author concludes that the high-protein-binding capacity of risperidone could lead to a competition for protein-binding with the high protein-binding capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (Van Wattum, 2001).

d) In 21 patients, repeated oral doses of risperidone 4 mg daily did not affect the pre-dose or average plasma concentrations or exposure (area under the concentration-time curve) of valproate 1000 mg daily compared to placebo. There was, however, a 20% increase in valproate maximum plasma concentration (Cmax) after risperidone coadministration (Prod Info Risperdal(R) Consta(TM), 2003e).

3.5.1.CX Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Antipsychotics and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Owens, 2001f; Prod Info Solian(R), 1999c; Duenas-Laita et al, 1999h; Brown & Levin, 1998b; Harry, 1997; Prod Info Nipolept(R), 1996; Metzger & Friedman, 1993a; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as antipsychotics and vasopressin, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CY Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic

dose (Prod Info Zomig(R), 2001). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998g), quetiapine (Owens, 2001ab), risperidone (Prod Info Risperdal(R) risperidone, 2000c), amisulpride (Prod Info Solian(R), 1999y), sertindole (Agelink et al, 2001x); sultopride (Lande et al, 1992z), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QT interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and antipsychotics is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.CZ Zotepine

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures (Hori et al, 1992). In addition, coadministration of drugs that potentiallly prolong the QTc interval, such as zotepine and risperidone, should be approached with caution (Sweetman, 2004; Prod Info Risperdal(R), 2002e).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking large doses of zotepine; (2) have a history of seizure disorders; (3) are of young age; or (4) have a past history of brain injury. The concurrent administration of agents that prolong the QT interval, such as zotepine and risperdone, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2004).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ai; Ravin & Levenson, 1997o; Gesell & Stephen, 1997g; Lo Vecchio et al, 1996g; Brown et al, 1993g).

4.0 Clinical Applications

Monitoring Parameters
Patient Instructions
Place In Therapy
Mechanism of Action / Pharmacology
Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Bipolar Disorder

1) A prolonged time to relapse to any mood episode (depression, mania, hypomania, or mixed) is indicative of a therapeutic response. Improvement of Young Mania Rating Scale (YMRS) has been used to evaluate the response to therapy.

b) Schizophrenia

1) A reduction in the severity or resolution of signs and symptoms of schizophrenia is indicative of efficacy. The Positive and Negative Syndrome Scale (PANSS), which measures positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility or excitement, and anxiety or depression, has been used to evaluate response to therapy.

c) Irritability Associated with Autistic Disorder

1) Reduction in irritability (eg, aggression, deliberate self-injury, temper tantrums, and quickly changing moods) in autistic patients is indicative of efficacy. The Aberrant Behavior Checklist Irritability subscale (ABC-I) has been used to evaluate response to therapy.

B) Toxic

1) Laboratory Parameters

a) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below (None Listed, 2004):

1) Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control (None Listed, 2004).

2) Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat testing should be done more frequently as clinically indicated(None Listed, 2004).

b) Perform CBC (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010) with differential, frequently during the first few months of therapy in patients with a history of low WBC or drug-induced leukopenia or neutropenia.

2) Physical Findings

a) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below (None Listed, 2004):

1) Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease, prior to treatment and review annually with patient (None Listed, 2004).

2) Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter (None Listed, 2004).

3) Measure waist circumference at baseline and annually thereafter (None Listed, 2004).

4) Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension (None Listed, 2004).

b) Monitor orthostatic vital signs in patients predisposed to hypotension, including dehydration and hypovolemia and those receiving concomitant antihypertensive medications (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

c) Examine patient for tardive dyskinesia before initiation and then annually. Patients at higher risk for tardive dyskinesia (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment (Marder et al, 2004).

d) Closely supervise patients for suicidality during risperidone therapy due to the increased risk of suicide attempts in patients with schizophrenia or bipolar disorder (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

4.2 Patient Instructions

A) Risperidone (By mouth)
Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to risperidone.

How to Use This Medicine:
Tablet, Liquid, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. You may mix your dose with water, low-fat milk, coffee, or orange juice. Do not mix with cola or tea.

If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not open the blister pack that contains the tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the tablet out. Do not push the tablet through the foil. Place the tablet in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Do not freeze the oral liquid.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

There are many other medicines that you should not use while you are taking risperidone. Taking risperidone with certain other medicines may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other medicines you are using.

Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine, furosemide (Lasix®), levodopa, fluoxetine (Prozac®), paroxetine (Paxil®), phenobarbital, ranitidine, or valproate (Depakene®, Depakote®). Tell your doctor if you are using clozapine (Clozaril®), quinidine, phenytoin (Dilantin®), or rifampin (Rifadin®). Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, and Zestril®.

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, plan to become pregnant, or if you are breast feeding.

Tell your doctor if you have a history of liver disease, kidney disease, stroke, or breast cancer. Make sure your doctor knows if you have heart problems, Parkinson's disease, seizures, or trouble swallowing.

Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using medicine for diabetes, your doctor may need to change your dose.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset

stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoid sunlamps and tanning beds.
Risperdal® M-Tab® contains aspartame (phenylalanine). If you have phenylketonuria (PKU), talk to your doctor before using this medicine.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Confusion, weakness, and muscle twitching.
Constant muscle movement that you cannot control (often in your lips, tongue, arms, or legs).
Dry mouth, increased thirst, muscle cramps, nausea or vomiting.
Fast, slow, irregular (uneven), or pounding heartbeat.
Fever, sweating, muscle stiffness.
In males: Painful, prolonged erection of your penis.
Lightheadedness, fainting, or seizures.
Severe diarrhea, vomiting, or stomach pain.
Skin rash.
Sudden or severe headache, problems with vision, speech, or walking.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Anxiety, trouble sleeping, increased dreaming.
Constipation, diarrhea, nausea, or upset stomach.
Darkening of your skin.
Drooling, or stuffy nose.
In women: Unusually heavy bleeding during your menstrual period.
Severe tiredness.
Trouble having sex.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Risperidone (Injection)

Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to risperidone.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine. This medicine is usually given every 2 weeks.

If a Dose is Missed:
This medicine needs to be given on a fixed schedule. If you miss a dose or forget to use your medicine, call your doctor or pharmacist for instructions.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
There are many other medicines that you should not use while you are taking risperidone. Taking risperidone with certain other medicines may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other medicines you are using.
Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine (Tagamet®), furosemide (Lasix®), levodopa (Larodopa®), fluoxetine (Prozac®), paroxetine (Paxil®), phenobarbital (Luminal®), ranitidine (Zantac®), or valproate (Depakene®, Depakote®). Tell your doctor if you are using clozapine (Clozaril®), quinidine, phenytoin (Dilantin®), or rifampin (Rifadin®). Make sure your doctor knows if you are also using medicine to lower blood pressure (such as atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or if you plan to become pregnant while you are using this medicine, or during the 12 weeks after you stop using it. Do not breastfeed while you are using this medicine and for at least 12 weeks after you receive the last shot.
Make sure your doctor knows if you have kidney disease, liver disease, diabetes, breast cancer, bone problems, brain tumor, bowel blockage, Reye's syndrome, Parkinson's disease, trouble with swallowing, or a history of seizures or neuroleptic malignant syndrome (NMS). Tell your doctor if you have any kind of blood vessel or heart problems, including low blood pressure, heart failure, a low amount of blood, heart rhythm problems, or a history of a heart attack or stroke.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using a medicine for diabetes, your doctor may need to change your

dose.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has forgetfulness or confusion related to aging (such as Alzheimer's disease or dementia).

Stop taking this medicine and check with your doctor right away if you have any of the following symptoms while using this medicine: convulsions (seizures), difficulty with breathing, a fast heartbeat, a high fever, high or low blood pressure, increased sweating, loss of bladder control, severe muscle stiffness, unusually pale skin, or tiredness. These could be symptoms of a serious condition called neuroleptic malignant syndrome (NMS).

Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

This medicine may make you dizzy, lightheaded, or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. Change positions slowly when getting up from a lying or sitting position.

This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

This medicine may cause some people to be agitated, irritable, or display other abnormal behaviors. It may also cause some people to have suicidal thoughts and tendencies or to become more depressed. If you or your caregiver notice any of these adverse effects, tell your doctor right away.

This medicine may increase your weight. Your doctor may need to check your weight regularly during treatment with this medicine.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Change in how much or how often you urinate.

Chills, cough, sore throat, and body aches.
Dry mouth, increased hunger or thirst, or muscle cramps.
Fast, slow, pounding, or uneven heartbeat.
Feeling depressed, agitated, or nervous.
Fever, sweating, confusion, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Mood or behavioral changes, or thoughts of hurting yourself or others.
Numbness or weakness in your arm or leg, or on one side of your body.
Painful, prolonged erection of your penis (in males).
Problems with balance or walking.
Seizures or tremors.
Swelling in your hands, ankles, or feet.
Trouble with speaking or swallowing.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision or change in vision.
Constipation, diarrhea, nausea, vomiting, or stomach pain or upset.
Dry mouth or drooling.
Headache.
Pain, swelling, or a lump under your skin where the shot is given.
Rash or itching skin.
Stuffy or runny nose.
Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including risperidone) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was

similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current risperidone users in 24,589 person-years was 2.91 (95% CI, 2.26 to 3.76, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Schizophrenia

1) Risperidone is a benzisoxazole derivative. It is approved for the treatment of schizophrenia. It blocks both serotonin 5-HT(2) and dopamine D(2) receptors. It is effective in chronic schizophrenia for positive and negative symptoms with a response rate of 50% to 75% (Foster & Goa, 1998; Rossi et al, 1997; Smith et al, 1996). At doses of 8 milligrams or less risperidone is associated with a lower risk of extrapyramidal symptoms than conventional antipsychotics (Foster & Goa, 1998). Comparative efficacy with haloperidol and other conventional neuroleptics in schizophrenia has shown that risperidone has a significantly higher clinical response rate and allows for significantly less prescribing of anticholinergic medications (Davies et al, 1998; Bech et al, 1998; Luebbe, 1996). Risperidone has also shown some efficacy in psychotic disorders associated with dementia, HIV, levodopa, and other medical conditions. Refractory obsessive-compulsive disorder and refractory depressions have also been relieved by risperidone in select cases.

C) Bipolar Mania

1) Long-acting injection risperidone alone or in combination with lithium or valproate is approved for the maintenance treatment of bipolar I disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Oral risperidone alone or in combination with lithium or valproate is approved for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

D) Irritability associated with Autistic Disorder

1) Risperidone is approved for the treatment of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) Mechanism Of Action

1) The mechanism by which risperidone exerts its antipsychotic effect is unknown. Risperidone is a selective monoaminergic antagonist with a strong affinity for serotonin Type 2 (5-HT2) receptors and a slightly

weaker affinity for dopamine Type 2 (D2) receptors. The antipsychotic activity of risperidone may be mediated through antagonism at a combination of these receptor sites, particularly through blockade of cortical serotonin receptors and limbic dopamine systems. Risperidone also has moderate affinity for the alpha 1-adrenergic, alpha 2-adrenergic, and H1-histaminergic receptors. The affinity of risperidone for the serotonin 5-HT1A, 5-HT1C, and 5-HT1D receptors is low to moderate, while its affinity for dopamine D1 and the haloperidol-sensitive sigma site is weak. Risperidone has negligible affinity for cholinergic-muscarinic, beta-adrenergic, and serotonin 5-HT1B and 5-HT3 receptors. Cardiovascular effects reflect the vascular alpha-adrenergic antagonistic activity of risperidone, as evidenced by such dose-related effects as hypotension and reflex tachycardia. The potential for proarrhythmic effects exists, due to risperidone's ability to prolong the QT interval in some patients. Risperidone changes sleep architecture by promoting deep, slow-wave sleep, thereby improving sleep patterns. This effect is most likely due to risperidone's blockade of serotonin receptors. Substantial and sustained elevations in serum prolactin levels are induced by risperidone. Tolerance to hyperprolactinemia does not occur, but the condition is reversible upon withdrawal of risperidone. Increases in prolactin concentrations are likely due to risperidone's blockade of dopamine receptors. Animal studies have shown that risperidone inhibits tryptamine- and serotonin-induced cyanosis and 5-hydroxytryptophan-induced head twitching; it also blocks central and peripheral manifestations of dopaminergic stimulation, including apomorphine-induced emesis and apomorphine- or amphetamine-induced stereotypy or hypermotility. The antiemetic effect in animals may also occur in humans, potentially masking signs and symptoms of other medical problems(Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009; Awouters & Schotte, 1994; Cohen, 1994a; Grant & Fitton, 1994) (Leysen & Janssen, 1994; Chouinard & Arnott, 1993; Ereshefsky & Lacombe, 1993; Hoyberg et al, 1993; Nyberg et al, 1993).

2) (Anon, 1991; Janssen et al, 1988; Megens et al, 1988).

4.5 Therapeutic Uses

4.5.A Autistic disorder - Irritability

FDA Labeled Indication

1) Overview

FDA Approval: Adult, no; Pediatric, yes (5 years and older, oral only)

Efficacy: Pediatric, Effective

Recommendation: Pediatric, Class IIa

Strength of Evidence: Pediatric, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone is indicated for the treatment of irritability associated with autistic disorder in children and adolescents age 5 to 16 years (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010).

Risperidone was more effective than placebo in improving the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in short-term (8 weeks), placebo-controlled studies (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006; McCracken et al, 2002); additionally, continued

risperidone therapy maintained efficacy up to 6 months and led to lower relapse rates compared to placebo (McCracken et al, 2002).

Treatment with oral risperidone was well tolerated and more effective in improving autism symptoms compared to placebo in children in a randomized, double-blind study (n=40) (Nagaraj et al, 2006).

3) Pediatric:

a) Risperidone was more effective than placebo for the short-term treatment of severe behavioral problems in children with autism in a randomized, double-blind, placebo-controlled study (n=101). Patients (ages 5 to 17 years) with autism accompanied by serious behavioral problems (tantrums, aggression, or self-injurious behavior) received placebo (n=49) or risperidone 0.5 to 3.5 milligrams (mg)/day (n=52; mean dose during last week, 1.8 mg/day) for 8 weeks. Primary efficacy measures were the score at eight weeks on the Irritability subscale of the Aberrant Behavior Checklist and the rating on the Clinical Global Impressions-Improvement (CGI-I) scale. A positive response was defined as a 25% or greater reduction in the Irritability score and a rating of much improved or very much improved on the CGI-I scale. The mean Irritability score for the risperidone group decreased by 56.9% following 8 weeks of treatment as compared with a 14.1% reduction in the placebo group (p less than 0.001). The rate of positive response was significantly higher in risperidone-treated patients as compared with placebo (69% vs 12%, respectively; p less than 0.001). Risperidone was generally well tolerated and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism (McCracken et al, 2002). Among secondary endpoints, risperidone significantly decreased the overall score on the Ritvo-Freeman scale, which was modified from an observational measure to a parent rating scale and included subscales for assessing sensory motor behaviors, social relatedness, affectual reactions, sensory responses, and language (subscales I, II, III, IV, and IV, respectively). Specifically, significant treatment and time interactions were noted for subscales I (effect size, 0.45; p=0.002), III (effect size, 1.1; p less than 0.001), and IV (effect size, 0.77; p=0.004). There was no statistically significant effect on the subscales scores for social relatedness (subscale II) or language (subscale V). The mean +/- standard deviation Children's Yale-Brown Obsessive Compulsive scale score (modified to only assess the compulsion subscale; total score range, 0 to 20) decreased from a baseline score of 15.51 +/- 2.73 to 11.65 +/- 4.02 in the risperidone group compared to 15.18 +/- 3.88 at baseline to 14.21 +/- 4.81 in the placebo group. For the total Maladaptive Behavior Domain (measured using the Vineland Adaptive Behavior Scales, there was a significant treatment and time interaction during the 8-week trial (effect size, 1.03; p less than 0.001), with decreases from mean baseline scores of 33.26 and 33.51 to 7.93 and 8.87 for the risperidone and placebo groups, respectively (McDougle et al, 2005).

1) Long-Term Extension

a) In a 24-week extension of the aforementioned study that included a 4-month, open-label extension followed by an 8-week, blinded placebo-controlled discontinuation phase, continued risperidone therapy maintained efficacy for autism and led to lower relapse rates compared to the placebo group. Following 8 weeks of double-blind therapy in 101 patients, a total of 63 responders (mean age, 8.6 years) from both the risperidone and placebo groups received open-label risperidone for another 16 weeks; risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 milligrams (mg)/day in children weighing 15 to 45 kilograms (kg) and up to 4.5 mg/day for children weighing over 45 kg. Response was defined as at least 25% reduction on the irritability subscale of the Aberrant Behavior Checklist (ABC) and a rating of much improved or very much improved on the Clinical

Global Impressions-Improvement (CGI-I) scale). Responders to the 4-month open-label extension therapy were randomized in a double-blind fashion either to continue risperidone at the same dose or to gradual placebo substitution (risperidone dose reduced by 25%/week) over 8 weeks and assessed for relapse (defined as a 25% increase in the ABC-Irritability (ABC-I) subscale score and a CGI-I scale rating of much worse or very much worse for at least 2 consecutive weeks). At the end of the 4-month, open-label extension, an intention-to-treat analysis revealed a minor but clinically insignificant increase in ABC-I score, going from a baseline (end of 8 weeks of initial therapy) mean +/- standard deviation (SD) score of 9.5 +/- 6.8 to 10.8 +/- 7.1. There was a significant time effect on the ABC-I scale at the end of the 4-month extension phase (p=0.02), Additionally, among 51 patients who completed the extension phase, 82.5% had a much improved or very much improved rating on the CGI-I scale. A preplanned interim analysis during the discontinuation phase revealed higher relapse rates in the placebo group compared to the risperidone group (62.5% (n=10) vs 12.5% (n=2); p=0.01), with a median time to relapse was 34 days and 57 days, respectively. This prompted early termination of the study (Research Units on Pediatric Psychopharmacology Autism Network, 2005). For secondary outcomes, improvements seen in the subscales I, III, and IV scores of the modified Ritvo-Freeman scale, the Children's Yale-Brown Obsessive Compulsive scale scores, and the total scores on the Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scales, after 8 weeks of initial therapy were maintained over the 4-month extension phase (McDougle et al, 2005).

b) Risperidone was more effective than placebo in improving the irritability symptoms of autism in an 8-week, placebo-controlled trial of children and adolescents with autistic disorder. Children (n=55; 5 to 12 years of age) with autistic disorder received placebo or risperidone 0.02 to 0.06 mg/kg/day once or twice daily, starting at 0.01 mg/kg/day (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day). Efficacy was evaluated using the Aberrant Behavior Checklist (ABC). The change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I) was the primary outcome measure. This subscale evaluated the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Risperidone significantly improved scores on the ABC-I subscale compared with placebo (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).

c) Treatment with oral risperidone was more effective in improving autism symptoms compared to placebo in children in a randomized, double-blind study (n=40). Consecutive children up to 12 years of age diagnosed with autism according to the DSM-IV criteria, with varying symptoms that included hyperactivity, aggression, stereotypies, and language difficulties were randomized to receive an oral suspension of either risperidone (initiated at 0.5 milligrams (mg)/day, increased to 1 mg/day 2 weeks later; n=19; mean age, 57.95 months) or placebo (n=20; mean age, 63 months) for 6 months. The primary efficacy measures were changes from baseline in the median Childhood Autism Rating Scale (CARS) and the mean Children's Global Assessment Scale (CGAS) scores at end of treatment. Among the study population, irritability was the most common autism symptom (92%). At endpoint, 63% (n=12/19) of children in the risperidone group showed an improvement of at least 20% from baseline CARS scores compared to none in the placebo group. Median CARS scores decreased from 39.5 (range, 32.5 to 46) at baseline to 32 (range, 24.5-40.5) at the end of treatment for the risperidone group compared to a decrease from 38.5 (range, 31.5-43 at baseline to 37.5 (30-42.5) at end of treatment for the placebo group (p less than 0.001). On the CGAS, significantly more patients in the risperidone group had improvements (ie, increase in CGAS score of at least 20% from baseline) compared to the placebo group (17 vs 2). Mean CGAS scores

increased from 29.79 and 32.65 at baseline in the risperidone and placebo groups, respectively, to 40.94 and 35.2, respectively, at the end of treatment (p =0.035). Among secondary endpoints, based on an internally-validated, 12-item parent questionnaire, risperidone improved functioning in domains of social responsiveness (n=7/19; p=0.014), nonverbal communication (n=8/19; p=0.008), decreased hyperactivity symptoms (n=7/19; p=0.002), and aggression and irritability (n=5/19; p=0.016). However, there were no significant improvements in the domains of restricted interests, emotional interaction, or verbal communication or speech. Overall, risperidone was well tolerated. Mild and transient dyskinesias occurred in 3 children. There was a nonstatistically significantly higher mean weight increase from baseline among risperidone-treated children (2.81 kilograms (kg; 17%) vs 1.71 kg (9.3%)) (Nagaraj et al, 2006).

4.5.B Behavioral syndrome - Dementia

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Cerebrovascular adverse events (stroke, transient ischemic attack) including fatalities have occurred in elderly individuals (mean age 85 years old) who received risperidone for treatment of dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009)

Risperidone improved behavioral and psychological symptoms in elderly patients with dementia, according to pooled data from 3 randomized, placebo-controlled, double-blind, parallel group, phase 3 trials (De Deyn et al, 2005).

Risperidone treatment of nursing home residents with aggressive behaviors and Alzheimer's dementia, vascular dementia, or mixed dementia had a significant improvement on the Cohen-Mansfield Agitation Inventory (CMAI) total aggression score compared with placebo in a 12-week, randomized, double-blind, parallel-group trial (n=301) (Brodaty et al, 2003).

Risperidone treatment was not better than placebo for improvements on the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) in aggressive patients with Alzheimer's disease, vascular dementia, or a mixed dementia in a 13-week, double-blind, placebo-controlled study (n=344) (DeDeyn et al, 1999).

3) Adult:

a) In a pooled analysis, risperidone therapy was superior compared to placebo in managing behavioral and psychological symptoms of dementia in elderly nursing home residents. The pooled data was from three randomized, placebo-controlled, double-blind, multicenter, parallel group, Phase III trials. Following a one-week single-blind washout period during which all other psychotropic medications were discontinued, patients were then randomized to receive risperidone (n=722) or placebo (n=428) for 12 weeks at a dose range of 0.25 to 1 milligram (mg) twice daily. Overall, the demographics and baseline characteristics were similar with the majority of patients being women, Caucasian, and suffering from dementia for an average of 5 or more years. Agitation and aggressive behaviors were assessed using the Cohen-Mansfield agitation

inventory (CMAI) scores. Risperidone produced significantly greater improvements compared to placebo in CMAI total scores from week 4 through week 12 (mean change from baseline to end point: -11.8 versus -6.4, respectively; p less than 0.001). Decreases in the total aggression and total non-aggression scores were also both statistically significant in favor of risperidone (p less than 0.001). The severity of behavioral and psychological symptoms associated with dementia were assessed using the rating scale for behavioral pathology in Alzheimer's disease (BEHAVE-AD). At all evaluation points, scores on the BEHAVE-AD total scale were significantly more improved with risperidone versus placebo (mean change from baseline to end point: -6.1 versus -3.6, respectively; p less than 0.001). The psychotic symptoms subscale of the BEHAVE-AD found that risperidone produced significantly greater improvements than placebo in patients with psychosis at baseline (mean change from baseline: -3.5 +/- 0.21 (n=434) versus -2.5 +/- 0.32 (n=252), respectively; p=0.003). The paranoid and delusional symptoms were significantly improved in the risperidone group compared to placebo (-1.7 versus -1; p less than 0.002). However, there was no significant difference between the groups regarding improvement in hallucinations (risperidone -0.4, placebo -0.3; p=0.191). The clinical global impression (CGI) scores were also significantly improved in the risperidone group versus the placebo group. A subgroup analysis on dementia type (Alzheimer's disease, vascular dementia and mixed dementia) found that the CMAI and BEHAVE-AD total scores were significantly improved in the risperidone group in both Alzheimer's disease and vascular dementia, but not in the mixed dementia subjects. Treatment-emergent adverse events were comparable between risperidone (84.3%) and placebo (83.9%). However, the number of patients who discontinued therapy due to treatment-emergent adverse events was higher in the risperidone treated group (16.7%) versus placebo (11.2%). Common adverse events leading to discontinuation in the risperidone group were somnolence, agitation, extrapyramidal disorders, aggressive reaction, pneumonia, injury, cerebrovascular disorder, and fall (De Deyn et al, 2005).

b) Risperidone was more effective than placebo in reducing aggression among nursing home residents with Alzheimer's dementia, vascular dementia, or mixed dementia and comorbid aggressive behaviors according to a 12-week, randomized, double-blind, parallel-group trial (n=301 evaluable). Elderly patients (mean 82.7 +/- 0.64 years old, placebo; 83.2 +/- 0.51 years old, risperidone) residing in a nursing home for at least 1 month, with a score of at least 4 on the Functional Assessment Staging Test, 23 or lower on the Mini-Mental State Examination, and a minimum aggression score on the Cohen-Mansfield Agitation Inventory (CMAI) were included in the study. Exclusion criteria included the use of a depot neuroleptic agent within 2 treatment cycles, or a history of treatment failure to risperidone therapy of at least 4 weeks' duration. Following a maximum 7-day washout period where existing neuroleptic agents were tapered and discontinued, patients were randomized to receive 12 weeks of either placebo (n=170), or risperidone 0.25 milligrams (mg) twice a day titrated to clinical effect in increments of 0.25 mg twice daily, every other day, up to 2 mg/day (n=167). The mean risperidone dose was 0.95 +/- 0.03 mg. Concomitant short-acting benzodiazepines, anticholinergics, low-dose tricyclic antidepressants, and narcotic analgesics were permitted. A difference of at least 4.15 points on the CMAI total aggression score (range, 14 to 98) between treatment groups was defined as clinically relevant. Discontinuation of therapy occurred in 32.9% (n=56) in the risperidone group and 26.9% (n=45) in placebo, mostly attributed to insufficient response (9.6% risperidone, 19.4% placebo) and adverse events (13.2% risperidone, 8.2% placebo). In an evaluation of the primary endpoint at week 12, the mean CMAI total aggression score decreased by 7.5 from baseline of 34.1 +/- 1.05 in the risperidone group (n=149) and by 3.1 from a baseline of 33 +/- 0.99 in placebo (n=152), resulting in a between-group difference of -4.4 (95% confidence interval (CI), -6.75 to -2.07; p less than

0.001). The mean change in the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) from baseline to week 12 (secondary endpoint evaluation) decreased by 6.8 in the risperidone group compared with 2.3 in placebo (between-group difference, -4.5; 95% CI, -6.45 to -2.46; p less than 0.001). The incidence of cerebrovascular adverse events was 9% in the risperidone group compared with 1.8% in placebo, among whom 5 patients treated with risperidone experienced a stroke and 1 patient treated with risperidone had a transient ischemic attack. Extrapyramidal-like adverse events occurred in 23.4% in the risperidone group and 15.9% in placebo group (Brodaty et al, 2003).

c) Although risperidone and haloperidol produced similar reductions in severity of behavioral symptoms among demented elderly patients, risperidone was not better than placebo in a 13-week, double-blind, placebo-controlled study (n=344) Agitated patients (55 years and older) with Alzheimer's disease, vascular dementia, or a mixed dementia were randomized to receive risperidone (n=115), haloperidol (n=115), or placebo (n=114). Outcomes were assessed using the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Both medications were initiated at 0.25 milligrams (mg) daily and increased by 0.25 mg every 4 days up to 1 mg twice daily. If indicated, the patient's dose could be further increased to a maximum of 2 mg twice daily. At the end of 12 weeks mean doses were risperidone 1.1 mg/day and haloperidol 1.2 mg/day. At baseline, the mean BEHAVE-AD score was 16.3, 16.5 and 16.6 for the risperidone, haloperidol and placebo groups, respectively. At week 12, the mean BEHAVE-AD total scores improved by 8.6, 7.5, and 6.2 in the risperidone, haloperidol and placebo group, respectively (p=0.05 for risperidone vs placebo), but the difference between risperidone and placebo did not sustain at end point (p=0.19). Percent of patients having at least a 30% improvement in BEHAVE-AD total score at 12 weeks was similar at 72% for risperidone, 69% for haloperidol, and 61% for placebo (p not significant). However, risperidone showed significantly greater improvements in the mean Cohen-Mansfield agitation inventory (CMAI) total aggression at week 12 over placebo (-8.3 vs -4.9; p=0.02) and BEHAVE-AD aggressiveness subscale score (-2.9 vs -1.5; p=0.002). Somnolence occurred in 18% of haloperidol patients, 12% of risperidone, and 4% of placebo patients (DeDeyn et al, 1999).

4.5.C Behavioral syndrome - Mental retardation

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone moderately improved aberrant behavior in adults with mental retardation compared with placebo in a 4-week, randomized, double-blind, placebo-controlled study (n=77) with continued improvement over 48 weeks in an open-label, extension study (n=58) (Gagiano et al, 2005)

A post hoc analysis (n=163) of two, 6-week, multicenter, double-blind, placebo-controlled studies demonstrated reduced aggression scores after treatment with risperidone in boys with below normal intelligence and either conduct disorder (CD) or oppositional defiant disorder (ODD) with or without attention-deficient hyperactive disorder (LeBlanc et al, 2005).

In a 1-year, open-label, multicenter, multinational, trial (n=504), risperidone moderately improved be-

havior and cognitive function in children with disruptive behavior disorders and borderline intellectual functioning or mild to moderate mental retardation (Croonenberghs et al, 2005).

Risperidone was safe and effective as a short- and long-term therapy (48 weeks) for the reduction of severe behavior problems in children with mild or moderate intellectual disabilities; below average intelligence; and a diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified, in a 6-week, randomized, double- blind, placebo controlled study (Findling et al, 2004; Aman et al, 2002).

3) Adult:

a) Risperidone moderately improved aberrant behavior in adults with mental retardation compared with placebo in a 4-week, randomized, double-blind, placebo-controlled study (n=77). Adults (18 to 65 years of age) with conduct disorder, oppositional defiant disorder, antisocial personality disorder, disruptive behavior disorder, or intermittent explosive disorder and borderline intellectual functioning or mild to moderate mental retardation (Wechsler or Stanford-Binet Intellectual Quotient of 35 to 84) were randomized to risperidone (n=39) or placebo (n=38). The initial oral dose was 0.5 milligrams/day (mg/day) on days 1 and 2, 1 mg/day on day 3, and based on response the dose could be increased by 1 mg/day at weekly intervals up to a maximum of 4 mg/day. The dose was reduced if movement disorders developed and anticholinergic drugs could be started if the movement disorders persisted. Other medications allowed were antidepressants, lithium, carbamazepine, and valproic acid. The primary efficacy endpoint was the change from baseline in the total Aberrant Behavior Checklist (ABC) score at 4 weeks. The mean risperidone dose was 1.45 +/- 0.08 mg/day (range, 1 to 4 mg/day). Concomitant anti-psychotropic drugs were used in 53.8% and 65.8% of the risperidone- and placebo-treated patients, respectively. Baseline total ABC scores were 51.7 +/- 4.2 and 47.6 +/- 3.5 for the risperidone- and placebo-treated patients, respectively. The risperidone-treated group experienced a 52.8% improvement compared with a 31.3% improvement (-27.3 +/- 3.3 vs -14.9 +/- 4; p=0.036) in total ABC score at 4 weeks. Improvement was noted at 2 weeks (p less than or equal to 0.07). The mean change from baseline ABC irritability subscale improved significantly compared with placebo (p less than or equal to 0.05) but the other subscales of lethargy/social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech did not improve compared with placebo. Behavior Problems Inventory (BPI) subscale of stereotypical behavior improved at week 4 for risperidone compared with placebo (-0.8 +/- 0.4 vs -0.2 +/- 0.3, respectively, p less than 0.05); however, other subscales of BPI (total score and self-injurious behavior, aggressive/destructive behavior) did not improve compared with placebo. Responder rates (response defined as not ill, very mildly ill, or mildly ill) based on the Clinical Global Impressions-Severity scale were 45.8% and 25%, respectively. The most disturbing behaviors identified by caregivers were aggressive behavior, which improved on the visual analog scale for the risperidone compared with the placebo group (-31.3 vs - 12.8, respectively, p less than 0.001). Risperidone- and placebo-treated patients experienced somnolence (23.1% vs 15.8%, respectively), injury (17.9% vs 13.2%, respectively), and headache (12.8% vs 7.9%, respectively). Mild movement disorders were reported in 3 risperidone-treated and 4 placebo-treated patients. Extrapyramidal Symptom Rating Scale (ESRS) did not increase for either the risperidone or placebo group. The median weight gain was 1 kilogram for the risperidone group and 0 kg for the placebo group (Gagiano et al, 2005).

1) Behavior continued to improve over 48 weeks in an open-label, extension, study (n=58). From the above double-blind study, 31 on placebo and 27 on risperidone chose to continue for another 48 weeks on risperidone. The mean modal dose of risperidone was 1.81 +/- 0.13 milligrams/day. For all patients the total Aberrant Behavior Checklist (ABC) score decreased by 9 points from baseline to endpoint

(p=0.012). ABC subscales significantly decreased (p less than or equal to 0.001 compared with double-blind baseline) by 10.7 +/- 1.5 for irritability, 3.3 +/- 0.9 for lethargy/social withdrawal, 0.8 +/- 0.2 for stereotypic behavior, 10.4 +/- 1.5 for hyperactivity, and 2.4 +/- 0.4 for inappropriate speech. Responder rates (response defined as not ill, very mildly ill, or mildly ill) based on the Clinical Global Impressions-Severity scale increased to 64.7% after 1 month and to 76.7% at endpoint. The most disturbing behaviors identified by caregivers were aggressive behavior, which went from a mean baseline visual analog score of 47.1 +/- 3.6 to 28.2 +/- 3.5 at endpoint. Cognition did not change over the 48 weeks as measured by the Cognition measured by Continuous Performance Task (CPT) and a modified version of the California Verbal Learning Test-Adult Version. Extrapyramidal Symptom Rating Scale (ESRS) or any of the ESRS subclusters did not increase between baseline and endpoint. One patient developed tardive dyskinesia, which resolved without sequelae after risperidone was stopped. The overall mean weight increase from baseline to 48 weeks was 3.8 +/- 0.6 kilograms (p less than or equal to 0.001) (Gagiano et al, 2005).

b) In one double-blind, placebo-controlled crossover study, 37 patients with behavioral abnormalities such as hostility, aggressiveness, irritability, agitation, hyperactivity, automutilation, and autism despite current therapy improved on risperidone versus placebo. The medications were given orally for 3 weeks, followed by 3 weeks of crossover treatment. Doses of risperidone were initially 2 milligrams twice a day; at weekly evaluations, daily dosage was increased by 4 mg/day up to a maximum total dose of 12 mg/day if no improvement in Clinical Global Impression (CGI) scores occurred. Risperidone caused significant improvement in CGI parameters throughout the duration of the study; placebo was not effective. No extrapyramidal symptoms occurred. No significant cardiovascular, biochemical, or urinalysis changes were reported (Vanden Borre et al, 1993a).

4) Pediatric:

a) A post hoc analysis (n=163) of two, 6-week, multicenter, double-blind, placebo-controlled studies demonstrated reduced aggression scores after treatment with risperidone in boys with below normal intelligence and either conduct disorder (CD) or oppositional defiant disorder (ODD) with or without attention-deficient hyperactive disorder. The 2 placebo-controlled studies (n=288) enrolled male and female patients, aged 5 to 12 years, with a diagnosis of CD, ODD, or disruptive behavior disorder not otherwise specified, who had a parent/caregiver-assessed rating of 24 or more on the conduct problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF); mild mental retardation, moderate mental retardation, or borderline intellectual functioning (intelligence quotient (IQ) of 36 to 84); and a Vineland Adaptive Behavior Scale score of 84 or less. The patients were randomized to either placebo or risperidone with starting oral doses of 0.01 milligrams/kilogram/day (mg/kg/day) and titrating to response up to a maximum of 0.06 mg/kg/day for a total of 6 weeks. The post hoc analysis was limited to boys with a diagnosis of CD or ODD who were subsequently assessed by an aggression score (AS) using 6 core aggression items from the N-CBRF. The mean age of the boys was 8.5 years and IQ of low-normal intellectual functioning to moderate mental retardation. The daily dose of risperidone over the 6 weeks was 0.04 mg/kg/day (range, 0.01 to 0.06 mg/kg/day) and the mean duration was 38.7 days (range, 1 to 49 days). At 6 weeks, the AS was 4.5 +/- 4.3 compared with 10.1 +/- 4.1 at baseline in boys treated with risperidone. At 6 weeks, the AS for placebo-treated boys was 8.3 +/- 5 compared with 10.6 +/- 3.9 at baseline. Boys with higher AS at baseline had greater responses than those with lower AS at baseline (LeBlanc et al, 2005).

b) In a 1-year, open-label, multicenter, multinational, trial (n=504), risperidone moderately improved behavior and cognitive function in children with disruptive behavior disorders and borderline intellectual

functioning or mild to moderate mental retardation. Children (5 to 14 years old) with conduct disorder, oppositional defiant disorder, or disruptive behavior disorder; a score of 24 or more on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF); mild mental retardation, moderate mental retardation, or borderline intellectual functioning (intelligence quotient (IQ) of 36 to 84); and a Vineland Adaptive Behavior Scale score of 84 or less received risperidone once daily in the morning or afternoon. The initial oral dose was 0.01 milligrams/kilograms/day (mg/kg/day) on days 1 and 2, 0.02 mg/kg/day on days 3, with subsequent dose increases based on response at weekly intervals not to exceed 0.02 mg/kg/day increases and a maximum dose of 0.06 mg/kg/day. Doses could be reduced if extrapyramidal symptoms (EPS) developed and an anticholinergic could be used for persistent EPS. The only psychotropic medications allowed were psychostimulants for attention-deficit/hyperactivity disorder as long as a constant dose in the previous 30 days was used and for premedication with benzodiazepines for medical procedures. Sleep and anxiety medications were not allowed. At baseline, the median age was 10 years (4 to 14 years) with a primary diagnosis of conduct disorder (45%) or oppositional defiant disorder (36%) with or without attention deficit hyperactivity disorder. The mean IQ was 64.2 +/- 13.4 and the mean Vineland Adaptive Behavior Scale score was 52.7 +/- 13.4. The median dose was 1.5 mg/day (range, 0.1 to 4.3 mg/day) with a mean duration of 307.3 +/- 5 days. Fourteen percent of the patients were on concomitant methylphenidate. At 1 year, the mean changes in the modification of the children's version of the California Verbal Learning Test (MCVLT-CV) were 0.7 +/- 0.1 for total long delay-free recall, 2.9 +/- 0.4 for the total short delay-free recall, and 0.7 +/- 0.2 for total correct (each p less than 0.001 compared with baseline). For the Continuous Performance Task easy and hard tests the mean change scores were 1.6 +/- 0.3 and 1.6 +/- 0.4, respectively for total hits; -2.9 +/- 0.6 and -4.2 +/- 0.7, respectively, for total false alarms; and -1.5 +/- 0.3 and -1.4 +/- 0.4, respectively, for total misses (each p less than 0.001 compared with baseline). The mean N-CBRF score decreased from 32.9 +/- 7.5 to 17 +/- 11 at 1 year, representing a mean change of -15.8 +/- 0.5 (p less than 0.001). Improvements were demonstrated as early as 1 week. The subscales of N-CBRF (compliant/calm, adaptive/social, insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive all significantly improved (p less than 0.001). At baseline, 72% of patients had marked to extremely severe symptoms based on the Clinical Global Improvement Severity scale compared with 12% at 1-year. Sixty-six percent were rated as not ill or having mild symptoms. At baseline, the mean aberrant Behavior Checklist total scores were 64.3 +/- 25 compared with 37.4 +/- 27 at 1-year representing a 28.3 +/- 1.4 decrease from baseline (p less than 0.001). The visual analog scale scores of the most troublesome symptoms (aggression, oppositional defiant behavior, and hyperactivity) improved by 40.3 +/- 1.3 from baseline (p less than 0.001). In general, adverse events were mild or moderate with the most common being somnolence (30%), rhinitis (27%), and headache (22%). At month 12, the mean Extrapyramidal Symptom Rating Scale total score changes from baseline was -0.4+/-0.2 (p less than 0.001). Antiparkinsonian medications were necessary in 5 patients (1%) and EPS led to discontinuation in 6 patients (1%). Tardive dyskinesia, which resolved after stopping risperidone, was experienced in 2 patients. Prolactin elevation in 32 patients (6.4%) may have resulted in adverse events. Mild to moderate gynecomastia was experienced in 22 boys and 3 girls. Other possible prolactin-related events, most of which were mild and resolved after risperidone discontinuation, were menstrual disturbances (6 patients) and galactorrhea (1 patients). Mean body weight increased by 7 +/- 2.1 kilogram (p less than 0.001) in children, half of this weight gain could be attributed to expected growth. Normal sexual maturation was observed (Croonenberghs et al, 2005).

c) Risperidone was safe and effective as a short- and long-term therapy for the reduction of severe behavior

problems in children with mild or moderate intellectual disabilities. In a 6-week, randomized, double-blind, placebo controlled study, patients (ages 5 to 12 years) with below average intelligence (IQ, 36 to 84) and a diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified received placebo (n=63) or risperidone (n=55) 0.02 to 0.06 milligrams (mg)/kilogram/day (mean dose, 1.16 mg/day). Efficacy of risperidone was assessed according to the change in score from baseline to endpoint on the conduct problem subscale of the Nisonger Child Behavior Rating Form. Patients treated with risperidone showed a significantly larger reduction in mean conduct problem subscale scores from baseline to endpoint as compared with placebo (-15.2 vs -6.2, respectively; p less than 0.001). Risperidone- treated patients also showed significantly better improvements than did placebo-treated patients on all other subscales of the Nisonger Child Behavior Rating Form. Risperidone was generally well tolerated and most adverse effects were mild to moderate, including somnolence (51%) and headache (29%). As a long-term, open-label extension, 107 patients from this controlled study received risperidone (initial, 0.01 mg/kg/day, titrated up to maximum of 0.06 mg/kg/day; mean dose 1.51 mg/day) for 48 weeks. Throughout the 48-week extension, symptom improvement was maintained in patients treated with risperidone during the controlled trial and significant symptom improvement was observed in patients who had received placebo during the controlled trial. Risperidone was generally well tolerated throughout the extension phase of the trial. Adverse events included headache (32.7%), somnolence (32.7%), rhinitis (28%), increased appetite (9.3%), weight gain (20.6%; mean increase from baseline, 5.5 kilograms), and transient, mild elevations in prolactin levels (mean maximum level, 27.6 nanograms/milliliter (ng/mL) in boys; 23.9 ng/mL in girls). Additional studies are needed to investigate the safety and efficacy of risperidone therapy beyond 1 year for the treatment of severe, disruptive behavior in pediatric patients (Findling et al, 2004; Aman et al, 2002).

4.5.D Bipolar I disorder

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (10 years and older, oral only)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Intramuscular long-acting risperidone is indicated as monotherapy or in combination with lithium or valproate for the maintenance treatment of bipolar I disorder in adults (Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010).

Oral risperidone is indicated for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in children aged 10 years of age and older and adults (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Khanna et al, 2005; Gopal et al, 2005; Vieta et al, 2004; Yatham et al, 2003; Vieta et al, 2001).

Oral risperidone, at doses ranging from 0.5 to 6 milligrams per day for 3 weeks, was effective in the treatment of acute manic or mixed episodes of bipolar I disorder in children aged 10 to 17 years in a multicenter, randomized, double-blind, placebo-controlled trial (Haas et al, 2009).

3) Adult:

a) Monotherapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV diagnostic criteria for bipolar disorder type I and who were stable on medications or experiencing an acute manic or mixed episode, long-acting intramuscular (IM) risperidone was effective for the maintenance treatment of bipolar I disorder. During a 26-week open-label period, a total of 501 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up if clinically desirable (or 12.5 mg in patients not tolerating the starting dose). Of the 501 treated patients, 303 (60%) were deemed to be stable and were randomized to double-blind treatment with either the same dose of IM risperidone or placebo. The results of the study showed that when compared to placebo, patients receiving monotherapy IM risperidone were delayed to reaching the study primary endpoint, which was the time to relapse to any mood episode (depression, mania, hypomania, or mixed). The majority of relapses were due to manic rather than depressive symptoms and based on their history of bipolar disorder, these patients had, on average, more manic episodes than depressive episodes (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral

a) Risperidone produced significantly greater reductions in mean Young Mania Rating Scale (YMRS) scores than did placebo in a 3-week, randomized, double-blind, multicenter study (n=291). Hospitalized adult patients who met DSM-IV criteria for bipolar I disorder with either manic or mixed episodes and had a score of at least 20 on the YMRS were randomized to either placebo (n=145) or risperidone (n=146) after a washout period of up to 3 days. Patients in the risperidone group received an initial dose of 3 milligrams (mg) once daily, with dose adjustments of 1-mg/day increment or decrement to achieve target dose of 1 to 6 mg/day. Nearly all patients (99%) received lorazepam (dose range, 1 to 8 mg) to manage agitation, irritability, restlessness, insomnia, or hostility during the washout period and the first 10 days of the double-blind treatment period; no other psychotropic drugs were allowed. Mean total YMRS scores (primary endpoint) improved from 37.1 at baseline to 14.5 at endpoint in the risperidone group (p less than 0.001), and the magnitude of the total YMRS scores change was greater in risperidone than placebo (-23.2 vs -10.8; 95% confidence interval, -15.6 to -9.3; p less than 0.001). The significant between-group difference in mean total YMRS score reduction was apparent as early as 1 week after initiation of therapy (-11.7 vs -8.3; p less than 0.01), and sustained at endpoint (-22.7 vs -10.5; p less than 0.001). Risperidone was associated with higher incidence of extrapyramidal disorder (35% vs 6%), tremor (10% vs 1%), and dystonia (5% vs 0%) compared with placebo (Khanna et al, 2005). In a posthoc analysis, remission (achieving and maintaining a YMRS score of 8 or lower) was achieved by 42% of the risperidone group and 13% of the placebo group, yielding an adjusted odds ratio for remission of 5.6 for risperidone (95% CI, 3 to 10.4). Significant independent predictors of remission were risperidone treatment and the absence of psychosis (Gopal et al, 2005).

b) Risperidone monotherapy was effective in the acute and continuation treatment of mania in patients with bipolar disorder. In an open- label, multicenter study, patients with acute mania and a score of at least 20 on the Young Mania Rating Scale (YMRS) received six months of risperidone monotherapy at a mean dose of 4.2 milligrams (mg) daily (range 1.5 to 4.5 mg/day). Significant improvements in the YMRS score were observed from baseline to weeks 1, 2, 4, 6, 12, and 24 (p less than 0.0001). Addi-

tionally, improvements in Clinical Global Impression and Positive and Negative Syndrome Scale scores were significant from week 4 onward as compared with baseline (p less than 0.0001). Extrapyramidal symptoms (ie, dystonia, hypokinesia) were significantly increased by week 4 (p=0.015) (correlating with the highest mean doses of risperidone), but then decreased significantly by study endpoint (p=0.027). Other adverse events included impotence, drowsiness, weight gain (mean increase, 3.2 kilograms), restlessness, dizziness, hypotension, incontinence, and galactorrhea. Within the initial 4 weeks of treatment, increased severity of manic symptoms was seen in four patients (4.2%) and the appearance of a depressive episode was observed in seven patients (7.3%). Randomized, controlled studies are needed to confirm the safety and efficacy of risperidone monotherapy for the long-term treatment of bipolar mania (Vieta et al, 2004).

c) In two placebo-controlled trials, risperidone monotherapy was more effective than placebo in reducing manic symptoms in patients with bipolar disorder. Patients meeting DSM-IV criteria for bipolar I disorder with manic or mixed episodes and with or without psychotic features received risperidone (1 to 6 milligrams (mg)/day; mean modal dose, 4.1 to 5.6 mg/day) or placebo for 3 weeks (n=246; n=286). In both trials, risperidone was more effective than placebo in the reduction of the Young Mania Rating scale (YMRS) scores of these patients (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV diagnostic criteria for bipolar disorder type I and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12 months and at least 2 episodes in the 6 months prior to starting the trial, long-acting intramuscular (IM) risperidone was effective for bipolar I disorder when used as combination therapy with lithium or valproate. During a 16-week open-label period, a total of 240 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up if clinically desirable (or 12.5 mg in patients not tolerating the starting dose) in addition to continuing their usual bipolar disorder therapy with all oral antipsychotics discontinued after the first 3 weeks of the initial injection of IM risperidone. Of the 240 treated patients, 124 (51.7%) were deemed to be stable for at least the last 4 weeks and were randomized to double-blind treatment with either the same dose of IM risperidone or placebo in addition to their usual bipolar disorder therapy for 52 weeks. The results of the 52-week study showed that when compared to placebo, patients receiving IM risperidone as combination therapy were delayed to reaching the study primary endpoint, which was the time to relapse to any new mood episode (depression, mania, hypomania, or mixed) compared to placebo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral

a) The efficacy of risperidone as a combination therapy for the treatment of manic or mixed episodes associated with bipolar disorder was established in one controlled trial, while a second controlled trial failed to show efficacy. In a randomized, controlled, combination trial, patients (n=148) on lithium or valproate therapy (therapeutic range, 0.6 to 1.4 mEq/L or 50 to 125 mcg/mL, respectively) with bipolar I disorder with or without psychotic features and with inadequately controlled manic or mixed symptoms received risperidone (1 to 6 mg/day; mean modal dose, 3.8 mg/day), an active comparator,

or placebo in combination with their original therapy. Combination therapy with adjunctive risperidone was more effective than lithium or valproate alone in the reduction of the YMRS total score. However, in a second combination trial in 142 patients on lithium, valproate, or carbamazepine with inadequately controlled manic or mixed symptoms, the addition of risperidone (1 to 6 mg/day; mean modal dose, 3.7 mg/day) was not superior to lithium, valproate, or carbamazepine (therapeutic range, 0.6 to 1.4 mEq/L, 50 to 125 mcg/mL, or 4 to 12 mcg/mL, respectively) alone in the reduction of the YMRS total score. The failure of this trial could be due to induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Risperidone (median modal dose of 4 milligrams) as an adjunct to mood stabilizer may be more effective in the treatment of manic episodes associated with bipolar disorder than placebo when combined with mood stabilizing drugs (n=151). Bipolar patients, aged 18 to 65 years of age, presenting with a manic or mixed episode and a score of at least 20 on the Young Mania Rating Scale (YMRS) were enrolled in a 3-week, double-blind, placebo-controlled study. To be eligible for this study the patient also had to be taking a mood stabilizer (lithium, divalproex or carbamazepine) for a minimum of 2 weeks prior to randomized assignment into treatment groups. Eligible patients were randomized to receive risperidone (n=75) or placebo (n=76) in addition to ongoing mood stabilizer. The primary efficacy measure was the change in YMRS score from baseline to endpoint. There was a decrease of 14.5 and 10.3 points on the YMRS score for the risperidone and placebo groups, respectively, at the end of the 3 weeks (p=0.089). Risperidone was equally effective in patients with or without psychotic features. When combined with carbamazepine, risperidone median dose-normalized plasma concentrations decreased by 40%. Due to a high number of dropouts in both groups the study was inadequately powered to determine the true treatment effects. Additional studies are ongoing (Yatham et al, 2003).

c) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorder and schizoaffective disorder, bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorder who were in a manic, hypomanic, depressive, or mixed episode (n=541; 430 completed the study) were given risperidone in combination with lithium, anticonvulsants, and antidepressants to clinical response and tolerability. The average dose of risperidone at the start of the study was 4 milligrams (mg) per day and at the end of the study, 3.9 mg/day. For all patients, scores on the Young Mania Rating Scale (YMRS) were significantly reduced at week 1 and at every point thereafter (p less than 0.001 for all but the subgroup of depressed patients, for whom p was less than 0.05). Mean scores on the YMRS decreased from 25.6 at baseline to 2.4 at 6 months. Likewise, scores on the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced from baseline at all evaluation times (p less than 0.0001), with scores declining from 12.8 at baseline to 4.1 at 6 months. Scores on the Positive and Negative Syndrome Scale (PANSS) declined from 72 at baseline to 40 at 6 months (p less than 0.0001). According to the Clinical Global Impressions scale (CGI), no patients were free from symptoms at baseline and only 5% were rated as "mildly ill." At study endpoint, 44% of patients showed no symptoms of mania or depression and a further 30% were "mildly ill." During the study, 25% of the patients experienced relapses into a mood state different from that at the start of the trial. Scores for extrapyramidal symptoms were lower at the end of study than at baseline (p less than 0.0001). There were significant reductions in dystonia, rigidity, hypoki-

nesia, hyperkinesia, dyskinesia, tremor, and akathisia subscores. There were no cases of new-emergent tardive dyskinesia. Nonextrapyramidal adverse reactions included increase in weight (2.4% of patients), drowsiness (1.3%), impotence (0.7%), and dysarthria (0.7%). There was a very low incidence of exacerbation mania in the first 6 weeks (1.8%) (Vieta et al, 2001).

d) Risperidone was associated with significantly greater improvement compared with placebo. A multicenter, double-blind, parallel-group study investigated adding risperidone, haloperidol, or placebo to a mood stabilizer (lithium or valproate) in 158 patients with acute mania. After completing the 3 week, double-blind phase of the study, patients were offered open-label risperidone therapy for an additional 10 weeks of follow-up. Improvement on the Young Mania Rating Scale and the Clinical Global Impressions-Improvement scale was greater with risperidone at 3 weeks. The investigators concluded that risperidone is a safe and effective addition to lithium or valproate for the treatment of bipolar mania (Ghaemi & Sachs, 1997).

4) Pediatric:

a) Monotherapy

1) Oral risperidone treatment was associated with significantly greater improvements in the Young Manic Rating Scale (YMRS) scores after 3 weeks of treatment compared with placebo in a randomized, placebo-controlled, double-blind, multicenter study of children and adolescents with manic or mixed episodes associated with bipolar I disorder (n=169). Subjects were children and adolescents (median age, 13 years; range 10 to 17 years) who met DSM-IV criteria for bipolar I disorder, with an acute manic or mixed episode as assessed by the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), and a total score of 20 or greater on the adolescent version of the YMRS. Subjects with additional DSM-IV diagnoses of attention-deficit hyperactivity disorder (ADHD) or disruptive behavior disorders (DBD) were allowed. Subjects were randomized to placebo (n=58), risperidone 0.5 to 2.5 milligrams (mg)/day (n=50), or risperidone 3 to 6 mg/day (n=61) for 3 weeks. Risperidone was initiated at a dose of 0.25 mg/day orally, with dose increases of 0.25 to 1 mg/day every 1 or 2 days, to achieve the minimum dose within the target range by day 7. Doses were increased from days 8 through 10 to reach the maximum tolerated dose within the target range, and the dose at day 10 was maintained through day 21 unless tolerability required an adjustment within the target range. Concomitant therapy with other antipsychotics, antidepressants, anticonvulsants, or antimanic medications was not allowed. Compared with the placebo group, reduction in YMRS scores from baseline to day 21 endpoint (primary outcome) was significantly greater in the risperidone 0.5 to 2.5 mg group (mean change difference, -9.2; 95% confidence interval (CI), -12.7 to -5.7) and the risperidone 3 to 6 mg group (mean change difference, -8; 95% CI, -11.3 to -3.6). A post hoc analysis demonstrated a higher clinical remission rate (YMRS score of 12 or below) with risperidone compared with placebo at endpoint (43% vs 16%). Serious adverse effects were reported in 5% of the placebo group, 6% of the risperidone 0.5 to 2.5 mg group, and 8% of the risperidone 3 to 6 mg group and included psychosis (3%, 2%, 7%, respectively) and suicide attempt (2%, 4%, and 3%, respectively). Common adverse events in the placebo group, the risperidone 0.5 to 2.5 mg group, and the risperidone 3 to 6 mg group included somnolence (19%, 42%, 56%), headache (33%, 40%, 38%), fatigue (3%, 18%, 30%), and abdominal pain (5%, 18%, 15%). The risperidone 3 to 6 mg group had higher percentages of subjects with at least 1 extrapyramidal symptom (25%) than the risperidone 0.5 to 2.5 mg group (8%) or the placebo group (5%). (Haas et al, 2009).

b) Combination Therapy

1) In a case series including 11 children and adolescents aged 5 to 16 years with difficult to manage mood disorders (suggestive of bipolar disorder) and aggressive behavior, 8 had therapeutic responses to risperidone 0.75 to 2.5 milligrams (mg) daily. The patients and symptoms were clinically very diverse and most were taking concurrent medications, such as mood stabilizers. No standardized psychometric instruments were used for assessment, so improvement was purely subjective. Seven patients were considered to have marked improvement and one patient was considered moderately improved. Side effects reported included sedation, weight gain and anxiety (Schreier, 1998).

4.5.E Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.F Dementia - Psychotic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Cerebrovascular adverse events (stroke, transient ischemic attack) including fatalities have occurred in elderly individuals (mean age, 85 years) who received risperidone for treatment of dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDAL(R) M-TAB(R) oral tablets, solution, orally disintegrating tablets, 2009).

According to an 8-week, randomized, double-blind trial (n=416), risperidone was no different from placebo for the treatment of Alzheimer's disease-associated psychosis (Mintzer et al, 2006).

Risperidone treatment resulted in a significant reduction in total score on the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) compared with placebo for the treatment of psychotic and behavioral symptoms of Alzheimer's dementia, vascular dementia, or mixed dementia in a 12-week, randomized, double-blind, trial (n=625) (Katz et al, 1999).

3) Adult:

a) According to an 8-week, randomized, double-blind trial (n=416), risperidone was no different from placebo for the treatment of Alzheimer's disease-associated psychosis, measured by the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Psychosis scale and the Clinical Global Impression of Change (CGI-C). Patients aged 55 years or older (mean, 83 +/- 7 years) residing in a nursing home or long-term care facility, with a score of at least 2 on the 4-point BEHAVE-AD Psychosis subscale, and between 5 and 23 on the Mini-Mental State Examination were included in the study. Exclusion criteria included recent injection of a neuroleptic agent. Following a 1-week washout period for existing psychotropic agents, patients were randomized to receive 8 weeks of either placebo (n=238), or risperidone 0.25 milligrams (mg) twice a day titrated to clinical effect up to 0.75 mg twice daily (n=235). The mean daily risperidone dose was 1.03 +/- 0.24 mg. Concomitant analgesics, and other psychotropic agents including

lorazepam, donepezil, and zolpidem tartrate were permitted. Discontinuation of therapy occurred in 25% for both treatment groups, and the most common reasons were inadequate response (risperidone, 6%; placebo, 7%) and intolerable side effects (risperidone, 11%; placebo, 10%). The adjusted mean of the BEHAVE-AD Psychosis subscale to week 8 improved by 2.9 +/- 3.55 points (from 7.6 +/- 4.1 at baseline) in the risperidone group and by 2.3 +/- 3.55 (from 8.2 +/- 4.85 at baseline) in the placebo group, resulting in a between-group difference of -0.6 (95% confidence interval (CI), -1.25 to 0.14; p=0.118). The distribution in CGI-C categories before and after treatment did not differ between drug groups (p=0.416). The incidence of cerebrovascular adverse events was 1.7% in the risperidone group, and 0.4% in placebo, of whom 1 patient treated with risperidone experienced a stroke and 4 patients treated with risperidone had a transient ischemic attack. Risperidone was associated with a higher incidence of extrapyramidal-like adverse events compared with placebo (8.5% vs 3.4%) (Mintzer et al, 2006).

b) According to a 12-week, randomized, double-blind, trial (n=625), risperidone treatment resulted in a significant reduction in total score of the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) compared with placebo for the treatment of psychotic and behavioral symptoms of Alzheimer's dementia, vascular dementia or mixed dementia among institutionalized patients. Patients aged 55 years or older (mean, 82.7 years) residing in a nursing home or chronic disease hospital, with a score of at least 4 on the Functional Assessment Staging Test, 23 or lower on the Mini-Mental State Examination, and a total score of at least 8 and a global rating of at least 1 on BEHAVE-AD were included in the study. Following a 3- to 7-day placebo washout period, patients were randomized to receive 12 weeks of either placebo (n=163), risperidone 0.5 milligrams (mg) (n=149), risperidone 1 mg (n=148), or risperidone 2 mg (n=165) per day. During the first week, patients receiving risperidone 1 mg or 2 mg per day were titrated in increments of 0.5 mg/day every 2 days. Concomitant use of benztropine, lorazepam, and chloral hydrate were permitted. Discontinuation of therapy occurred in 21.5%, 30.4%, 41.8% in the risperidone 0.5 mg, 1 mg, and 2 mg groups, and in 27% in the placebo group. The most common reasons for therapy discontinuation were adverse events (8%, 16%, and 24%, and 12% in risperidone 0.5 mg, 1 mg, and 2 mg, and placebo group, respectively). In an evaluation of the primary endpoint at week 12, risperidone 1 mg and 2 mg were associated with statistically significant improvement in the BEHAVE-AD total score compared with placebo (see table below). In a secondary endpoint evaluation, only the risperidone 2-mg group showed statistically significant improvement in the BEHAVE-AD psychosis subscale compared with placebo. There were dose-dependent increases seen in somnolence, extrapyramidal symptoms, and peripheral edema (Katz et al, 1999).

Mean Change in BEHAVE-AD Score from Baseline to Week 12

Total Score
Psychosis Subscale
Aggressiveness Subscale
placebon=118
-5.2 +/- 0.6
-1.9 +/- 0.4
-1.2 +/- 0.3
risperidone 0.5 mgn=117
-6.4 +/- 0.7p=0.13
-2.2 +/- 0.4p=0.316

-1.9 +/- 0.3p=0.02
risperidone 1 mgn=102
-7.4 +/- 0.7p=0.02
-2.6 +/- 0.4p=0.054
-2.2 +/- 0.3p=0.006
risperidone 2 mgn=98
-8.5 +/- 0.7p less than 0.001
-3.2 +/- 0.3p=0.002
-3 +/- 0.3p less than 0.001
BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; mg = milligrams; p-value in comparison with placebo

c) Risperidone was effective and well-tolerated for the treatment of psychotic symptoms and behavioral disturbances in elderly patients with comorbid medical illnesses and medications. In a review of medical records, 122 hospitalized psychogeriatric patients newly treated with risperidone were assessed. Patients received risperidone for agitation or psychosis associated with dementia (53%), a major mood disorder (29%), or other disorder (18%). Most were also medically ill and received other psychotropic (76%) or cardiovascular drugs (70%). Risperidone appeared to be effective in 85% of cases. In the demented group of patients with agitation or psychotic features, 82% were rated as improved. Patients starting on low doses and undergoing slow dosage increases, were less likely to have any adverse drug events (p=0.002). Risperidone was discontinued in 11% due to side effects and in 7% due to lack of efficacy (Zarate et al, 1997).

4.5.G Depression, Refractory; Adjunct

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Improvement was demonstrated with risperidone compared with placebo augmentation of antidepressant therapy in difficult-to-treat depression in a double-blind, 4-week, placebo-controlled, study (n=97); however, the treatment effect was diminished around week 4 (Keitner et al, 2009).
There were modest but statistically significant improvements in treatment-resistant depression with 6 weeks of risperidone augmentation to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized trial in adults (n=274) (Mahmoud et al, 2007).
Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was not sustained in the long-term (9 months) in a multinational, double-blind, placebo-controlled study (n=243) (Rapaport et al, 2006).

3) Adult:
a) General Information
1) Risperidone, as augmentation to antidepressant medication, has provided some benefit in the

short-term (4 to 6 weeks) in patients with treatment-resistant or difficult-to-treat depression (Mahmoud et al, 2007), (Keitner et al, 2009); however, continuation of risperidone augmentation for 24 weeks failed to prevent relapse of depression (Rapaport et al, 2006). There were modest but statistically significant improvements with 6 weeks of risperidone augmentation compared with placebo in a multicenter, double-blind, placebo-controlled, randomized trial (n=274) (Mahmoud et al, 2007). In another double-blind, 4-week, placebo-controlled, study (n=97), initial improvement demonstrated with risperidone compared with placebo augmentation diminished around 4 weeks (Keitner et al, 2009). Risperidone augmentation did not prevent relapse in the long-term (9 months) in a multinational, double-blind, placebo controlled study (n=243) (Rapaport et al, 2006).

b) Clinical Trials

1) Improvement was demonstrated with risperidone compared with placebo augmentation of antidepressant therapy in difficult-to-treat depression in a double-blind, 4-week, placebo-controlled study (n=97); however, the treatment effect was diminished around week 4. Patients (n=147) with unipolar, nonpsychotic major depression were enrolled in an open-label treatment phase to receive antidepressant monotherapy for 5 weeks if they were currently not on antidepressant drugs, if they were not currently receiving antidepressant therapy at an adequate dose and duration, or if they had poorly documented antidepressant therapy. At the end of the open-label phase, partial responders and non-responders with a Montgomery-Asberg Depression Rating Scale (MADRS) rating of 15 or more were enrolled in the double-blind, randomized phase (n=43). Additionally, patients (n=54) with well documented failure of current antidepressant therapy of adequate dose and duration were enrolled in the double-blind phase directly, without going through the open-label phase. Patients with bipolar I, bipolar II, or psychotic features were among those excluded. During the double-blind phase, patients continued on the same dose of their antidepressant drug and were randomized to additionally receive either risperidone (n=62) or placebo (n=33) for 4 weeks. Risperidone was initiated at 0.5 milligrams (mg) per day, and the dose was increased, if necessary, to 2 mg/day by day 21 and 3 mg/day thereafter (mean dose at end of 4 weeks, 1.6 mg/day). Based on Clinical Global Impression (CGI) scores, the majority of patients were moderately ill at baseline (risperidone, 68.8%; placebo, 69.7%) and mean baseline MADRS scores were 25.8 +/- 5.7 and 25.5 +/- 5.4 in the risperidone and placebo groups, respectively. In the modified intent-to-treat population (received at least 1 dose of study drug and competed at least 1 set of assessments), the primary outcome of remission (MADRS rating of 10 or less) was achieved in 51.6% (n=32/62) and 24.2% (n=8/33) of patients in the risperidone- and placebo-treated groups, respectively, at the end of 4 weeks (p=0.011). The corresponding rates of remission for those who completed all 4 weeks of treatment (n=82) were 52.7% and 29.6%, respectively (p=0.052). Treatment difference was evident after 2 weeks, with remission rates of 37.3% and 15.6% in the risperidone and placebo groups, respectively. Notably, while both treatments demonstrated improvement over time, the difference in treatment was not statistically significant at week 4. The odds ratio for remission with risperidone compared with placebo was 3.33 (95% CI, 1.303 to 8.526; p=0.011). Among other outcomes, rates of response (50% decrease from baseline MADRS rating) at 4 weeks were 54.8% and 33.3% in the risperidone and placebo groups, respectively (p=0.049), with significant differences seen after 1 week of treatment (24.2% and 6.1%, respectively; p=0.031). When remission and response were evaluated on the Hamilton Depression Scale (HAM-D), treatment differences between risperidone and placebo were not statistically significant. Patient ratings of overall life satisfaction and contentment were significantly better in the risperidone group compared with the placebo group (from 1.3 to 2.5 and 1.2 to 1.7, respectively,

p=0.014), with differences apparent by 2 weeks of treatment. The overall frequency of side effects was similar in the risperidone (84.4%) and placebo (81.8%) groups (Keitner et al, 2009).

2) There were modest but statistically significant improvements in treatment-resistant depression with 6 weeks of risperidone augmentation to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized trial in adults (n=274). An open-label, 4-week, run-in period identified 274 patients (age range, 18 to 65 years) with unremitting major depression, with a Clinical Global Impression-Severity of Illness (CGI-S) score of 4 or more, and a Carroll Depression Scale score of 20 or more while on their current antidepressant monotherapy at the recommended dosage. These patients were then randomized to 6 weeks of augmentation therapy with either oral risperidone (n=141) or placebo (n=133). The risperidone dose was 0.25 milligrams (mg) every day for 3 days, then 0.5 mg every day for days 4 to 15, followed by 1 mg every day for days 16 to 28. At the investigator's determination of ineffective treatment on day 29, risperidone was either continued at 1 mg/day or the dose was increased to 2 mg/day, or double-blind treatment was discontinued. At the start of randomization, the mean time since diagnosis of depression was 16.7 +/- 12.3 years, and mean Hamilton Rating Scale for Depression 17-item (HRSD-17) scores for the risperidone- and placebo-treated patients were 24.3 and 24.9 (p=0.73), respectively. All patients continued on their baseline antidepressant regimen, which consisted of a selective serotonin reuptake inhibitor (risperidone group, 59.1%; placebo group, 59.5%), a serotonin-norepinephrine reuptake inhibitor (22.6% and 19.8%, respectively), or other agents such as bupropion and trazodone (17.6% and 19.9%, respectively). The primary outcome was the change from baseline to 6 weeks in the HRSD-17 total score; response was defined as a 50% or more reduction in score and remission was defined as a total score of 7 or less. The final risperidone dose was 1 mg for 65.7% and 59.5% of risperidone- and placebo-treated patients, respectively. Results for the primary outcome are listed in the table below (Mahmoud et al, 2007).

Outcome
Risperidone
Placebo
Difference (95% CI)
p value
Mean (+/- SE) HRSD-17
Week 4*
15.4 +/- 0.52
17.3 +/- 0.52
-1.9 +/- 0.69 (95% CI, -3.3 to -0.5)
p=0.006
Week 6**
13.4 +/- 0.54
16.2 +/- 0.53
-2.8 +/- 0.72 (95% CI, -4.2 to -1.4)
p less than 0.001
Remission Rates
Week 4*
13.6%
6%

--
p=0.041
Week 6**
24.5%
10.7%
--
p=0.004
Response Rates
Week 4*
35.6%
18.8%
--
p=0.002
Week 6**
46.2%
29.5%
--
p=0.004
KEY: SE = standard error; CI = confidence interval; HRSD-17 = Hamilton Rating Scale for Depression 17-item score *risperidone: n=118; placebo: n=117 ** risperidone: n=106; placebo: n=112.

Secondary outcomes, which included clinician-rated measures (measured by CGI-S) and patient-rated measures (measured by Quality of Life Enjoyment and Satisfaction Questionnaire, Patient Global Improvement Scale, Sheehan Disability Scale), improved significantly more with risperidone compared with placebo at week 6. The number needed to treat with 6 weeks of risperidone augmentation to achieve 50% baseline symptom improvement in treatment-resistant depression was 6. Risperidone was well-tolerated, with premature study discontinuation due to adverse effects occurring in 5.8% of risperidone-treated patients and 2.3% of placebo-treated patients. Frequency of motor events was similar between the risperidone and placebo groups (akathisia, 0.7% and 0%, respectively; dystonia, 0% and 0.8%; tremor, 0.7% and 0.8%) and did not require use of benztropine (Mahmoud et al, 2007).

3) Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was not sustained in the long-term (9 months) in a multinational, double-blind, placebo-controlled study (n=243). The study design consisted of the following 3 phases: 4 to 6 weeks of open-label citalopram monotherapy (initial dose, 20 milligrams (mg); target dose range, 40 mg to 60 mg), 4 to 6 weeks of open-label risperidone augmentation, and a 24-week double-blind, placebo-controlled continuation of the risperidone phase. Patients (n=502) enrolled in the open-label citalopram monotherapy phase had major depressive disorder, single or recurrent episode, with or without psychotic features, a score of 20 or more on the Hamilton Rating Scale for Depression (HAMD-17), and were treatment-resistant (failure to respond to at least 1 but not more than 3 antidepressant trials of at least 6 weeks' duration at the labeled doses). Patients who either failed to respond (less than 50% reduction in HAMD-17 total score) after 6 weeks or were unchanged or worse after 4 weeks with citalopram were augmented with open-label, oral risperidone (n=390). For patients aged 18 to 54 years, risperidone was initiated at 0.5 mg/day and increased up to 2 mg/day (goal, 1 mg/day); patients aged 55 to 85 years old received 0.25 mg/day initially, with dose increases permitted up to 1 mg/day (goal, 0.5 mg/day). Patients achieving a

HAMD-17 score of 7 or less or a Clinical Global Impressions (CGI)-Severity score of 1 or 2 during the risperidone augmentation (n=243, 63% of the open-label risperidone phase) were then randomized to receive either placebo (n=120; mean age, 48.4 years) or to continue on risperidone (n=123; mean age, 47.8 years) for 24 weeks. Time to relapse, the primary outcome, was defined as 1 or more of the following: 6 (much worse) or 7 (very much worse) on the CGI-Change score, 16 or higher on the HAMD-17 score, lack of efficacy leading to discontinuation, or intentional self-injury or suicidal ideation. There were more women than men in the double-blind continuation phase (71.3% vs 56.3%). The mean duration of illness in the risperidone and placebo groups at baseline was 17.9 +/- 12.3 years and 17.6 +/- 13.9 years, respectively. Among those entering the double-blind phase, 63.1% were complete non-responders (less than 25% reduction in HAMD-17 score) and 36.9% were partial responders (25% to 49% reduction in HAMD-17) to open-label citalopram. Based on Kaplan-Meier analysis, the median time to relapse was 102 days and 85 days (p=0.52) for the risperidone augmentation group and placebo augmentation group, respectively, with relapse rates of 53.3% and 54.6%, respectively. The HAMD-17 baseline scores worsened by 7.6 +/- 8.8 points from a baseline (start of double-blind phase) score of 6 +/- 3 in the risperidone group and by 7.9 +/- 8.1 points from a baseline score of 6.3 +/- 2.9 in the placebo group (for both, p less than 0.001 compared with baseline). The Montgomery-Asberg Depression Rating Scale scores worsened by 11.2 +/- 12.6 points from a baseline score of 6.8 +/- 4.7 in the risperidone group and 10.4 +/- 11.2 points from a baseline score of 8.1 +/- 4.6 (for both, p less than 0.001 compared with baseline) in the placebo group. The mean prolactin concentrations were 35.4 +/- 53.4 nanograms/milliliters (ng/mL) and 6.6 +/- 21 ng/mL (p less than 0.001) in the risperidone and placebo groups, respectively; galactorrhea occurred in 2.5% and 0%, respectively. During the double-blind phase, the mean weight increase was 1.3 +/- 3.8 kilograms (kg) in the risperidone group compared with a mean loss of 0.5 +/- 2.9 kg in the placebo group (Rapaport et al, 2006).

4.5.H Parkinson's disease - Psychotic disorder

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

4.5.I Pervasive developmental disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In children with autism spectrum disorder, responders to 24 weeks of open-label therapy with oral risperidone therapy had lower relapse rates when randomized to continue additional 8 weeks of double-blind treatment with risperidone versus placebo (Troost et al, 2005).

Treatment with oral risperidone relieved several behavioral symptoms associated with pervasive de-

velopment disorder in children aged 5 to 12 years in an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) (Shea et al, 2004).

3) Pediatric:

a) In an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) in children, treatment with oral risperidone relieved several behavioral symptoms associated with pervasive development disorder (PDD). Pediatric outpatients aged 5 to 12 years (mean age, 7.5 years; greater than 75% male) with a DSM-IV Axis I diagnosis of PDD and a total score of 30 or more on the Childhood Autism Rating Scale (CARS), with or without mental retardation were randomized to receive either an oral solution of either risperidone (n=40) or placebo (n=39) in 1 or 2 divided doses for 8 weeks. Risperidone was initiated at 0.01 milligram/kilogram/day (mg/kg/day) and increased to 0.02 mg/kg/day on day 3. At day 8, the dose was further increased at a maximal increment of 0.02 mg/kg/day, and subsequent increments or decrements were allowed up to a maximum daily dose of 0.06 mg/kg/day. Primary efficacy of change in irritability from baseline to endpoint was assessed on the irritability subscale of the Aberrant Behavior Checklist (ABC). Secondary assessments included scores on the other 4 ABC subscales (hyperactivity/noncompliance, inappropriate speech, lethargy/social withdrawal, and stereotypic behavior), the parent-rated Nisonger Child Behavior Rating Form (N-CBRF), and the Clinical Global Impression-Change (CGI-C; 7-point scale ranging from very much improved to very much worse). At baseline, autistic disorder was the most common form of PDD (risperidone, 67.5%; placebo, 71.8%), of whom 57.5% and 53.8% of patients in the risperidone and placebo groups, respectively, were diagnosed with severe autism. At endpoint, patients in the risperidone group had received a mean risperidone daily dose was 0.05 mg/kg/day (mean daily dose, 1.48 mg) for a mean duration of 52.7 days (range, 2 to 62 days). An intention-to-treat analysis (included all patients receiving at least 1 study dose and with at least 1 postbaseline assessment) at endpoint revealed greater decreases from baseline irritability scores in the risperidone group (64% improvement) compared to placebo (30.7% improvement). Based on CGI-C scores, global improvements occurred in 87.2% and 39.5% of risperidone- and placebo-treated patients, respectively, with 54% and 18% of patients, respectively, reporting a rating of much improved or very much improved (p less than 0.001). Additionally, there was a greater decrease in the Visual Analog Scale score of aggression (most frequently reported troublesome symptom; 23.4%) in the risperidone-treated patients compared to placebo (mean score decrease, 38.4 vs 26.2; p less than or equal to 0.05). Results of the primary and key secondary endpoints are listed in the table below. Treatment-emergent adverse events were mild in severity, with somnolence (72.5% vs 7.7%), upper respiratory tract infection (37.5% vs 15.4%), rhinitis (27.5% vs 10.3%), and increased appetite (22.5% vs 10.3%) being the most commonly reported among risperidone-treated patients (Shea et al, 2004).

Efficacy measure
Risperidone (n=39)
Placebo (n=38)
Baseline
Endpoint (change from baseline)
Baseline
Endpoint (change from baseline)
ABC subscale (mean +/- SD)
Irritability
18.9 +/- 8.8

-12.1 +/- 5.8*
21.2 +/- 9.7
-6.5 +/- 8.4
Hyperactivity/noncompliance
27.3 +/- 9.7
-14.9 +/- 6.7*
30.9 +/- 8.8
-7.4 +/- 9.7
Inappropriate speech
4.6 +/- 3.4
-2.6 +/- 2.6**
4.8 +/- 3.7
-1.6 +/- 3
Lethargy/social withdrawal
13.7 +/- 7
-8.6 +/- 5.9***
14.3 +/- 8.2
-5.7 +/- 6.9
Stereotypic behavior
7.9 +/- 5
-4.3 +/- 3.8**
8.1 +/- 5.6
-2.4 +/- 4
N-CBRF (parent version) subscale (mean +/- SD)
Conduct problem
16.8 +/- 9.4
-10.4 +/- 7.4*
23.3 +/- 12
-6.6 +/- 9.5
Hyperactive
17.2 +/- 5.8
-8.1 +/- 4.6**
18.9 +/- 5.3
-5.6 +/- 6.6
Self-Isolated/ritualistic
7.5 +/- 4.1
-4.8 +/- 3.9
8.2 +/- 4.5
-3.6 +/- 4.6
Insecure/anxious
8.7 +/- 8.1
-4.6 +/- 6.5**
10.6 +/- 7.6

-3.5 +/- 5.5
Overly sensitive
6.9 +/- 3.4
-3.8 +/- 2.8**
7.4 +/- 3.5
-2.7 +/- 3.2
Self-injurious/sterotypic
4.2 +/- 4.2
-2.6 +/-3.3
3.5 +/- 4.2
-1.3 +/- 2.8
Key: n=number of subjects; ABC=Aberrant Behavior Checklist ; N-CBRF=Nisonger Child Behavior Rating Form; SD=standard deviation*p less than or equal to 0.001 vs placebo**p less than or equal to 0.05 vs placebo***p less than or equal to 0.01 vs placebo

(Shea et al, 2004)

b) In a double-blind extension phase, continued treatment with risperidone was more effective than placebo in preventing relapse of autism spectrum disorder symptoms among responders to 24 weeks of open-label risperidone therapy. Children aged 5 to 17 years (n=36) meeting the DSM-IV (Third Revision) criteria for a pervasive development disorder (PDD) and who demonstrated clinically significant tantrums, aggression, self-injurious behavior, or a combination of these problems were enrolled in the open-label phase to receive oral risperidone. In children weighing under 45 kilograms (kg), risperidone was initiated at 0.5 milligrams (mg) at bedtime, increased to 0.5 mg twice daily a week later, and subsequently increased in 0.5-mg increments to a maximum dose of 2.5 mg/day by day 29. Doses could be increased up to 3.5 mg/day by day 29 in children weighing more than 45 kg. Patients with an at least 25% reduction from the baseline Aberrant Behavior Checklist (ABC) Irritability score (baseline mean score, 23) and a rating of much improved or very much improved on the Clinical Global Impression (CGI) of Severity scale after 8 weeks were classified as responders (26/36) and allowed to continue taking risperidone for another 16 weeks. At 24 weeks of open-label treatment, 69% (18/26) of patients were rated as much improved or very much improved on the CGI Symptom Change (CGI-SC) scale, with significant decreases in ABC Irritability subscores as well; most improvements occurred by week 8 of treatment. Completers of the additional 16 weeks of therapy were randomized in a double-blind fashion to either continue taking risperidone (n=12) or placebo (gradual withdrawal for 3 weeks and placebo only for 5 weeks; n=12) for 8 weeks. Relapse was defined as the occurrence of CGI Symptom Change (CGI-SC) scores of much worse or very much worse for at least 2 consecutive weeks and a minimum increase of 25% from the last ABC Irritability score. An intention-to-treat analysis revealed relapses (primary endpoint) in 3 and 8 patients in the risperidone and placebo groups, respectively (p=0.049), with a longer mean time to relapse in patients maintained on risperidone (7 vs 6 days; p=0.0475). Compared with ABC Irritability subscale scores of 11.1 and 12.7 in the risperidone and placebo groups, respectively, at week 24, scores at the end of the study (week 32) were 12.6 (14% increase) and 20.3 (60% increase; p=0.043), respectively. Improvements noted at week 24 among other ABC subscales, such as social withdrawal, stereotypy, hyperactivity, and inappropriate speech, were well maintained until the end of the study in the risperidone group, but there were no statistically significant differences between the groups at study end. Treatment-emergent adverse events were mild to moderate and included increased appetite (62%), anxiety (39%), fatigue (35%), and increased

thirst (26%). At week 24, the mean weight gain from baseline was 5.7 +/- 2.8 kg (range, 1.2 to 11.7 kg; p less than 0.0001). It should be noted that the majority (75%) of the study population had a form of PDD other than autistic disorder and 63% had average or above-average intelligence (Troost et al, 2005).

4.5.J Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (13 years and older, oral only)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone (oral and IM) is indicated for the treatment of schizophrenia in adults and orally administered risperidone is also indicated in children age 13 and older (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

Approved for maintenance treatment of schizophrenia in adults (Prod Info RISPERDAL(R) oral solution, oral tablets, 2010; Prod Info RISPERDAL(R)M-TAB(R) orally disintegrating tablets, 2010; Prod Info RISPERDAL(R)CONSTA(R) IM injection, 2010)

Oral risperidone, at doses ranging from 1 to 6 milligrams per day, was effective in the treatment of schizophrenia in adolescents aged 13 to 17 years in 2 short-term (6 and 8 weeks), double-blind, controlled trials (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult:

a) General Information

1) Risperidone is effective for the positive and negative symptoms associated with chronic schizophrenia with a response rate of 50% to 75% (Foster & Goa, 1998a; Rossi et al, 1997a; Smith et al, 1996a). Dose ranges of risperidone 4 to 16 milligrams have shown statistically greater improvement than placebo in Clinical Global Impression (CGI) and total Positive and Negative Syndrome Scale (PANSS) scores. The 4 to 6 milligram dose appears to be the most effective (Marder & Meibach, 1994a; Chouinard et al, 1993a; Marder, 1992; Muller-Spahn, 1992a). At doses of 8 milligrams or less risperidone is associated with a lower risk of extrapyramidal symptoms than conventional antipsychotics (Foster & Goa, 1998a). Comparative efficacy with haloperidol and other conventional neuroleptics has shown that risperidone has a significantly higher clinical response rate and allows for significantly less prescribing of anticholinergic medications (Davies et al, 1998)(Bech et al, 1998a; Luebbe, 1996a). Patients treated with risperidone have a lower relapse rate than those treated with haloperidol (Csernansky et al, 2002a). Patients have also been successfully switched from depot antipsychotics to risperidone (Desai et al, 1999).

b) Monotherapy

1) Intramuscular

a) Long-acting injectable risperidone was significantly more effective than placebo in the treatment of patients with schizophrenia. In a randomized, double-blind, placebo-controlled, multicenter study,

patients (n=400) with schizophrenia received intramuscular injections of long-acting risperidone (25 milligrams (mg), 50 mg, or 75 mg) or placebo every two weeks for 12 weeks. During a one week run-in period, patients received oral risperidone (titrated to a dose of 4 mg/day) for at least 3 days. Patients also received oral risperidone (2 mg/day, 4 mg/day, or 6 mg/day) or placebo for the first three weeks of the double-blind period of the study. Mean Positive and Negative Syndrome Scale (PANSS) total scores were significantly more improved in patients receiving long-acting risperidone 25 mg, 50 mg, or 75 mg as compared with those who received placebo (p=0.002, p less than 0.001, p less than 0.001, respectively). Improvements in positive and negative symptoms were also significantly greater in all three long-acting risperidone groups as compared with the placebo group (p less then or equal to 0.05, all values). Clinical improvement was defined as at least a 20% reduction in PANSS total scores and was observed in only 17% of placebo patients as compared with 47%, 48%, and 39% of patients in the 25 mg, 50 mg and 75 mg long-acting risperidone groups, respectively (p less then 0.001). While the 75 mg dose of long-acting risperidone was efficacious, it offered no additional benefit over the 25 mg and 50 mg doses. Long-acting risperidone was well tolerated and extrapyramidal adverse events were mild throughout the study period. Small increases in body weight from baseline to endpoint were observed in risperidone-treated patients and these changes appeared to be dose- related (Kane et al, 2003).

2) Oral

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in elderly patients. In an international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventional antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=nonsignificant). The severity of EPS symptoms was reduced in both groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean QTc changes were not considered clinically relevant (Jeste et al, 2003a).

b) Risperidone treatment resulted in mild to substantial improvement in psychotic symptoms in approximately two-thirds of the elderly Chinese patients (age 65 years or greater) participating in an open, 4-week study. Doses of risperidone were titrated on the basis of clinical responses and adverse effects and ranged from 0.25 to 7 milligrams (mg) per day (mean 2.1 mg/day). The mean dose for functional psychoses was greater than that for organic mental disorders (2.8 mg/day vs 1.6 mg/day,

p=0.001). Patients with schizophrenia received the highest mean dose (4.1 mg/day). With improvement defined as a reduction of 25% or more in baseline scores on various rating instruments, improvement occurred in 61% to 78% of patients. Patients with vesicular dementia responded better than Alzheimer's patients. Of the 110 patients, 81 had one or more adverse effects. Weakness of the legs or walking problems, dizziness, and peripheral edema were the most common side effects (Hwang et al, 2001a).

c) Risperidone is beneficial in the treatment of patients with chronic schizophrenia, compared with conventional neuroleptics (CNs), and these benefits may appear only after longer-term treatment. A randomized, open, parallel, multicenter study compared the long-term (12 months) effectiveness of risperidone with that of CNs. One hundred eighty-four subjects were randomized to receive either risperidone or CN and 165 of them completed the follow-up. Outcome measures were taken at 3, 6, and 12 months and included in the Positive and Negative Syndrome Scale (PANSS) and the Extrapyramidal Symptom Rating Scale. Within this 12-month follow-up, risperidone was found to be superior to CNs in terms of both the average change in score from baseline on the PANSS (p=0.006) and the proportion of good responders (as defined by a 20% decrease in total PANSS scores; p=0.03). For positive symptoms, the effectiveness of the risperidone treatment tended to increase over time and at 12 months, the percentage of good responders in the risperidone group was twice as large as that in the CN group (30% vs 15%; p=0.03). A worsening of akathisia was less frequent in subjects receiving risperidone than in those receiving CNs (p=0.02) (Bouchard et al, 2000).

d) In an open, multicenter trial, risperidone was found to be effective in outpatients (Chouinard et al, 1998). Patients (n=333) with subchronic or chronic schizophrenia treated on an outpatient basis were screened initially while on their current neuroleptic therapy. Their current therapy was discontinued and risperidone started at 2 milligrams (mg) daily and increased to 6 mg daily over 3 days. After 2 weeks the dose could be titrated to a maximum of 10 mg or a minimum of 4 mg. At the end of the 8-week study, the mean risperidone dose was 6.1 mg daily in 244 patients completing the study. The mean total Positive and Negative Syndrome Scale (PANSS) for schizophrenia decreased significantly from 86.3 to 63.6 (p=0.0001). Clinical improvement (20% or more decrease from baseline in total PANSS score) was seen in 85% of patients. The most frequent adverse events reported were insomnia, nausea, headache, somnolence, dizziness, fatigue, anxiety, vomiting, and ejaculation failure/disorder.

e) In an open multicenter trial, risperidone was viewed as an efficacious and well tolerated medication which demonstrated good overall antipsychotic action and above standard improvement in negative symptomology in 254 chronic schizophrenic patients with and without exacerbation who were treated with risperidone 1 to 5 milligrams twice daily for 8 weeks, following an abrupt discontinuation of previous psychotropic medications; significant improvement in the overall Brief Psychiatric Rating Scale was observed at every evaluation time (p less than 0.0001); 73% of patients showed improvement in negative symptomology; a significant improvement was noted in the extrapyramidal symptom scores in all patients, including those who discontinued therapy early (p less than 0.0001); the Clinical Global Impression scores significantly improved for those finishing the study (p less than 0.0001); 98% of those finishing the study tolerated risperidone very well or well; 32% of patients discontinued treatment early, of which 51% dropped out within the first 2 weeks, probably due to adverse reactions stemming from the abrupt discontinuation of all previous psychotropics; the research team now recommends initial overlapping of therapies, especially for those patients previously medicated with sedatives (Phillip, 1997).

c) Combination Therapy

1) Addition of celecoxib to risperidone therapy for patients with an acute exacerbation of schizophrenia resulted in greater improvement than did risperidone therapy alone. In a randomized, double-blind study, 25 patients were given risperidone 2 to 6 milligrams (mg) per day plus celecoxib 400 mg/day and 25 patients were given risperidone plus placebo. Both groups showed improvement in psychopathology over the 5- week study, mainly with reductions in scores on the positive symptoms subscale of the Positive and Negative Syndrome Scale (PANSS) (p=0.006) and on the general psychopathology subscale (p=0.01). Negative symptoms were not significantly affected. Celecoxib therapy resulted in an improvement in total PANSS score relative to that of the placebo group (p=0.05). There were no significant effects of celecoxib on the group-by-time interaction on any of the subscales, although a trend favoring celecoxib was evident on all subscales. The main influence of celecoxib occurred in weeks 2 to 4, resulting in earlier improvement. The use of biperiden for treating side effects of risperidone was not significantly different for the 2 groups. The use of benzodiazepines for treating anxiety and agitation appeared less in the celecoxib group, but the difference for the 2 groups was not statistically significant. Side effects of celecoxib were not observed (Muller et al, 2002).

2) In an open trial, risperidone added to clozapine was well tolerated and produced significant reductions of symptoms after 4 weeks as measured by the Brief Psychiatric Rating Scale (42.2 to 30.3, p=0.0002). Patients enrolled had either persistent psychotic or negative symptoms despite optimal doses of clozapine (n=10) or a maximal clozapine dose limited by significant side effects (n=2). Clozapine doses were kept constant while risperidone doses were increased to a maximum of 6 milligrams (mg) per day. The two agents were well-tolerated, however, complaints included mild akathisia, hypersalivation, and worsening fatigue (Henderson & Goff, 1996). Two other cases of refractory schizophrenic patients responding to combination therapy have been reported (Morera et al, 1999). Doses used were clozapine 300 mg with risperidone 4.5 mg, and clozapine 400 mg with risperidone 6 mg.

3) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorder and schizoaffective disorder, bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorder who were in a manic, hypomanic, depressive, or mixed episode (n=541; 430 completed the study) were given risperidone in combination with lithium, anticonvulsants, and antidepressants to clinical response and tolerability. The average dose of risperidone at the start of the study was 4 milligrams (mg) per day and at the end of the study, 3.9 mg/day. For all patients, scores on the Young Mania Rating Scale (YMRS) were significantly reduced at week 1 and at every point thereafter (p less than 0.001 for all but the subgroup of depressed patients, for whom p was less than 0.05). Mean scores on the YMRS decreased from 25.6 at baseline to 2.4 at 6 months. Likewise, scores on the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced from baseline at all evaluation times (p less than 0.0001), with scores declining from 12.8 at baseline to 4.1 at 6 months. Scores on the Positive and Negative Syndrome Scale (PANSS) declined from 72 at baseline to 40 at 6 months (p less than 0.0001). According to the Clinical Global Impressions scale (CGI), no patients were free from symptoms at baseline and only 5% were rated as "mildly ill." At study endpoint, 44% of patients showed no symptoms of mania or depression and a further 30% were "mildly ill." During the study, 25% of the patients experienced relapses into a mood state different from that at the start of the trial. Scores for extrapyramidal symptoms were lower at the end of study than at baseline (p less than 0.0001). There were significant reductions in dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia subscores. There were no cases of new-emergent tardive dyskinesia. Nonextrapyramidal ad-

verse reactions included increase in weight (2.4% of patients), drowsiness (1.3%), impotence (0.7%), and dysarthria (0.7%). There was a very low incidence of exacerbation mania in the first 6 weeks (1.8%) (Vieta et al, 2001).

d) Refractory

1) Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were considered treatment- refractory, approximately 45% showed sufficient clinical improvement after 3 months of treatment with olanzapine or risperidone to be discharged from the hospital. The 79 patients were not suited to treatment with clozapine either because of medical contraindications or because of unwillingness to submit to the weekly blood drawings. Patients were given olanzapine 10 to 30 milligrams (mg) per day or risperidone 4 to 10 mg/day. Treatments were titrated quickly to the maximum tolerated dose and continued for 3 months. Mean scores on the Brief Psychiatric Rating Scale decreased from 67 to 53 for the olanzapine group (n=32) and from 63 to 52 for the risperidone group (n=47) (p less than 0.001 for both groups). Of the 34 patients who were discharged from the hospital, only 3 required rehospitalization during the 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months (Dinakar et al, 2002).

2) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatment-resistant schizophrenic patients than did haloperidol therapy. In a randomized, double-blind comparison of treatment with risperidone (n=30) and haloperidol (n=29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose and flexible dose regimen. Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from baseline performance at both the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated patients did not change significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on neurocognitive abilities (Green et al, 1997).

e) First-Episode Psychosis

1) Low-dose risperidone significantly delayed the time to relapse and was as effective as haloperidol in treating initial symptoms of first-episode psychosis in a multicenter, double-blind, randomized, controlled flexible-dose study (n=555). Patients diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder based on DSM-IV criteria for no greater than 1 year, had less than 2 hospitalizations for psychosis, had cumulative exposure to antipsychotic agents for less than 12 weeks, and were treated with an antipsychotic agent at the time of enrollment were eligible for the study. They were randomized to receive risperidone (mean age, 25.2 +/- 6.84 years; n=278) or haloperidol (mean age, 25.7 +/- 6.87 years; n=277). Following a 3- to 7-day washout period, with the exception of extremely ill patients, study medication was started at 1 milligram/day (mg/day) that could be increased to 2 mg/day on day 4 and at 1 mg/day increment each week thereafter, to a maximum dose of 4 mg/day. For patients who did not respond sufficiently at 4 mg/day, the dose could be titrated to 8 mg/day as tolerated. Clinical improvement, relapse and extrapyramidal symptoms were assessed weekly during the first 4 weeks, then every 4 weeks for the next 5 months, every 2 months during months 6 through 15, and every 3 months thereafter, until the last enrolled patient completed 2 years of treatment. After 3 months, 73.6% of patients who received risperidone achieved clinical improvement (greater than 20% decrease on the PANSS score) compared to 76.2% of patients in the haloperidol arm (p=0.48). The total PANSS score improved by 21 from baseline of 83.7 in the risperidone arm and improved by 20.6 from baseline of 81.1 in the haloperidol arm (between-arm difference, p=0.49). At study endpoint, 75.5% and 77.8% achieved clinical improvement in the risperidone and haloperidol arms, respectively. The corresponding median

time to clinical improvement was 26 days in the risperidone arm compared with 22 days in the haloperidol arm (p=0.22). Among the 400 subjects who responded, risperidone was associated with fewer relapses (42.1% vs 54.7%) and longer median time from clinical improvement to first relapse (466 days vs 205 days p=0.008) compared with haloperidol. Risperidone was associated with less acute extrapyramidal symptoms (5.09% vs 6.17%; p=0.04). Out of 46 patients expressing suicidal ideation during the study, there were fewer patients (7.2%) and no completed suicides in the risperidone arm compared with 9.4% of the patients and 3 completed suicides in the haloperidol arm. Abnormal prolactin values (males, greater than 18 nanograms/milliliter (mL); females greater than 25 nanograms/mL) were reported in 73.8% of the patients who received risperidone and 49.8% of the patients who received haloperidol. Additionally 14 prolactin-related adverse events (eg, gynecomastia, hyperprolactinemia, galactorrhea) and 1 prolactin-related adverse event (hyperprolactinemia) were reported in the risperidone and haloperidol arms, respectively (Schooler et al, 2005).

2) Treatment with risperidone was as effective as haloperidol in treating negative symptoms among inpatients with first-episode schizophrenia in a 8-week, multicenter, parallel-group, double-blind, randomized, controlled study (n=296); furthermore, risperidone was associated with lower prevalence of extrapyramidal symptoms compared with haloperidol. Patients with acute manifestation of first-episode schizophrenia according to International Classification of Diseases (ICD-10) codes and DSM-IV criteria were randomized to receive either risperidone 2 milligrams/day (mg/day) (mean age, 29.5 +/- 9.5 years; n=148) or haloperidol 2 mg/day (mean age, 30.7 +/- 10 years; n=148) for 8 weeks. If required, the dose could be adjusted by 1 mg/day to 2 mg/day between days 3 and week 1, and weekly thereafter to a maximum of 8 mg/day, not exceeding 4 mg/day by week 2. Additionally, dosage reduction of 1- to 2-mg decrements was permitted for extrapyramidal symptoms. Patients who had received psychotropic medications underwent a 4- to 7-day washout period. The mean dose taken in the risperidone arm was 3.8 +/- 1.5 mg/day compared to 3.7 +/- 1.5 mg/day in the haloperidol arm. More than one-half of the patients in both treatment arms received concomitant lorazepam. The primary efficacy outcome was assessed based on the negative scale of the Positive and Negative Syndrome Scale (PANSS). The Simpson-Angus Scale (SAS) was used to measure prevalence of extrapyramidal symptoms (primary tolerability criterion). At baseline, the mean PANSS negative score was 19.3 +/- 8.2 overall. Based on the intent-to-treat analysis, both treatment arms demonstrated improvement in the mean PANSS negative scores from baseline to week 8 (p less than 0.001), but there was no difference between the risperidone and haloperidol (16 +/- 6.6 vs 15.8 +/- 7.1; estimated difference, -0.13 ; p=0.85). Clinical response rate (defined as a rating of 3 or less in selected PANSS items, 30% or greater reduction from baseline PANSS total score, and a Clinical Global Impression (CGI) severity score of 4 or less) was 49.3% in the risperidone arm and 49.6% in the haloperidol arm. The corresponding time to response was 41 days and 38.6 days in the risperidone and haloperidol arms, respectively (p=0.753). After 8 weeks, the risk of developing extrapyramidal symptoms was higher in the haloperidol arm compared with the risperidone arm (51.5% vs 36.5%; odds ratio, 2.09; p=0.005) (Moller et al, 2008).

3) In a multicenter, double-blind, randomized study (n=183), treatment with risperidone was associated with lower occurrence of extrapyramidal symptoms and was as effective as haloperidol in improving symptom severity of first-episode psychosis. Patients with a diagnosis of provisional schizophreniform disorder or schizophrenia based on the DSM-III-R criteria, without prior treatment, with first psychotic episode that required treatment with an oral antipsychotic agent and who received emergency treatment for a maximum of 3 days for the disorder were eligible for the study. The eligible patients were ran-

domized to receive a starting dose of risperidone 2 milligrams/day (mg/day) (median age 26 years, range 15 to 50 years; n=99) or haloperidol 2 mg/day (median age 24 years, range 16 to 45 years; n=94). The dose could be titrated in increments of 2 mg/day to a maximum of 8 mg twice daily for clinical response or reduced at any time to a minimum of 2 mg/day due to adverse effects. At 6 weeks, 79 patients in the risperidone arm compared to 58 patients in the haloperidol arm completed the study. The mean daily dose was 6.1 mg (range, 2 mg to 16 mg) and 5.6 mg (range 2 mg to 16 mg) in the risperidone and haloperidol arms, respectively. According to the total Positive and Negative Syndrome Scale (PANSS) scores change from baseline, 63% of patients who received risperidone compared to 56% of patients who received haloperidol achieved clinical improvement (p=0.19). The corresponding change in PANSS total score from baseline to endpoint was -30.9 +/-2.5 and -29.3 +/-2.7 in the risperidone and haloperidol arms, respectively. The PANSS scores showed clinical improvement in 74% of patients in the low-dose risperidone arm (6 mg/day or less; n=34) compared to 59% in the high-dose risperidone arm (greater than 6 mg/day; n=62). Shifts from baseline to a worst score for the Extrapyramidal Symptoms Rating Scale (ESRS) was greater in the haloperidol arm compared to the risperidone arm; especially in the hyperkinesia factor (p less than 0.01), and in the total ESRS score (p less than 0.05). Furthermore, 75% and 50% of patients required antiparkinsonian medications in the haloperidol and risperidone arms, respectively. The ESRS shifts were worse in the high-dose risperidone arm compared to the low-dose risperidone arm. The most common nonextrapyramidal adverse events reported included insomnia, agitation, headache, and anxiety. Nine patients withdrew from the study due to adverse events or insufficient efficacy in the risperidone arm compared to 17 patients in the haloperidol arm (p=0.03) (Emsley, 1999).

4) Pediatric:

a) In 2 short-term (6 and 8 weeks), double-blind, controlled trials, oral risperidone, at doses ranging from 1 to 6 milligrams (mg) per day, was effective in the treatment of schizophrenia in adolescents aged 13 to 17 years. Patients met the DSM-IV diagnostic criteria for schizophrenia and were experiencing an acute episode at the time of enrollment. In the first trial (trial 1), patients were randomized to receive either risperidone 1 to 3 mg/day (n=55; mean modal dose, 2.6 mg), risperidone 4 to 6 mg/day (n=51; mean modal dose, 5.3 mg), or placebo (n=54) for 6 weeks. In the second trial (trial 2), patients were randomized to receive either risperidone 0.15 to 0.6 mg/day (n=132; mean modal dose, 0.5 mg) or risperidone 1.5 to 6 mg/day (n=125; mean modal dose, 4 mg). In both studies, risperidone was initiated at 0.5 mg/day and titrated up to the target dose range by approximately day 7 (except for the risperidone 0.15 to 0.6 mg/day group in trial 2, where risperidone was initiated at 0.05 mg/day). Eventually, the dosage was increased to the maximum tolerated dose by day 14. Compared to placebo, a significant reduction occurred in the Positive and Negative Syndrome Scale (PANSS) score in all risperidone dose groups ranging from 1 to 6 mg/day (primary efficacy endpoint). Reductions in the PANSS scores in the 1 to 3 mg/day group were comparable to the 4 to 6 mg/day group in trial 1 and to the 1.5 to 6 mg/day group in trial 2. The 1.5 to 6 mg/day group showed statistically significantly greater efficacy than the 0.15 to 0.6 mg/day group in trial 2, with no additional benefit evident beyond the 3 mg/day dose. Adverse events reported at a higher incidence than placebo in both the risperidone 1 to 3 mg/day and 4 to 6 mg/day dose groups in trial 1 included parkinsonism (13%-16%), tremor (10%-11%), dystonia (9%-18%), dizziness (7%-14%), akathisia (7%-10%), somnolence (12%-24%), and anxiety (6%-7%) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) The results of a small study suggest that risperidone may be effective in the treatment of schizophrenia in adolescent patients. In a prospective, open-label trial, eleven patients (mean age, 17.27 years) with first-episode, early-onset schizophrenia received risperidone (initial, 0.5 milligrams (mg)/day, titrated based on clinical response and adverse effects; mean dose, 3.14 mg/day) for 6 weeks. At 6 weeks, the Positive and Negative Syndrome Scale (PANSS) total score and positive symptoms score were significantly reduced from baseline (p less than 0.01 and p less than 0.0001, respectively), however, a significant reduction was not observed for the negative symptoms score on the PANSS (p=ns). Total scores for the Brief Psychotic Rating Scale were significantly reduced from baseline to week 6 (p less than 0.01). From baseline to endpoint, Clinical Global Impression-Severity (CGI-S) scores decreased by 31.6% (p less than 0.001) and CGI-Improvement scores decreased by 45.5% (p less than 0.0001). The most common adverse events observed were weight gain (72%), somnolence (72%), depression (63%), orthostatic hypertension (45%), emotional indifference (45%), akathisia (36%). Because three patients in this study improved significantly at a dose of only 1 mg/day, the authors suggest that lower initial doses of risperidone should be utilized in adolescents, as compared with adults, in order to minimize the risk of extrapyramidal side effects. Larger, controlled studies are needed to further define the safety and efficacy of risperidone for the treatment of schizophrenia in pediatric patients (Zalsman et al, 2003).

4.5.K Tardive dyskinesia

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Amisulpride

4.6.A.1 Schizophrenia

a) Amisulpride and risperidone therapies were equally effective in the treatment of positive and negative symptoms in Taiwanese patients with schizophrenia. In a randomized, double-blind, multi-center study, schizophrenic patients with productive positive symptoms received oral amisulpride 400 to 800 milligrams (mg) per day (mean dose, 630 mg/day) or risperidone 4 to 8 mg per day (mean dose, 6.88 mg/day) for 6 weeks following a 3-to-6-day washout period. At 6 weeks, patients in both treatment groups showed significant improvements in the Positive and Negative Symptom Scale (PANSS) total score and the three PANSS sub- scale scores, but no significant differences existed between treatment groups. The occurrence of adverse events was also similar between groups. Akathisia (16%), tremor (12%), and constipation (12%) were most commonly reported with risperidone administration while insomnia (17.3%) and constipation (17.3%) were most frequently reported in the amisulpride group (Hwang et al, 2003).

4.6.B Citalopram

4.6.B.1 Dementia - Psychotic disorder

a) Citalopram reduced agitation and psychosis scores in hospitalized patients with dementia, while risperidone reduced psychosis scores but not agitation. In a 12-week, randomized, double-blind study, 103 patients with dementia of varying etiology were enrolled upon admission to an inpatient geropsychiatric unit for agitation and/or psychotic symptoms. Patients were randomized to receive either citalopram (n=53, titrated to a mean dose of 31.1 mg/day) or risperidone (n=50, titrated to a mean dose of 1.35 mg/day). Primary outcomes were symptoms measured with the Neurobehavioral Rating Scale (NBRS) for agitation, and for NBRS for psychosis. Significantly more females were randomized to risperidone (n=38) than to citalopram (n=25; p=0.003). The citalopram group had higher total NBRS scores at baseline than the risperidone group (60.3 vs 52.6; p=0.044), but baseline NBRS-agitation and NBRS-psychosis scores were not significantly different. In the citalopram arm, the mean NBRS-agitation scores improved by -1.26 points (95% confidence intervals (CI), -2.527 to -0.001, p=0.05) and the mean NBRS-psychosis scores improved by -1.9 points (95% CI, -3.165 to -0.639; p less than 0.004). In the risperidone group, the reduction in mean NBRS-agitation score was not significant (-0.73 points; 95% CI -2.145 to 0.676, p=0.3) but the mean NBRS-psychosis score decreased by -2.16 points (95% CI, -3.56 to -0.751; p less than 0.004). There were no significant differences in NBRS score changes between the two groups. The overall dropout rate was 56.3%, with 47.2% of the citalopram patients and 40% of the risperidone patients completing the trial. The primary reasons for dropouts were similar between the two groups, with psychiatric worsening being most common (28 patients), followed by adverse events (13), and other concomitant medical illness (11). Adverse events were measured with the Udvalg for Kuriske Undersogelser (UKU) side effect scale. At the end of the study, the mean UKU score increased in the risperidone group (2.33; 95% CI, 0.588 to 4.065; p less than 0.01), primarily due to sedation. In the citalopram group, the mean UKU score did not differ significantly from baseline, and was significantly lower compared with the risperidone group (-2.61, 95% CI; -4.957 to -0.677; p less than 0.011). The study was not designed with a placebo arm due to ethical concerns (Pollock et al, 2007).

4.6.C Clozapine

4.6.C.1 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. A total of 157 patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional

thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.C.2 Schizophrenia

a) Clozapine was superior to risperidone for improving positive and negative symptoms of schizophrenia in patients with poor previous response to treatment. In a prospective, double-blind study, patients meeting DSM-IV criteria for schizophrenia and having had poor response to previous treatment underwent a single-blind placebo run-in period when all psychotropic and anticholinergic medications were withdrawn. They were then randomly assigned to treatment with clozapine (n=138) or risperidone (n=135). Starting with daily doses of clozapine 12.5 milligrams (mg) and risperidone 1 mg, dosages were titrated over a period of 4 weeks to a minimum of 300 mg/day and 4 mg/day, respectively, and possibly to 600 mg/day and 6 mg/day. Patients unable to tolerate the minimum dose were withdrawn from the study. During the next 8 weeks, doses were adjusted at 2-week intervals within the range of 200 to 900 mg/day for clozapine and 2 to 15 mg/day for risperidone. For patients who completed the 12-week study (n=201), median final daily doses were 600 mg for clozapine and 9 mg for risperidone. Changes in the Positive and Negative Syndrome Scale of the BPRS (Brief Psychiatric Rating Scale) and in the Clinical Global Impression (CBI) scale were significantly greater in the clozapine group than in the risperidone group for the intent-to-treat population (those who received at least one dose of treatment medication and had one post-dose BPRS evaluation) and in the per- protocol population (those who completed the 28-day dose-setting period) (p less than 0.008 for all comparisons). Eighty-six percent of patients in the clozapine per-protocol population and 70% in the risperidone per-protocol population showed 20% or more improvement in the BPRS score (for difference between groups, p less than 0.01). By the end of the study, 94 (76%) patients in the clozapine group and 81 (64%) in the risperidone group no longer met the severity of psychopathology inclusion criteria (p less than 0.05). Extrapyramidal symptoms occurred significantly less frequently in the clozapine group than in the risperidone group (13% vs 28%, p=0.008). However, convulsions, dizziness, sialorrhea, tachycardia, and somnolence occurred significantly more frequently among those receiving clozapine. No case of agranulocytosis was observed during the study. Granulocytopenia occurred with low incidence in both groups (1% clozapine, 2% risperidone). Low neutrophil count was significantly more frequent among risperidone-treated patients (3% vs 11%, p less than 0.01). Hypotension occurred more frequently among risperidone-treated patients (p less than 0.01). Weight gain was significantly greater for the clozapine group (2.4 kilograms vs 0.2 kilograms; p less than 0.002) (Azorin et al, 2001).

4.6.C.3) Adverse Effects

a) Adverse effects and death were more commonly reported as the reasons for the discontinuation of clozapine while ineffectiveness was more often reported as the reason for discontinuation of risperidone (long-acting injection) in a retrospective, phase 3 study (n=322). Patients with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders who received clozapine (n=161), and had mean duration of therapy of 12.3 +/- 18.6 months (range, 0.25 to 100 months; median, 3 months) were matched by age (mean age, 40 +/- 12.6 years; range, 18 to 83 years) and gender at discontinuation to patients who discontinued risperidone long-acting injection (n=161). The risperidone patients (mean age, 39.9 +/- 13.1 years , range 18 to 83 years) were matched without knowledge of the reason for discontinuation of therapy (mean duration of therapy of 5.9 +/- 8.7 months; range, 0.5 to 46 months; me-

dian, 3 months). The reasons for discontinuation differed significantly between clozapine and risperidone injection; additionally, death as reason for discontinuation was significantly more common with clozapine (13%) vs risperidone injection (1.9%) (Taylor et al, 2009).

Reasons for Discontinuation: Clozapine vs RisperidoneReason
Clozapine (n=161) n (%)
Risperidone (n=161) n (%)
OR (95% CI)
p value
Patient's decision
77 (47.8)
64 (39.7)
1.41 (0.89 to 2.21)
0.139
Adverse effects
57 (35.4)
32 (19.9)
2.19 (1.31 to 3.67)
0.0023
Ineffectiveness
3 (1.9)
59 (36.6)
0.034 (0.01 to 0.14)
less than 0.0001
Death
21 (13)
3 (1.9)
7 (2.09 to 23.5)
0.0003
Other
3 (1.9)
3 (1.9)
-
-

The cause of death reported in clozapine patients (mean age, 49.2 +/- 14.5 years, range 30 to 83 years) included: pneumonia (n=5), lung carcinoma (n=3), other carcinoma (n=2), myocardial infarction (n=2), cerebrovascular accident (n=2), clozapine overdose (n=2), gastrointestinal hemorrhage (n=1), cardiac arrest (n=1), left ventricular failure (n=1), asphyxia during restraint (n=1) and sepsis (n=1). There was no incidence of neutropenia or agranulocytosis at the time of death in any of the patients. The cause of death in the risperidone patients included: myocardial infarction (n=1), left ventricular failure (n=1) and sudden unexplained death (n=1). The mortality rate for clozapine patients was 8.5 per 1000 patient-years (95% CI, 5.53 to 13.07) vs 5.3 per 1000 patient-years (95% CI, 1.7 to 16.61) (Taylor et al, 2009).

b) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of pancreatitis than patients receiving a conventional antipsychotic medication. In a retrospective, phar-

macovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003).
c) Clozapine was associated with fewer extrapyramidal side effects (EPS) than was risperidone (Miller et al, 1998). Outpatients receiving stable doses of clozapine (n=41), risperidone (n=23), or conventional antipsychotics (n=42) were screened for EPS. Utilizing the Barnes Akathisia Scale, akathisia was noted in 7.3% of clozapine patients, 13% of risperidone patients, and 23.8% of conventional antipsychotic users. From the Simpson-Angus scale, rigidity and cogwheeling were noted in 4.9% and 2.4% of clozapine patients, 17.4% and 17.4% of risperidone patients, and 35.7% and 26.2% of conventional antipsychotic users, respectively. However, salivation was noted in 36.6% of clozapine patients, 8.7% of risperidone patients, and 4.8% of conventional antipsychotic users.
d) Insomnia and extrapyramidal side effects were more common with risperidone, and sedation and weight gain were more common with clozapine in a single-blind, crossover pilot study of the side effect profiles of the 2 drugs (Daniel et al, 1996). Twenty outpatients with schizophrenia or schizoaffective disorder were randomized to each drug for 6 weeks separated by a 1-week tapering-off period before crossover. The mean doses at week 6 were 6.1 milligrams/day (range 1 to 10 mg/d) of risperidone and 375 milligrams/day (range 75 to 800 mg/d) of clozapine. Three patients dropped out of the study; there was no significant difference in therapeutic effect between the 2 treatment groups. Mean body weight was greater (p less than 0.005) and sleepiness and lack of alertness were reported more often after the clozapine treatment phase. Restlessness and insomnia were more frequent complaints after the risperidone phase. A longer, double-blind study with a large sample of patients is needed to further elucidate the therapeutic differences and side effect profiles of these 2 drugs.

4.6.D Haloperidol

4.6.D.1 Behavioral syndrome - Dementia

a) In a randomized, double-blind, crossover study, elderly residents treated with a mean risperidone dose of 0.8 mg/day showed significantly greater improvement in the severity and frequency of behavioral and psychological symptoms of dementia (BPSD) compared with patients receiving a mean haloperidol dose of 0.83 mg/day, and risperidone-treated patients experienced fewer extrapyramidal symptoms (EPS). In this 18-week study, dementia patients (n=120) with behavioral disturbances residing in a single long-term care institution in Korea (mean age 80.9 years; Alzheimer disease, 65.8%; vascular dementia, 28.3%; mixed dementia, 5.8%; female, 82%), were randomly assigned to risperidone-first or haloperidol-first and then crossed over to the alternate treatment. Each 8-week treatment period was preceded by a 1-week washout period. Patients were not permitted to take concomitant antidepressants, antipsychotics, and mood stabilizing agents. Lorazepam was allowed during the first 4 weeks if limited to 4 days/week. Study drugs were started at 0.5 mg at bedtime and adjusted upward in increments of 0.5 mg once every 4 or more days to a maximum of 1.5 mg/day. Dosage adjustments were made by 1 of 2 psychiatrists blinded to the study drug and not involved in rating behaviors. Drug dosage could be titrated downward at anytime by any

amount. The Korean versions of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD-K), the Cohen-Mansfield Agitation Inventory (CMAI-K), and the Clinical Global Impression of Change scale (CGI-C) were used to assess efficacy, and the Extrapyramidal Symptom Rating Scale (ESRS) was used to assess tolerability. A total of 114 (95%) of patients completed the study. Treatment with both risperidone and haloperidol demonstrated significant reductions from baseline in the total scores on the BEHAVE-AD-K and CMAI-K; however, treatment with risperidone demonstrated superiority to haloperidol for the total score on BEHAVE-AD-K and its subscales of aggressiveness, anxieties and phobias, and for the total score on CMAI-K and its subscales of aggressive behavior, physically non-aggressive behavior, and verbally agitated behavior. The BEHAVE-AD-K total score improved from 19.2 to 12 with risperidone compared with an improvement from 19.2 to 14.5 with haloperidol (between-group difference p=0.004). The CMAI-K total score improved from 89.3 to 75.1 with risperidone compared with an improvement form 89.4 to 83.5 with haloperidol (between-group difference p less than 0.0001). On the ESRS and its 3 subscales of parkinsonism, expressive automatic movements, dystonia, or dyskinetic movements, risperidone was not associated with significant increases in EPS, while haloperidol was associated with a significant worsening. Somnolence, insomnia, and sialorrhea were reported more frequently during treatment with haloperidol (Suh et al, 2004).

b) Some Chinese patients with dementia, who were non-responders to haloperidol, responded to risperidone with decreased behavioral disturbances and improved mood. Thirty-five Chinese patients who had shown insufficient response to an 8- week trial with haloperidol (i.e., having a total score of more than 10 on the Brief Psychiatric Rating Scale (BPRS) at the end of 8 weeks) (typical dose 1 gram/day) were switched abruptly from haloperidol to risperidone 0.5 milligrams (mg) at bedtime for weeks 1 to 4 and then (if tolerated) to 1 mg at bedtime for weeks 5 to 12. At week 13, the regimen was shifted again to haloperidol at the dose used in the earlier trial. Twenty-nine patients completed the trial. Sixteen patients responded (defined as 25% decrease in the BPRS score) by the end of the risperidone trial. After haloperidol resumption, the mean BPRS score stayed the same, but the number of responders decreased to 15. Patients with vascular dementia were almost 6 times more likely to respond to risperidone than patients with Alzheimer's disease. Mean scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale decreased (6.1 at baseline to 1.9 at 12 weeks of risperidone treatment) and increased after switching back to haloperidol (to 2.4 after 4 weeks of haloperidol). Thirty- four of the 35 patients tolerated both doses of risperidone and haloperidol 1 mg/day. One patient experienced moderate rigidity with risperidone 1 mg/day, which was relieved by reduction of the dose to 0.5 mg/day. Patients experienced fewer extrapyramidal symptoms with risperidone than with haloperidol (Lane et al, 2002).

c) Both risperidone and haloperidol in low doses reduced the severity and frequency of behavioral and psychological symptoms of elderly Chinese patients with dementia. Risperidone was associated with less severe exacerbation of extrapyramidal symptoms (EPS). In a randomized, double-blind trial, 55 elderly Chinese patients (mean age 80 years) with Alzheimer's dementia or vascular dementia and with behavioral disturbance, were given either risperidone or haloperidol for 12 weeks after a 2-week washout period for elimination of psychotropic and antiparkinsonian drugs. The starting dose for both treatment drugs was 0.5 milligrams (mg) at night; doses were adjusted individually in increments of 0.5 mg no faster than every other day, to a maximum of 2 mg/day. At 12 weeks, the mean daily dose of haloperidol was 0.9 mg, and that of risperidone, 0.85 mg. Significant improvements on the Cohen- Mansfield Agitation Inventory (CMAI) were evident in both groups (haloperidol, p less than 0.001; risperidone, p=0.002). Significant reduction was seen at 2 weeks in the risperidone group and at 4 weeks in the haloperidol group. With

risperidone, there were significant improvements in scores for psychosis, activity disturbances, aggressiveness and diurnal rhythm disturbances, whereas with haloperidol, improvement in only the aggressiveness score reached statistical significance. However, none of the measures showed a significant difference between the treatment groups. With haloperidol, there was a significant worsening of EPS (p less than 0.001), whereas, with risperidone, EPS scores were only modestly worsened. Final EPS scores were significantly higher for haloperidol (p=0.001) (Chan et al, 2001).

4.6.D.2 Bipolar I disorder

a) In a 12-week, randomized, double-blind, multicenter trial (n=435) among patients with acute mania of bipolar disorder, both risperidone and haloperidol were more effective than placebo in improving Young Mania Rating Scale (YMRS) total scores. Adult patients who met DSM-IV criteria for bipolar I disorder and were voluntarily hospitalized for a current manic episode were eligible; all patients had a YMRS score of at least 20 and a Montgomery-Asberg Depression Rating Scale (MADRS) of 20 or less. After a 3-day washout period, patients were randomized to a 3-week treatment titration phase of risperidone (n=153), haloperidol (n=144), or placebo (n=138); followed by a 9-week continuation phase at a stable dose. The initial risperidone dose was 2 milligrams (mg) orally once daily, adjusted in 1-mg increments or decrements for a target dose of 1 to 6 mg/day by day 5 (mean modal dose at study end, 4.1 +/- 1.8 mg/day). Haloperidol was initiated at 4 mg orally daily, adjusted in 2-mg increments or decrements for a target dose of 2 to 12 mg/day by day 5 (mean modal dose at study end, 7.4 +/- 3.7 mg/day). Lorazepam or chloral hydrate were allowed to manage agitation, irritability, restlessness, insomnia, or hostility during the first 10 days of the study. At baseline, the YMRS total score was 32.1, 31.3 and 31.5 in the risperidone, haloperidol and placebo arm, respectively. Based on the analysis among patients who received at least one dose of study medication, both risperidone (-15.1 +/- 10.3) and haloperidol (-13.9 +/- 10.3) showed significant improvement in the mean YMRS total scores compared with placebo (-9.4 +/- 11; both p less than 0.001 vs placebo) by wk 3 of treatment; and there was not a significant difference between the risperidone group and the haloperidol group. The mean 12-week change in total YMRS scores from baseline was -20.7 +/- 13 in the risperidone compared with -18.4 +/- 12 in the haloperidol group (95% confidence interval, -3.94 to 1.03). The most common adverse effects were extrapyramidal disorder (risperidone, 24%; haloperidol, 43%, placebo, 9%), somnolence (risperidone, 10%; haloperidol, 6%, placebo, 1%), and hyperkinesia (risperidone, 10%; haloperidol, 19%; placebo, 3%) (Smulevich et al, 2005).

4.6.D.3 First episode psychosis - Schizophrenia

a) Low-dose risperidone significantly delayed the time to relapse and was as effective as haloperidol in treating initial symptoms of first-episode psychosis in a multicenter, double-blind, randomized, controlled flexible-dose study (n=555). Patients diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder based on DSM-IV criteria for no greater than 1 year, had less than 2 hospitalizations for psychosis, had cumulative exposure to antipsychotic agents for less than 12 weeks, and were treated with an antipsychotic agent at the time of enrollment were eligible for the study. They were randomized to receive risperidone (mean age, 25.2 +/- 6.84 years; n=278) or haloperidol (mean age, 25.7 +/- 6.87 years; n=277). Following a 3- to 7-day washout period, with the exception of extremely ill patients, study med-

ication was started at 1 milligram/day (mg/day) that could be increased to 2 mg/day on day 4 and at 1 mg/day increment each week thereafter, to a maximum dose of 4 mg/day. For patients who did not respond sufficiently at 4 mg/day, the dose could be titrated to 8 mg/day as tolerated. Clinical improvement, relapse and extrapyramidal symptoms were assessed weekly during the first 4 weeks, then every 4 weeks for the next 5 months, every 2 months during months 6 through 15, and every 3 months thereafter, until the last enrolled patient completed 2 years of treatment. After 3 months, 73.6% of patients who received risperidone achieved clinical improvement (greater than 20% decrease on the PANSS score) compared to 76.2% of patients in the haloperidol arm (p=0.48). The total PANSS score improved by 21 from baseline of 83.7 in the risperidone arm and improved by 20.6 from baseline of 81.1 in the haloperidol arm (between-arm difference, p=0.49). At study endpoint, 75.5% and 77.8% achieved clinical improvement in the risperidone and haloperidol arms, respectively. The corresponding median time to clinical improvement was 26 days in the risperidone arm compared with 22 days in the haloperidol arm (p=0.22). Among the 400 subjects who responded, risperidone was associated with fewer relapses (42.1% vs 54.7%) and longer median time from clinical improvement to first relapse (466 days vs 205 days p=0.008) compared with haloperidol. Risperidone was associated with less acute extrapyramidal symptoms (5.09% vs 6.17%; p=0.04). Out of 46 patients expressing suicidal ideation during the study, there were fewer patients (7.2%) and no completed suicides in the risperidone arm compared with 9.4% of the patients and 3 completed suicides in the haloperidol arm. Abnormal prolactin values (males, greater than 18 nanograms/milliliter (mL); females greater than 25 nanograms/mL) were reported in 73.8% of the patients who received risperidone and 49.8% of the patients who received haloperidol. Additionally 14 prolactin-related adverse events (eg, gynecomastia, hyperprolactinemia, galactorrhea) and 1 prolactin-related adverse event (hyperprolactinemia) were reported in the risperidone and haloperidol arms, respectively (Schooler et al, 2005).

b) Treatment with risperidone was as effective as haloperidol in treating negative symptoms among inpatients with first-episode schizophrenia in a 8-week, multicenter, parallel-group, double-blind, randomized, controlled study (n=296); furthermore, risperidone was associated with lower prevalence of extrapyramidal symptoms compared with haloperidol. Patients with acute manifestation of first-episode schizophrenia according to International Classification of Diseases (ICD-10) codes and DSM-IV criteria were randomized to receive either risperidone 2 milligrams/day (mg/day) (mean age, 29.5 +/- 9.5 years; n=148) or haloperidol 2 mg/day (mean age, 30.7 +/- 10 years; n=148) for 8 weeks. If required, the dose could be adjusted by 1 mg/day to 2 mg/day between days 3 and week 1, and weekly thereafter to a maximum of 8 mg/day, not exceeding 4 mg/day by week 2. Additionally, dosage reduction of 1- to 2-mg decrements was permitted for extrapyramidal symptoms. Patients who had received psychotropic medications underwent a 4- to 7-day washout period. The mean dose taken in the risperidone arm was 3.8 +/- 1.5 mg/day compared to 3.7 +/- 1.5 mg/day in the haloperidol arm. More than one-half of the patients in both treatment arms received concomitant lorazepam. The primary efficacy outcome was assessed based on the negative scale of the Positive and Negative Syndrome Scale (PANSS). The Simpson-Angus Scale (SAS) was used to measure prevalence of extrapyramidal symptoms (primary tolerability criterion). At baseline, the mean PANSS negative score was 19.3 +/- 8.2 overall. Based on the intent-to-treat analysis, both treatment arms demonstrated improvement in the mean PANSS negative scores from baseline to week 8 (p less than 0.001), but there was no difference between the risperidone and haloperidol (16 +/- 6.6 vs 15.8 +/- 7.1; estimated difference, -0.13 ; p=0.85). Clinical response rate (defined as a rating of 3 or less in selected PANSS items, 30% or greater reduction from baseline PANSS total score, and a Clinical Global Impres-

sion (CGI) severity score of 4 or less) was 49.3% in the risperidone arm and 49.6% in the haloperidol arm. The corresponding time to response was 41 days and 38.6 days in the risperidone and haloperidol arms, respectively (p=0.753). After 8 weeks, the risk of developing extrapyramidal symptoms was higher in the haloperidol arm compared with the risperidone arm (51.5% vs 36.5%; odds ratio, 2.09; p=0.005) (Moller et al, 2008).

c) In a multicenter, double-blind, randomized study (n=183), treatment with risperidone was associated with lower occurrence of extrapyramidal symptoms and was as effective as haloperidol in improving symptom severity of first-episode psychosis. Patients with a diagnosis of provisional schizophreniform disorder or schizophrenia based on the DSM-III-R criteria, without prior treatment, with first psychotic episode that required treatment with an oral antipsychotic agent and who received emergency treatment for a maximum of 3 days for the disorder were eligible for the study. The eligible patients were randomized to receive a starting dose of risperidone 2 milligrams/day (mg/day) (median age 26 years, range 15 to 50 years; n=99) or haloperidol 2 mg/day (median age 24 years, range 16 to 45 years; n=94). The dose could be titrated in increments of 2 mg/day to a maximum of 8 mg twice daily for clinical response or reduced at any time to a minimum of 2 mg/day due to adverse effects. At 6 weeks, 79 patients in the risperidone arm compared to 58 patients in the haloperidol arm completed the study. The mean daily dose was 6.1 mg (range, 2 mg to 16 mg) and 5.6 mg (range 2 mg to 16 mg) in the risperidone and haloperidol arms, respectively. According to the total Positive and Negative Syndrome Scale (PANSS) scores change from baseline, 63% of patients who received risperidone compared to 56% of patients who received haloperidol achieved clinical improvement (p=0.19). The corresponding change in PANSS total score from baseline to endpoint was -30.9 +/-2.5 and -29.3 +/-2.7 in the risperidone and haloperidol arms, respectively. The PANSS scores showed clinical improvement in 74% of patients in the low-dose risperidone arm (6 mg/day or less; n=34) compared to 59% in the high-dose risperidone arm (greater than 6 mg/day; n=62). Shifts from baseline to a worst score for the Extrapyramidal Symptoms Rating Scale (ESRS) was greater in the haloperidol arm compared to the risperidone arm; especially in the hyperkinesia factor (p less than 0.01), and in the total ESRS score (p less than 0.05). Furthermore, 75% and 50% of patients required antiparkinsonian medications in the haloperidol and risperidone arms, respectively. The ESRS shifts were worse in the high-dose risperidone arm compared to the low-dose risperidone arm. The most common nonextrapyramidal adverse events reported included insomnia, agitation, headache, and anxiety. Nine patients withdrew from the study due to adverse events or insufficient efficacy in the risperidone arm compared to 17 patients in the haloperidol arm (p=0.03) (Emsley, 1999).

4.6.D.4 Schizophrenia

a) In an 8-week, multicenter, randomized, double-blind study of patients with chronic schizophrenia (n=1362), clinical improvement based on Positive and Negative Syndrome Scale for Schizophrenia (PANSS) scores was not significantly different with any of 5 doses of risperidone or haloperidol, but extrapyramidal symptoms were lower with risperidone doses of 12 mg and less compared with haloperidol. Patients who met DSM-III-R criteria for schizophrenic disorder and had a total PANSS score between 60 and 120 were randomized to risperidone with a daily dose of 1 milligram (mg; n=229; mean age, 38.4 years), 4 mg (n=227; mean age, 38.1 years), 8 mg (n=230; mean age 37.6 years), 12 mg (n=226; mean age 37.9 years), or 16 mg (n=224; mean age 38.5 years) or to haloperidol 10 mg daily (n=226; mean age 38.1 years). After a placebo washout period in which all psychotropic and antiparkinson agents were withdrawn

(mean duration, 6.5 days; 6 days or less in 25% of patients with acute psychotic exacerbations), study medications were administered in divided doses twice daily to achieve target doses by the end of the first week; and target doses were maintained for the remaining 7 weeks. Lorazepam, oxazepam, or temazepam was allowed for sedation, and biperiden or procyclidine was allowed for extrapyramidal symptoms (EPS). Clinical improvement, a 20% or greater reduction in baseline total PANSS score (primary outcome), was not statistically significantly different in any of the treatment groups: risperidone 1 mg (54.4%, 95% confidence interval (CI), 47.7% to 61%), risperidone 4 mg (63.4%; 95% CI, 56.8% to 69.7%), risperidone 8 mg (65.8%; 95% CI, 59.2% to 71.9%), risperidone 12 mg (58.2%; 95% CI, 51.5% to 64.7%), risperidone 16 mg (60.5%; 95% CI, 53.8% to 67%), and haloperidol 10 mg (58.7%; 95% CI, 52% to 65.3%). There were also no significant differences between any of the risperidone groups and the haloperidol group in mean change from baseline in PANSS total scores or total Brief Psychiatric Rating Scale (BPRS) scores. Compared with baseline total Extrapyramidal Symptom Rating Scale (ESRS) scores, the mean shift of the maximum total ESRS score was significantly lower in the risperidone 1 mg (0.8 +/- 0.19), 4 mg (0.9 +/- 0.25), 8 mg (1.6 +/- 0.26), and 12 mg (1.9 +/- 0.25) groups than in the haloperidol group (2.7 +/- 0.27; p less than 0.05 for all comparisons) (Peuskens, 1995).

b) Results of a multicenter, randomized, double blind trial assessing cognitive function in patients experiencing early episodes of schizophrenia or a related psychosis demonstrated that overall improvement in cognitive functioning was superior with risperidone than with haloperidol. Patients (n=533) were randomized to receive either risperidone or haloperidol on a one-to-one randomization basis for a period of 2 years or more. There were no significant differences in sex, race or ethnicity, age, diagnosis, or previous neuroleptic treatment in either group. Dosing strategies were equivalent in both groups where patients were started on 1 milligram per day (mg/day) of the study drug and titrated up to 4 mg/day, or in some cases, to a maximum of 8 mg/day. Patients in the risperidone group received the trial medication (mean modal total dose 3.3 mg/day) for an average of 192 days while patients in the haloperidol group received treatment (mean modal total dose 2.9 mg/day) for an average of 218 days. Cognitive assessments, performed at several different follow-up intervals, included examinations of verbal and visuospatial episodic memory, vigilance, executive functioning, processing speed, and verbal fluency. An intention-to-treat analysis conducted with a focus on the 3-month assessment revealed that there was significant improvement from baseline in the risperidone group (n=169) for all measures except category verbal fluency and letter verbal fluency (p less than 0.05). In the haloperidol group (n=169), statistically significant improvements from baseline were noted in episodic memory, vigilance, and visuomotor speed but not in executive functioning and verbal fluency. Comparison between the two groups showed that, after 3 months of treatment, the risperidone group was significantly more beneficial than the haloperidol group on the composite measure of cognitive functioning. In addition, cognitive improvement as a result of treatment with risperidone was not affected by changes in symptoms. Risperidone therapy also proved to be superior than haloperidol in relapse prevention and extrapyramidal side effects (Harvey et al, 2005).

c) The risk of relapse of schizophrenia was significantly less with long-term treatment with risperidone than with haloperidol. In a randomized, double-blind study, 365 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in a stable condition were given flexible doses of either risperidone or haloperidol. The trial was continued until the last enrolled patient had completed one year of treatment. Means of modal daily doses were 4.9 milligrams (mg) for risperidone and 11.7 mg for haloperidol. At the end of the study, 25% of the risperidone group and 40% of the haloperidol group had relapsed. The risk of relapse was significantly higher among patients assigned to haloperidol (risk ratio

1.93; p less than 0.001). The risk of premature discontinuation was greater for the haloperidol group than for the risperidone group (risk ratio 1.52), mainly because of relapse. Median duration of treatment for the risperidone group was 364 days and for the haloperidol group, 238 days (p=0.02). The subtypes of relapse (psychiatric hospitalization, clinical deterioration, increase in level of care, suicidal or homicidal ideation) were similar in the 2 groups. In the risperidone group, there were improvements from baseline in positive and negative symptoms, disorganized thoughts, and anxiety- depression, whereas symptoms were not improved with haloperidol. The severity of extrapyramidal symptoms was reduced from baseline in the risperidone group and increased in the haloperidol group. Differences between the groups were significant (p less than 0.02 for total score on the Extrapyramidal Symptom Rating Scale). The most frequent adverse events were somnolence (14% with risperidone and 25% with haloperidol), agitation (10% and 18% respectively), and hyperkinesia (5% and 20%, respectively). Those taking risperidone had a mean increase in body weight of 2.3 kilograms (kg) and those taking haloperidol had a mean decrease of 0.73 kg (p less than 0.001) (Csernansky et al, 2002).

d) Results of a subanalysis of data from the multinational, double-blind, randomized, parallel-group trial reported that the reduction in negative symptoms was significantly better in patients receiving risperidone 16 mg/day than haloperidol 10 mg/day (p less than 0.05). Patients with chronic schizophrenia (n=169) were treated with risperidone 1 mg, 4 mg, 8 mg, 12 mg, or 16 mg, or haloperidol 10 mg/day for 8 weeks. Improvement was noted in each group. Risperidone onset was faster than haloperidol. An analysis of the Positive and Negative Syndrome Scale cluster scores revealed significantly greater improvement in the risperidone-treated patients than in the haloperidol group on 2 clusters: activity and anxiety/depression (p less than 0.05) (Moller et al, 1997).

e) Risperidone was more effective than haloperidol in a double-blind, placebo-controlled, multicenter study. A total of 388 schizophrenic patients were randomly assigned to receive 4 fixed doses of risperidone (2, 6, 10, and 16 milligrams/day, on a BID schedule), haloperidol 20 milligrams daily or placebo for 8 weeks (Marder & Meibach, 1994). Patients receiving risperidone 6 to 16 milligrams showed statistically greater improvement than placebo or haloperidol in Clinical Global Impression (CGI) and total Positive and Negative Syndrome Scale (PANSS) scores. Of the four doses studied, the 6, 10, and 16 milligram doses were all effective with the 6 milligram dose being the most effective. Similar results have been reported (Chouinard et al, 1993; Marder, 1992).

f) In an 8-week, double-blind study, 1362 schizophrenic patients were randomly assigned to receive either risperidone 1, 4, 8, 12, 16 milligrams/day, on a BID schedule, or haloperidol 10 milligrams daily. Significantly greater improvement in Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total score, the PANSS General Psychopathology subscale, the BPRS Activity and Anxiety/Depression cluster, was observed in the risperidone 4 milligram and 8 milligram groups versus the haloperidol-treated patients. In addition, a greater percentage of patients treated with risperidone 4 and 8 milligrams achieved clinical improvement on the PANSS and BPRS as compared with the haloperidol group (Muller-Spahn, 1992).

4.6.D.5) Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of pancreatitis than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or

haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003a). **b)** Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidone caused few or no extrapyramidal symptoms. Mean changes in Extrapyramidal Symptom Rating Scale (ESRS) scores from baseline to worst score were significantly lower in each risperidone group than the haloperidol group (p less than 0.001) (Simpson & Lindenmayer, 1997).

4.6.E Lithium

4.6.E.1 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperidol in mania and found comparable results with risperidone. Patients (n=45) were assigned to take risperidone (as monotherapy), dosed at 6 mg per day, haloperidol at 10mg per day, or 800 to 1000 mg daily of lithium. All 3 groups showed a similar improvement on Brief Psychiatric Rating Scale and Young Mania Rating Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worsen in any of the risperidone treated patients (Segal et al, 1998).

4.6.F Olanzapine

4.6.F.1 Agitation, acute - Psychotic disorder

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvements on the Excited Component for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated for acute psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased over time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated measures of analysis of PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of treatment or in the interaction of treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in the olanzapine ODT group compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences between the treatment groups for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.6.F.2 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F.3 Schizophrenia

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in elderly patients. In an international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventional antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EPS symptoms was reduced in both groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean QTc changes were not considered clinically relevant (Jeste et al, 2003).

b) In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder. One hundred fifty patients were randomized to either olanzapine (10 to 20 milligrams per day (mg/d) (n=75) or risperidone (4 to 12 mg/day) (n=75) treatment for a period of 28 weeks. During the study, olanzapine- treated patients were significantly more likely to maintain a therapeutic response throughout the course of therapy than risperidone- treated patients (p=0.048). However, the proportion of patients who responded to treatment

was not significantly different between groups. Overall, the incidence of side effects was similar between groups, but significantly more risperidone-treated patients required an anticholinergic to control treatment-emergent extrapyramidal effects than did those receiving olanzapine (45% vs 25%, p=0.016) (Edgell et al, 2000).

c) Olanzapine and risperidone were equally efficacious in treating patients with first-episode schizophrenia spectrum disorders; however, both medications caused substantial rapid weight gain with significantly more weight gained recorded by olanzapine-treated patients. In this open-label randomized study, patients (mean age 23.3 years; 70% male) with first-episode schizophrenia (75%), schizophreniform disorder (17%), or schizoaffective disorder (8%) and less than 12 weeks of lifetime antipsychotic medication treatment were randomly assigned to treatment with olanzapine (2.5 to 20 mg per day) or risperdal (1 to 6 mg per day). Data represents response rates at 4 months in an ongoing study assessing first-episode patients over 3 years. At study entry, patients reported substantial positive symptoms and less pronounced negative symptoms, with a slightly greater than 2 year history of psychotic symptoms. Data analysis included all patients taking 1 dose of medication following randomization. Mean modal doses were 11.8 mg/day and 3.9 mg/day for olanzapine and risperidone, respectively. Response rates were similar with olanzapine (43.7%; 95% CI, 28.8% to 58.6%) and risperidone (54.3%; CI, 39.9% to 68.7%); and mean time to response was 10.9 weeks and 10.4 weeks with olanzapine-treated and risperidone-treated patients, respectively. Mean length of time that patients maintained their responder status was 6.6 weeks (95% CI, 5.6 to 7.7) with olanzapine and 9.5 weeks with risperidone (95% CI, 8.6 to 10.4). The study may have lacked adequate power to detect a difference between these 2 antipsychotics as power was based on recruitment of 130 patients which was not achieved. Weight gain was a significant adverse event in both treatment groups. Mean weight at study entry for all subjects was 70.1 kg. At 4 months, the increase in weight relative to baseline was 17.3% (95% CI, 14.2% to 20.5%) and 11.3% (95% CI, 8.4% to 14.3%) in olanzapine-treated and risperidone-treated patients, respectively. Body mass index at baseline and at 4 months was 24.3 (95% CI, 22.8 to 25.7) and 28.2 (95% CI, 26.7 to 29.7) in olanzapine-treated patients; and 23.9 (95% CI, 22.5 to 25.3) and 26.7 (95% CI, 25.2 to 28.2) in risperidone-treated patients. Differences in extrapyramidal symptom severity scores and prescription-use for extrapyramidal symptoms and akathisia favored olanzapine over risperidone, but did not reach a level of statistical significance (Robinson et al, 2006).

d) Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment of schizophrenic symptomology. In an international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder, the olanzapine group had a significantly better overall response rate (greater than 40% decrease in the Positive and Negative syndrome Scale) and was significantly superior to risperidone in the treatment of negative symptomatology. Based on the Kaplan-Meier survival curves, a significantly greater number of the olanzapine patients maintained their response at 28 weeks compared to the risperidone group. Overall adverse reactions were significantly less with olanzapine, in particular extrapyramidal side effects, hyperprolactinemia and sexual dysfunction, with the exception of weight gain; suicide attempts occurred significantly less in the olanzapine group (Tran et al, 1997). The use of possibly unequivalent doses in this study has been subsequently criticized (Schooler, 1998; Gheuens & Grebb, 1998).

4.6.F.4) Adverse Effects

a) BLOOD GLUCOSE ELEVATION: In a retrospective, multicenter, nonrandomized, cohort analysis of

outpatient prescription records for antipsychotics (risperidone, olanzapine and typical antipsychotics (chlorpromazine, fluphenazine, haloperidol, and perphenazine as a single group)) during a 5-year period, patients treated with olanzapine had a greater risk of developing blood glucose elevations than those treated with risperidone. Patients selected for inclusion in the study filled at least 2 prescriptions within a 60-day period and had at least 1 plasma glucose reading both before and during administration of the medication (n=5238). Patients were excluded in a stepwise fashion in identify patients with true treatment-emergent blood glucose elevation. Based on 113 patients who had no prior glucose readings equal to or above 160 mg/dL before medication exposure, the odds ratio (OR) of developing at least one random blood glucose readings of 200 mg/dL was 0.78 (95% confidence interval (CI), 0.4 to 1.49; p=0.48) for risperidone relative to typical antipsychotics, and 1.66 (95% CI, 0.89 to 3.09; p=0.11) for olanzapine relative to typical antipsychotics. However, the difference was significant between olanzapine and risperidone (OR, 2.14; 95% CI, 1.31 to 3.49; p=0.003). Covariates of age, sex, ethnicity, psychiatric diagnosis and the number of glucose readings were taken into consideration (Duncan et al, 2007).

b) EXTRAPYRAMIDAL SYMPTOMS: Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine- and clozapine-treated patients. As compared with olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

c) PANCREATITIS: The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of pancreatitis than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol.

In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003b).

4.6.G Paliperidone Palmitate

4.6.G.1 Schizophrenia

a) In a 13-week, multicenter, randomized, double-blind, double-dummy, active-controlled, noninferiority study, paliperidone palmitate injection once monthly without oral supplementation was noninferior to risperidone long-acting injection every 2 weeks with oral supplementation in reducing the total Positive and Negative Symptom Scale Score (PANSS) in patients with schizophrenia (n=1220). Patients who had a DMS-IV diagnosis of schizophrenia for at least 1 year and had not received mood stabilizers (including lithium and anticonvulsants) in the previous 6 months were eligible for enrollment. Prior to double-blind study treatment, there was a 7-day washout/oral tolerability testing period in which patients discontinued disallowed psychotropic medications and patients without previous exposure to risperidone or paliperidone received oral paliperidone extended-release 6 mg daily for 4 to 6 days. Patients were then randomized 1:1 to receive paliperidone palmitate injection (n=607) 234 mg on day 1, 156 mg on day 8, and then flexible dosing on days 36 (78 or 156 mg) and day 64 (78, 156 or 234 mg); or flexible dosing of risperidone long-acting injection (n=613) every 2 weeks on days 8 and 22 (25 mg), days 36 and 50 (25 or 37.5 mg), days 64 and 78 (25, 37.5, or 50 mg). Patients in the risperidone group also received risperidone 1 to 6 mg/day orally on days 1 to 28 and the paliperidone group received a matching placebo. Both groups also received placebo injections to match the number of injections given in the alternate group. Antidepressant therapy (except for monoamine-oxidase inhibitors) at doses stable for 30 days prior to study entry, antiparkinsonian drugs for the treatment of extrapyramidal symptoms (EPS), and oral benzodiazepines were the only concurrent treatments allowed during the study. Based on the per-protocol population (n=765; defined as patients who had both a baseline measurement and at least 1 postrandomization measurement, and had at least 36 days drug exposure during the double-blind phase), the mean PANSS total score (primary endpoint) improved from 84.9 at baseline to an endpoint of 66.2 in the paliperidone palmitate arm and from 83.5 to 65.6 in the risperidone long-acting injection arm. Paliperidone was noninferior to risperidone because the difference between paliperidone and risperidone in the mean PANSS total score change from baseline to endpoint was no more than the prespecified noninferiority margin of 5 points (-18.6 vs -17.9; between-group difference, 0.4; 95% confidence interval (CI), -1.62 to 2.38). Additionally, a similar proportion of patients in both the paliperidone and risperidone treatment groups achieved 30% improvement in PANSS score (53% vs 48.5%; relative risk, 1.1; 95% CI, 0.97 to 1.25). Analysis of the safety population (n=1214) showed that paliperidone palmitate was associated with higher incidence of insomnia (9.4% vs 6.7%), injection site pain (5.1% vs 0.8%), and anxiety (4.3% vs 2.1%) than risperidone; while risperidone was associated with higher incidence of constipation than paliperidone (3.1% vs 0.8%). Glucose, EPS, cardiac-related adverse events, and discontinuation rates (range, 0.3% to 0.5%) were similar in both groups (Pandina et al, 2010).

4.6.H Paroxetine

4.6.H.1 Panic attack

a) In an 8-week, randomized, single-blind, comparative trial (n=56) of low-dose risperidone and paroxetine in the treatment of panic attacks, both treatments were effective in reducing the occurrence and severity of panic attacks but there was no difference in the efficacy of each to improve anxiety associated with panic disorders. Thirty-three (8 men, 25 women) subjects were randomized to risperidone and 23 (8 men, 15 women) to paroxetine. The average age of the group was 40.36 +/- 12.37 years. Risperidone was initiated at 0.25 mg/day, adjusted as necessary for lack of response or sedation (maximum dose of 16 mg/day). Paroxetine was initiated at 30 mg/day, increased to a maximum of 60 mg/day if needed. The average risperidone dose was 0.53 mg (range 0.125 mg to 1 mg). All subjects in the paroxetine group received 30 mg/day except for one who required a dose of 40 mg. Subject assessments were conducted by a clinical rater blinded to medication status, using the 17-item Hamilton Depression Rating Scales (Ham-D-17), the Hamilton Anxiety Rating Scale (Ham-A), the Panic Disorder Severity Scale (PDSS), the Sheehan Panic Anxiety Scale-Patient (SPAS-P) and the Clinical Global Impressions Scale (CGI). Twenty subjects in the risperidone group and 9 in the paroxetine group completed all study visits. A significant decrease in CGI score was demonstrated in all subjects (p less than 0.001), but there was no significant difference between the groups. The CGI score improved from 4.4 +/- 0.6 at baseline to 2.84 +/- 1.02 at final assessment in the risperidone arm. Similarly, paroxetine resulted in a CGI score improvement from 3.81 +/- 1.33 to 2.67 +/- 0.71 at final assessment. All subjects, regardless of treatment, demonstrated a significant decrease in outcome scores for the PDSS total score, PDSS item 1, PDSS item 2, Ham-A and Ham-D. There was no statistical difference between treatment groups by the end of the study, and there was no significant change in SPAS-p scores over time (Prosser et al, 2009).

4.6.I Perphenazine

4.6.I.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.I.2 Schizophrenia

a) Risperidone and perphenazine were equally efficacious in a double-blind, multicenter, parallel-group study in which 107 chronic schizophrenics with acute exacerbation were enrolled (Hoyberg et al, 1993a). No statistically significant differences in clinical improvement (defined as a 20% reduction in total Positive and Negative Syndrome Scale score at endpoint) were found between the two treatment groups. Clinical Global Impression severity scores were also comparable. Patients with predominantly negative symptoms treated with risperidone had significantly lower Brief Psychiatric Rating Scale hostility scores compared to patients taking perphenazine.

4.6.J Quetiapine

4.6.J.1 Bipolar I disorder, Acute manic and mixed episodes

a) In a randomized, double-blind, multiphase, parallel-group, active- and placebo-controlled study (n=493), paliperidone extended-release (ER) therapy was more effective than placebo and not different from quetiapine in improving Young Mania Rating Scale (YMRS) scores among patients with bipolar I disorder experiencing an acute manic or mixed episode. Enrolled patients (age, 39 +/- 10 yr; 65% manic; 35% mixed) had a minimum YMRS score of 20, had no known or suspected rapid cycling, schizoaffective disorder, antisocial personality disorder or a history of substance abuse. Following a 1-week washout period where all antimanic medications were discontinued, patients were randomized 2:2:1 to a 3-week, double-blind acute treatment phase of paliperidone ER (n=195; 3 to 12 mg/day; initial dose, 6 mg/day; dose titration by 3 mg every 2 days), quetiapine (n=193; 400 to 800 mg/day; initial dose, 100 mg/day; forced titration to 400 mg/day on day 4; dose adjustment by 200 mg every 2 days), or placebo (n=105); during which patients were hospitalized for 10.4 +/- 5.66 days. Patients then proceeded to a 9-week, double-blind, maintenance phase on the same therapy except patients who received placebo in the acute phase were switched to paliperidone ER. At the end of the 3-week acute treatment phase, the mean change in YMRS total score from baseline (primary endpoint) was -13.2 +/- 8.68 in the paliperidone ER group compared with -7.4 +/- 10.74 in the placebo group (difference, -5.5; 95% confidence interval (CI), -7.57 to -3.35; p less than 0.001). Quetiapine also resulted in greater YMRS total score improvement compared with placebo (-11.7 +/- 9.28 vs -7.4 +/- 10.74; between-group difference, -4.2; 95% CI, -6.45 to -1.95; p less than 0.001), but was not statistically different from paliperidone ER (p=0.099). In the secondary analysis at the 12-week endpoint, paliperidone ER was noninferior to quetiapine based on the prespecified noninferiority margin of greater than -4 as the lower limit of the 95% CI. The mean change in YMRS total score at week 12 from baseline was -15.2 +/- 10.26 in the paliperidone group compared with -13.5 +/- 11.02 in the quetiapine group (difference, 1.7; 95% CI, -0.47 to 3.96). There was no significant difference between paliperidone ER and quetiapine with regards to three efficacy scales (Global Assessment of Functioning (GAF), Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression-Bipolar Disorder-Severity Scale (CG-BP-S)). The number needed to treat (NNT) to achieve a clinical response (50% or greater reduction from baseline) for the paliperidone ER group was 5 (95% CI, 4 to 11) and 7 (95% CI, 4 to 40) for the quetiapine group. Common adverse events for quetiapine relative to paliperidone ER during the 3-week treatment phase included somnolence (18% vs 10%), sedation (16% vs

8%), dizziness (12% vs 6%), and dry mouth (15% vs 5%). On the other hand, paliperidone was associated with higher incidence of akathisia (10% vs 3%), drooling (6% vs 0%) and hypertonia (5% vs 1%) compared with quetiapine at 12-week follow-up. Nineteen percent of patients in the paliperidone ER group received anticholinergic medications during the acute or maintenance phases of treatment compared with 10% in the quetiapine group and 8% in the placebo/paliperidone ER group for treatment-emergent extrapyramidal symptoms. At week 12, more patients in the quetiapine group (17%) compared with the paliperidone group (up to 8%) experienced weight increase of 7% or greater. Paliperidone (13.9% to 18%) was associated with more patients who "switched to depression" at 12 weeks compared with the quetiapine (5.8%; p=0.044) (Vieta et al, 2010).

4.6.J.2 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.J.3 Psychotic disorder

a) Quetiapine and risperidone were similarly efficacious in treating psychotic symptoms and had similar overall tolerability, but quetiapine treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing depression. In a 4- month, open-label study, patients with schizophrenia, schizoaffective disorder, or other psychotic disorders (including bipolar disorder, major depressive disorder and various forms of dementia) were randomized in a ratio of 3:1 to receive quetiapine (n=553) or risperidone (n=175). A total of 64% of the study population had schizophrenia or schizoaffective disorder while 24% had bipolar I disorder or major depressive disorder. The starting dosage of quetiapine was 50 milligrams/day (mg/day), which was increased in 50- or 100- mg increments every 1 to 2 days, to a maximum of 800 mg/day, given in divided doses. Risperidone was started at 1 mg twice daily, with upward titration to a target dose of 3 mg twice daily by day 3. Dosages were individually titrated to maximize efficacy while minimizing adverse reactions (mean prescribed dose: quetiapine 253.9 mg, risperidone 4.4 mg). At the beginning of the study, approximately half of each group had EPS. There was a steady decline in the number of patients reporting EPS in both groups as the study progressed. The incidence of EPS in the

quetiapine group was lower than in the risperidone group at one month (41.1 vs 47.3) but not at the end of the study (38.6 vs 39.2). The percentage of patients requiring a change of treatment due to EPS or requiring anti-EPS medication was lower in the quetiapine group than in the risperidone group (7% vs 20.5%). Approximately one third of patients in each group withdrew before completion of the study. A higher percentage withdrew from risperidone treatment for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from quetiapine treatment because of adverse effects (8.7% vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizziness, which all occurred significantly more often with quetiapine treatment (p less than 0.05). Occurrence of weight gain was low in both groups (Mullen et al, 2001).

4.6.K Ziprasidone

4.6.K.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

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Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999i.

Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999j.

Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999k.

Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999l.

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TOC

Risperidone

Class: 28:16.08.04 Atypical Antipsychotics

Special Alerts:

[Posted 06/13/2011] **ISSUE:** FDA notified healthcare professionals and the public of medication error reports in which patients were given risperidone (Risperdal) instead of ropinirole (Requip) and vice versa. In some cases, patients who took the wrong medication needed to be hospitalized.

The FDA determined that the factors contributing to the confusion between the two products include:

- Similarities of both the brand (proprietary) and generic (established) names
- Similarities of the container labels and carton packaging
- Illegible handwriting on prescriptions
- Overlapping product characteristics, such as the drug strengths, dosage forms, and dosing intervals.

BACKGROUND: Risperidone (Risperdal) is an antipsychotic medication used to treat mental illnesses including schizophrenia, bipolar disorder, and irritability associated with autistic disorder. Ropinirole (Requip) is a dopamine agonist used in the treatment of Parkinson's disease and Restless Legs Syndrome.

RECOMMENDATION: Healthcare Professionals are reminded to clearly print or spell out the medication name on prescriptions and make certain their patients know the name of their prescribed medication and their reason for taking it. For more information visit the FDA website at: http://www.fda.gov/Safety/MedWatch/SafetyInformationand http://www.fda.gov/Drugs/DrugSafety.

[Posted 02/22/2011] **ISSUE:** FDA notified healthcare professionals that the Pregnancy section of drug labels for the entire class of antipsychotic drugs has been updated. The new drug labels now contain more and consistent information about the potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy.

The symptoms of EPS and withdrawal in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays.

BACKGROUND: Antipsychotic drugs are used to treat symptoms of psychiatric disorders such as schizophrenia and bipolar disorder.

RECOMMENDATION: Healthcare professionals should be aware of the effects of antipsychotic medications on newborns when the medications are used during pregnancy. Patients should not stop taking these medications if they become pregnant without talking to their healthcare professional, as abruptly stopping antipsychotic medications can cause significant complications for treatment. For more information visit the FDA website at:http://www.fda.gov/Safety/MedWatch/SafetyInformation andhttp://www.fda.gov/Drugs/DrugSafety.

Introduction

Risperidone has been described as an atypical or second-generation antipsychotic agent.(1)(2)(3)(5)(6)(7)(8)(9)(10)(11)(12)(13)(60)

Uses

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Psychotic Disorders

Risperidone is used for the symptomatic management of psychotic disorders.(1)(2)(3)(4)(5)(6)(7)(8)(10)(12)(13) Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse.(20)(60) Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia.(20)(60) Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.(16)(17)(18)(60)

Schizophrenia and Other Psychotic Disorders

Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings.(1)(3)(4)(5)(6)(8)(12)(28)(29) Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors.(19)(60) Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment.(19)(60) The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms.(60) Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition).(60) Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.(60) For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia.(1)(3)(4)(5)(22)(25)(28)(29) Data from limited clinical studies indicate that

risperidone improves both positive and negative manifestations of schizophrenia,(1)(3)(4) but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic.(22) Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year.(23)(24) In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol.(23) In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.(1)(3)(4)(5)(12)

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia.(60) Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages.(60) Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent.(60) However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established,(26)(27) and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.(60)

Geriatric Considerations

Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's type† (Alzheimer's disease, presenile or senile dementia), vascular dementia†, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events.(1)(14)(35)(36)(37)(38) In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI).(35)(36)(37) However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo.(1) In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo.(98)(104)(See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.(98)(104)

Bipolar Disorder

- Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder.(99)(100)(101)(104) Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features.(99)(104) The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score).(99)(104) In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily.(99)(104) In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily.(104) Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.(99)(104)

- Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features).(100)(104) In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy.(100)(104) Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 3.8 mg daily.(100)(104) Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within therapeutic ranges of 0.6–1.4 mEq/L for lithium and 50–120 mcg/mL for valproate.(100)(104) Addition of risperidone to lithium or valproate was shown to be superior to continued monotherapy with lithium or valproate as assessed by reduction of Y-MRS total score.(100)(104)

- In a second 3-week, placebo-controlled trial, inpatients and outpatients with bipolar mania receiving lithium, valproate (as divalproex), or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive risperidone or placebo in conjunction with their original therapy.(101)(104) Risperidone was given in a flexible dosage range of 1–6 mg daily, with an initial dosage of 2 mg daily; the mean modal dosage was 3.7 mg daily.(101)(104) Addition of risperidone to lithium, valproate, or carbamazepine therapy (with plasma drug concentrations maintained within therapeutic ranges of 0.6–1.4 mEq/L, 50–120 mcg/mL, or 4–12 mcg/mL, respectively) was not found to be superior to lithium, valproate, or carbamazepine given alone as assessed by reduction of the Y-MRS total score.(101)(104) A possible explanation for the failure of this trial was enzymatic induction of clearance of risperidone and its principal active metabolite, 9-hydroxyrisperidone, by carbamazepine in the subgroup of patients receiving combined therapy with these drugs, resulting in subtherapeutic plasma concentrations of risperidone and 9-hydroxyrisperidone.(101)(104)

- For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate.(102) For more severe manic or mixed episodes, combined therapy with an antipsychotic and lithium or valproate is

recommended as first-line therapy.(102) For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The manufacturer states that efficacy of risperidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) in the treatment of acute manic episodes or for prophylactic use in patients with bipolar disorder.(104)

Autistic Disorder

Risperidone is used for the management of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.(31)(33)(104)(105)(106)(107)(108)

Short-term efficacy of risperidone in children and adolescents with autistic disorder has been demonstrated in 2 placebo-controlled trials of 8 weeks' duration in children and adolescents (aged 5–16 years) who met the DSM-IV criteria for autistic disorder.(31)(104)(105) Over 90% of the patients in these 2 trials were under 12 years of age and the majority weighed over 20 kg (weight range: 16–104.3 kg).(31)(104)(105) The principal rating instruments used for assessing efficacy in these trials were the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Change (CGI-C) scale.(31)(104)(105) The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I), which measures the emotional and behavioral symptoms of autism, including aggression toward others, deliberate self-injuriousness, temper tantrums, and rapidly changing moods.(31)(104)(105) The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.(31)(104)

In the first 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5 to 16 years received twice daily placebo or risperidone 0.5–3.5 mg daily on a weight-adjusted basis, starting at 0.25 mg daily or 0.5 mg daily if baseline weight was less than 20 kg or 20 kg or greater, respectively; dosage was then titrated according to clinical response.(31)(104) Risperidone (mean modal dosage of 1.9 mg/day; equivalent to 0.06 mg/kg daily) was found to substantially improve scores on the ABC-I subscale and the CGI-C scale compared with placebo in this study.(31)(104)

In the second 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5–12 years were given an initial risperidone dosage of 0.01 mg/kg daily, which was then titrated up to 0.02–0.06 mg/kg daily based on clinical response.(104)(105) Risperidone (mean modal dosage of 0.05 mg/kg daily; equivalent to 1.4 mg daily) improved scores on the ABC-I subscale compared with placebo.(104)(105)

The efficacy of risperidone for long-term use (i.e., longer than 8 weeks) in children and adolescents with autistic disorder has been demonstrated in an open-label extension of the first 8-week, placebo-controlled trial in which patients received risperidone for 4 or 6 months (depending on whether they received risperidone or placebo in the double-blind study).(31)(104)(106) During the open-label treatment period, patients were maintained on a mean modal risperidone dosage of 1.8–2.1 mg daily (equivalent to 0.05–0.07 mg/kg daily).(104)(106)

Children and adolescents who maintained their positive response to risperidone (defined as at least a 25% improvement on the ABC-I subscale and a CGI-C rating of much improved or very much improved) during the 4–6 month open-label treatment period (average duration of therapy was 140 days) were randomized to receive either risperidone or placebo during an 8-week, double-blind withdrawal trial.(104)(107) A substantially lower relapse rate was observed in the risperidone group compared with the placebo group during the

pre-planned interim analysis of data from this trial.(104)(107) Based on the interim analysis results, the study was terminated since a statistically significant effect on relapse prevention was demonstrated.(104)(107) Relapse was defined as at least a 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline for the randomized withdrawal phase).(104)(107) The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.(104)

Although not curative, pharmacologic agents, such as risperidone, generally are used in children and adolescents with autistic disorder to reduce behavioral disturbances associated with autism and to help facilitate the child's or adolescent's adjustment and engagement in intensive, targeted educational interventions.(32)(34)(104)(105)(106)(107)(108) In clinical studies, risperidone was not found to improve certain core symptoms of autism (e.g., language deficits, impaired social relatedness).(31)(32)(33)(34)(108) However, the drug was more effective than placebo for improving scores on subcales for sensory motor behaviors, affectual reactions, and sensory responses in a controlled study.(108) The possible risks, including clinically important weight gain, tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug, should be considered.(31)(34)(104)

Risperidone also has been used for the treatment in a limited number of adults† with autistic disorder and other pervasive developmental disorders.(109)

Dosage and Administration

Supplementary dosing info/calc

Administration

Risperidone is administered orally or by IM injection.(103)

Oral Administration

Risperidone is administered orally, either in a once-daily dose or in 2 equally divided doses daily.(1)(104) Because risperidone can cause orthostatic hypotension, twice-daily oral administration may be preferable during initiation of therapy and in patients who may be more susceptible to orthostatic hypotension, such as geriatric or debilitated patients.(1)(15) If once-daily dosing is being considered in geriatric or debilitated patients, it is recommended that the patient be titrated on a twice-daily regimen for 2–3 days at the target dose.(1) Subsequent switching to the once-daily dosing regimen can be done thereafter.(1) Some experts state that once-daily administration of risperidone may be sufficient in most patients receiving maintenance therapy because of the extended half-life of the drug's principal active metabolite (9-hydroxyrisperidone).(15)

In children and adolescents receiving risperidone for the management of irritability associated with autistic disorder who experience persistent somnolence, administering the drug once daily at bedtime, twice-daily administration, or a reduction in dosage may be helpful.(104)

Since food reportedly does not affect the rate or extent of GI absorption of risperidone, the drug can be administered without regard to meals.(1)(14) Compatibility tests show that risperidone oral solution is compatible in the following beverages: water, coffee, orange

juice, and low-fat milk; such testing also indicates that risperidone oral solution is *not* compatible in cola or tea.(1)

Patients receiving risperidone orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing.(1) The tablet should not be pushed through the foil.(1) With dry hands, the blister backing should be peeled completely off the blister.(1) The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid.(1) Risperidone orally disintegrating tablets should not be divided or chewed.(1)

IM Administration

The commercially available risperidone powder for injection containing the drug in extended-release microspheres must be reconstituted prior to administration using the components of the dose pack supplied by the manufacturer.(103) The dose pack should be allowed to reach room temperature before reconstituting the injection.(103) Risperidone extended-release microspheres should be reconstituted using only the diluent in the prefilled syringe supplied by the manufacturer.(103) The entire contents of the prefilled syringe should be injected into the vial, and the vial should be shaken vigorously while the plunger rod is held down with the thumb for at least 10 seconds to ensure a homogeneous suspension; the reconstituted suspension should appear uniform, thick, and milky.(103) The manufacturer's prescribing information should be consulted for additional details on use of the components of the dose pack to reconstitute and administer risperidone injection.(103) The manufacturer states that different dosage strengths of IM risperidone should not be combined in a single administration.(103)

Following reconstitution, immediate use is recommended because the suspension will settle over time.(103) If more than 2 minutes pass before administration, the vial should again be vigorously shaken to resuspend the drug.(103) The contents of the vial must be used within 6 hours of reconstitution and should not be exposed to temperatures exceeding 25°C.(103)

The entire contents of the vial should be administered by deep IM injection into the upper outer quadrant of the gluteal area every 2 weeks, alternating buttocks.(103) The injection should *not* be administered IV.(103)

Dosage

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Schizophrenia

Oral Dosage

Risperidone has a bell-shaped dose-response curve,(4)(28) with therapeutic efficacy of oral dosages of 12–16 mg daily lower than that of dosages of 4–8 mg daily in adults.(28) Because dosage information contained in the manufacturer's labeling principally is derived from early clinical studies of the drug in patients not typical of the general population of patients treated in the community (i.e., in hospitalized, chronically-ill schizophrenic patients accustomed to high-dose antipsychotic therapies), dosage of risperidone should be individualized according to the patient's response and tolerance.(4)(14)(30) Clinicians also

may consider consulting published protocols for specific dosage information, particularly in geriatric or younger patients, and in those experiencing their first psychotic episode.(30)

The manufacturer's labeling states that the initial oral dosage of risperidone in adults generally is 1 mg twice daily, with dosage increase in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dosage of 6–8 mg daily (administered once daily or in 2 equally divided doses).(1) However, more recent evidence from open labeled studies and clinical experience with the drug indicates that an initial dosage of 1–2 mg daily, with dosage increases in increments of 0.5–1 mg daily titrated over 6–7 days, as tolerated, to a target dose of 4 mg daily may be more appropriate for the management of schizophrenia in most otherwise healthy adult patients.(30) Because steady-state plasma concentrations of 9-hydroxyrisperidone (an active metabolite of risperidone) may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of at least 7 days.(1)(2) Lower initial dosages (e.g., 1 mg daily) and slower dosage titrations to an initial target dosage of 2 mg daily may be appropriate for younger patients and in those being treated for their first psychotic episode; dosage may then be titrated up to 4 mg daily depending on clinical response at the lower dosage and adverse neurologic effects.(30) Such patients appear to benefit optimally from risperidone dosage of 1–3 mg daily.(30) A substantial number of patients being treated for their first psychotic episode start to develop extrapyramidal symptoms once dosages are increased above 2 mg daily.(30) Dosage reductions should be considered in any patient who develops extrapyramidal symptoms.(30)

While antipsychotic efficacy has been established in clinical trials at oral dosages ranging from 4–16 mg daily, maximum efficacy of the drug was observed in most patients at risperidone dosages of 4–8 mg daily.(1)(15) In addition, the manufacturer and some clinicians state that dosages exceeding 6 mg daily, when given in 2 divided doses, did not result in further improvement but were associated with increases in some adverse effects, including extrapyramidal manifestations.(1)(15)(30) Therefore, the manufacturer states that dosages exceeding 6 mg (in 2 divided doses) daily generally are not recommended and those exceeding 16 mg daily have not been evaluated for safety.(1) In a single study of once-daily dosing, efficacy results generally were stronger for 8 mg than for 4 mg.(1)

The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to risperidone or concomitant administration with other antipsychotic agents.(1) While immediate discontinuance of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, gradual discontinuance of the drug may be appropriate for most patients.(1) In all cases, the period of overlapping antipsychotic administration should be minimized.(1) The first risperidone dose should be administered in place of the next scheduled parenteral antipsychotic dose in schizophrenic patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral risperidone therapy.(1)

The optimum duration of oral risperidone therapy currently is not known, but maintenance therapy with risperidone 2–8 mg daily has been shown to be effective for up to 2 years.(1)(23) Patients should be reassessed periodically to determine the need for continued therapy with the drug.(1) If risperidone therapy is reinitiated after a drug-free period, the manufacturer recommends that the appropriate recommended schedule of careful dosage titration be employed.(1)

IM Dosage

For the management of schizophrenia, the recommended initial adult IM dosage of risperidone injection extended-release microspheres is 25 mg administered by deep IM injection in the gluteal area every 2 weeks.(103) The manufacturer recommends that

patients first receive oral risperidone to establish tolerability of the drug before the extended-release risperidone injection is used.(103) To ensure that adequate plasma antipsychotic concentrations are maintained prior to the main release of risperidone from the injection site, therapy with oral risperidone or another oral antipsychotic agent (e.g., for patients being switched from other oral antipsychotic therapy to IM risperidone) should be given with the first IM injection of risperidone, and such oral therapy should be continued for 3 weeks, then discontinued.(103) If risperidone injection is used in patients previously receiving other oral antipsychotic agents, the need for continuing any concomitant therapy for managing extrapyramidal manifestations should be periodically reevaluated.(103)

Some patients not responding to the initial dosage of 25 mg every 2 weeks may benefit from increasing the IM dosage to 37.5 or 50 mg every 2 weeks.(103) However, the dosage should not be increased more frequently than every 4 weeks, and clinical effects of the increased dosage should not be expected earlier than 3 weeks after the first injection of the higher dose.(103) The maximum IM dosage should not exceed 50 mg every 2 weeks since higher dosages were associated with an increased incidence of adverse effects, but no additional clinical benefit was observed.(103)

Although no controlled studies have been conducted to establish the optimum duration of IM risperidone therapy in patients with schizophrenia, oral risperidone has been shown to be effective in delaying time to relapse with longer term use.(103) It is recommended that responding patients be continued on treatment with IM risperidone at the lowest dose needed.(103) Patients should periodically be reassessed to determine the need for continued treatment.(103)

If therapy with IM risperidone is reinitiated after a drug-free period, oral risperidone (or another oral antipsychotic agent) should again be administered for supplementation.(103)

Bipolar Disorder

For the management of acute manic and mixed episodes associated with bipolar disorder as monotherapy or as combined therapy in adults, an initial risperidone oral dosage of 2–3 mg given once daily was found to be effective in clinical trials.(99)(100)(101)(104) Dosage may be increased or decreased by 1 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials.(99)(104) In these trials, the short-term (i.e., 3-week) antimanic efficacy of risperidone was demonstrated in a flexible dosage ranging from 1 to 6 mg daily.(99)(104) Safety of dosages exceeding 6 mg daily has not been established.(99)(104)

The optimum duration of risperidone therapy for bipolar disorder currently is not known.(104) While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone beyond 3 weeks.(104) Therefore, the manufacturer states that clinicians who elect to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.(104)

Autistic Disorder

For the management of irritability associated with autistic disorder in children 5 years of age and older and adolescents, an initial risperidone oral dosage of 0.25 mg daily is recommended for patients weighing less than 20 kg and 0.5 mg daily is recommended for patients weighing 20 kg or more.(104) The drug may be administered either once or twice daily.(31)(104)(105)

Dosage should be individualized according to clinical response and tolerability of the patient.(104) After a minimum of 4 days following initiation of therapy, the dosage may be increased to the recommended dosage of 0.5 mg daily for patients weighing less than 20 kg and 1 mg daily for patients weighing 20 kg or more; this dosage should then be maintained for a minimum of 14 days.(104) In patients not responding adequately, increases in dosage may be considered at intervals of 2 weeks or longer in increments of 0.25 mg daily for patients weighing less than 20 kg or 0.5 mg daily for patients weighing 20 kg or more.(104) Exercise caution with risperidone dosages in smaller children who weigh less than 15 kg.(104) Safety and effectiveness in pediatric patients less than 5 years of age not established.(104)

In clinical trials, 90% of patients who responded to risperidone therapy (based on at least 25% improvement in the Irritability subscale of the Aberrant Behavior Checklist [ABC-I]) received dosages from 0.5–2.5 mg daily.(31)(104)(105) The maximum daily dosage in one of the pivotal trials, when the therapeutic effect reached a plateau, was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or more, and 3 mg in patients weighing more than 45 kg.(31)(104) Dosage data for children weighing less than 15 kg currently are lacking.(104)

Once adequate clinical response has been achieved, consider a gradual reduction in dosage to achieve an optimal balance of efficacy and safety.(104) Patients experiencing excessive somnolence may benefit from a once-daily dosage administered at bedtime or administering half the daily dosage twice daily, or a reduction in dosage.(104)

The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.(104)

Geriatric Patients and Others at Risk of Orthostatic Hypotension

Like other α-adrenergic blocking agents, risperidone can induce orthostatic hypotension (e.g., manifested as dizziness, tachycardia, and occasionally syncope), particularly during initiation of therapy with the drug.(1)(15) The manufacturer and some clinicians state that the risk of this effect can be minimized by limiting the initial oral dosage of risperidone to 1 mg twice daily in otherwise healthy adults and to 0.5 mg once or twice daily in geriatric or debilitated patients, in patients with renal or hepatic impairment, and in those predisposed to, or at risk from, hypotension.(1)(15) Dosages in such patients should then be increased gradually at increments of not more than 0.5 mg twice daily as necessary and tolerated.(1)(15) Increases beyond a dosage level of 1.5 mg twice daily generally should occur at intervals of at least 7 days.(1) However, other clinicians recommend initiating risperidone therapy at a dosage of 0.25 mg daily in geriatric patients and gradually increasing the dosage as tolerated.(30) (See Cautions: Geriatric Precautions.) Most geriatric patients should not be maintained at an oral dosage exceeding 3 mg daily.(15)

For geriatric patients with schizophrenia, the recommended IM risperidone dosage of the extended-release injection is 25 mg every 2 weeks.(103) Oral risperidone (or another oral antipsychotic agent) should be given with the first risperidone extended-release injection and should be continued for 3 weeks to ensure that adequate antipsychotic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site.(103)

Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning, slowly rising

from a seated position).(103) These patients should avoid sodium depletion or dehydration and circumstances that accentuate hypotension (e.g., alcohol intake, high ambient temperature).(103) Monitoring of orthostatic vital signs should be considered.(103)

Particular caution also is warranted in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) and in those for whom such reactions would pose a risk, and cautious dosage titration and careful monitoring are necessary in such patients.(1)(103) Dosage reduction should be considered in any patient in whom hypotension develops.(1)(103)

Dosage in Renal and Hepatic Impairment

Because elimination of risperidone may be reduced and the risk of adverse effects, particularly hypotension, increased in patients with renal impairment, oral risperidone therapy should be initiated at a reduced dosage of 0.5 mg twice daily in adults and increased as necessary and tolerated at increments of 0.5 mg twice daily; increases beyond a dosage level of 1.5 mg twice daily should be made at intervals of at least 7 days.(1) Likewise, this reduced oral dosage should be employed in patients with hepatic impairment because of the risk of an increased free fraction of risperidone in such patients.(1)

If IM risperidone is used for management of schizophrenia in adult patients with renal or hepatic impairment, the patient should be treated with titrated doses of oral risperidone prior to initiating treatment with the extended-release injection.(103) The recommended starting oral risperidone dosage is 0.5 mg twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week.(103) If a dosage of at least 2 mg daily of oral risperidone is well tolerated, an IM dosage of 25 mg of the extended-release injection can be administered every 2 weeks.(103) Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun.(103) In some patients, slower titration may be medically appropriate.(103)

Cautions

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Although risperidone differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives.(1) Not all adverse effects of the phenothiazines have been reported with risperidone, but the possibility that they may occur should be considered.(1) Adverse effects of risperidone and the phenothiazines are numerous and may involve nearly all organ systems.(1) Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal.(1) In some patients, unexpected death associated with antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex.(1) (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy.(1)

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with schizophrenia who received the drug in 2 short-term (6–8 week) clinical studies and with an incidence of at least twice that of those who received placebo included

nervous system (e.g., anxiety, dizziness, extrapyramidal symptoms, somnolence), GI (e.g., constipation, dyspepsia, nausea), dermatologic (e.g., rash), respiratory (e.g., rhinitis), and cardiovascular (e.g., tachycardia) effects.(1) Approximately 9% of patients receiving risperidone in phase 2 or 3 studies discontinued treatment because of adverse effects compared with about 7% of those receiving placebo and 10% of those receiving an active control drug (haloperidol).(1)(22) Adverse effects commonly associated with discontinuance of therapy and considered to be possibly or probably related to risperidone include extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.(1)

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with bipolar mania who received the drug as monotherapy in the US placebo-controlled trial and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, dystonia, akathisia, parkinsonism, vision abnormalities) and GI (e.g., dyspepsia, nausea, increased salivation) effects.(99)(104) In the US placebo-controlled trial of risperidone in conjunction with mood stabilizers (lithium or valproate), the most common adverse effects associated with risperidone administration were somnolence, dizziness, parkinsonism, increased saliva, akathisia, abdominal pain, and urinary incontinence.(100)(104) In the US placebo-controlled trial of risperidone monotherapy, approximately 8% of patients receiving risperidone discontinued therapy because of adverse effects compared with about 6% of those receiving placebo.(99)(104) Adverse effects associated with discontinuance of therapy in this study and considered to be possibly, probably, or very likely related to risperidone included paroniria, somnolence, dizziness, extrapyramidal reaction, and involuntary muscle contractions; each of these occurred in 1 risperidone-treated patient (0.7%) but in none of those receiving placebo.(99)(104) In the US placebo-controlled trial of risperidone used in conjunction with mood stabilizers, there was no overall difference in the incidence of discontinuance because of adverse effects (4% for risperidone and 4% for placebo).(100)(104)

The most frequent adverse effects of oral risperidone reported in at least 5% of pediatric patients with autistic disorder who received the drug in 2 placebo-controlled trials and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, fatigue, tremor, dystonia, dizziness, parkinsonism, automatism, dyskinesia, confusion), GI (e.g., increased appetite, increased salivation, constipation, dry mouth), respiratory (e.g., upper respiratory tract infection), cardiovascular effects (e.g., tachycardia), and weight gain.(31)(104)(105) Somnolence was the most frequent adverse effect in these trials, occurring in 67% of the risperidone-treated patients and in 23% of patients receiving placebo.(104) Average weight gain over 8 weeks was 2.6 kg for the risperidone-treated patients compared with 0.9 kg for patients receiving placebo.(104) Extrapyramidal symptoms occurred in approximately 28% of the risperidone-treated patients compared with 10% of those receiving placebo.(104)

The most frequent adverse effects associated with use of risperidone extended-release IM injection reported in at least 5% of adult patients with schizophrenia in clinical trials and with an incidence of at least twice that of those receiving placebo included somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, and increased weight.(103)

Nervous System Effects

Tardive Dyskinesia

Like other antipsychotic agents (e.g., phenothiazines), risperidone has been associated with tardive dyskinesias.(1)(21) Although it has been suggested that atypical antipsychotics appear to have a lower risk of tardive dyskinesia,(21) whether antipsychotic drugs differ in

their potential to cause tardive dyskinesia is as yet unknown.(1) In one open-label study, an annual incidence of tardive dyskinesia of 0.3% was reported in patients with schizophrenia who received approximately 8–9 mg of oral risperidone daily for at least 1 year.(21) The prevalence of this syndrome appears to be highest among geriatric patients (particularly females).(1) The risk of developing tardive dyskinesia and the likelihood that it will become irreversible also appear to increase with the duration of therapy and cumulative dose of antipsychotic agents administered;(1)(21) however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages.(1) For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Extrapyramidal Reactions

Extrapyramidal reactions occurred in 17% of patients with schizophrenia receiving oral risperidone dosages of 10 mg daily or less and in 34% of patients receiving dosages of 16 mg daily in clinical studies.(1) Although the incidence of extrapyramidal manifestations in patients receiving risperidone dosages of 10 mg daily or less was similar to that reported in patients receiving placebo, the incidence increased as the dosage of the drug increased, suggesting a dose-related effect.(1) At recommended therapeutic dosages of risperidone (4–8 mg daily) for schizophrenia, the severity of extrapyramidal reactions appears to be comparable to placebo and clozapine 400 mg daily, and substantially less than that associated with haloperidol 10 or 20 mg daily.(4) Similarly, the severity of parkinsonian symptoms, as assessed on the parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (ESRS), is also linearly related to risperidone dosages of 2–16 mg daily, with the incidence of parkinsonian symptoms at risperidone dosages of 6 mg daily or less comparable to that of placebo and substantially less than that seen with haloperidol dosages of 20 mg daily.(1)(4)

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents.(1) NMS requires immediate discontinuance of the drug and intensive symptomatic and supportive care.(1) For additional information on NMS, see Neuroleptic Malignant Syndrome under Nervous System Effects: Extrapyramidal Reactions in Cautions, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects

Dose-related somnolence was a commonly reported adverse effect associated with risperidone treatment.(1) Approximately 8% of adult patients with schizophrenia receiving 16 mg of oral risperidone daily and 1% of patients receiving placebo reported somnolence in studies utilizing direct questioning or a checklist to detect adverse events, respectively.(1)

Insomnia,(1) agitation,(1) and anxiety have been reported in 20–26% of patients receiving risperidone.(1) In addition, headache,(1) dizziness,(1) and aggressive reaction have been reported in 12–14, 4–7, and 1–3% of schizophrenia patients, respectively.(1)

Adverse nervous system effects reported in 1% or more of patients with schizophrenia who received risperidone in clinical studies include increased sleep duration(1) or dream activity,(1) diminished sexual desire,(1) fatigue,(1) and nervousness.(1) Impaired concentration,(1) depression,(1) apathy,(1) catatonic reaction,(1) euphoria,(1) increased libido,(1) amnesia,(1) dysarthria,(1) vertigo,(1) stupor,(1) paraesthesia,(1)malaise,(1) seizure,(1) and confusion(1) also have been reported in 0.1–1% of patients.(1) In addition, aphasia,(1) cholinergic syndrome,(1) choreoathetosis,(1) coma,(1) delirium,(1) emotional lability,(1) hypoesthesia,(1) hypotonia,(1) hyperreflexia,(1) leg cramps,(1) migraine,(1)

nightmares,(1) tongue paralysis,(1) torticollis,(1) withdrawal syndrome,(1) and yawning(1) have been reported in fewer than 0.1% of patients.(1) Mania(1) also has been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.(1)

Cardiovascular Effects

Orthostatic Hypotension

Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period has been reported in patients receiving risperidone, probably reflecting the drug's α-adrenergic antagonistic properties.(1) The risk of orthostatic hypotension and syncope may be minimized by limiting initial doses in geriatric patients and patients with renal or hepatic impairment.(1) (See Dosage and Administration.) Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.(1) A dose reduction should be considered if hypotension occurs.(1) Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia).(1) Clinically important hypotension has been observed with concomitant use of risperidone and antihypertensive drug therapy.(1)

Other Cardiovascular Effects

Pooled analysis of results of placebo-controlled studies indicates that risperidone therapy is not associated with statistically significant changes in ECG parameters (e.g., PR, QT, or QT_c intervals, heart rate).(1) In pivotal clinical studies, however, tachycardia, which may be dose dependent, occurred in 3 or 5% of patients with schizophrenia receiving daily oral dosages of risperidone of 10 mg or less or 16 mg, respectively.(1) In addition, palpitation,(1) hypertension,(1) hypotension,(1) AV block,(1) and myocardial infarction have occurred in 1% or more of patients receiving risperidone.(1) Ventricular tachycardia,(1) angina pectoris,(1) atrial premature complexes (APCs, PACs),(1) T-wave inversions, (1) ventricular extrasystoles,(1) ST depression,(1) and myocarditis have occurred in fewer than 0.1% of patients receiving the drug in clinical trials.(1) Atrial fibrillation,(1) pulmonary embolism,(1) cerebrovascular disorders (including stroke and transient ischemic attack) (see Cautions: Geriatric Precautions), (1) (14) and rarely, sudden death(1) and/or cardiopulmonary arrest also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.(1)

Endocrine and Metabolic Effects

Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone.(1)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56)(57)(71)(72)(73)(74)(78)(97) While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., risperidone, clozapine,

olanzapine, quetiapine).(1)(44)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56)(58)(59)(96)

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available.(1)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56) While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., risperidone, quetiapine) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.(14)(44)(57)(58)(59)(60)(61)(62)(64)(65)(66)(67)(68)(69)(70)(75)(76)(79)(80)(81)(82)(83)(84)(85)(86)(87)(88)(89)(90)(91)(92)(93)(94)(95)

Similar to other antipsychotic agents, risperidone causes elevated prolactin concentrations, which may persist during chronic use of the drug.(1) Risperidone appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents.(104) The clinical importance of elevated serum prolactin concentrations is as yet unknown for most patients receiving these drugs.(1) Gynecomastia(1) and breast pain in men(1) have been reported in fewer than 0.1% of patients.(1) In addition, galactorrhea, amenorrhea, and impotence have been reported with agents that increase serum prolactin concentrations, including risperidone.(1)

Hyponatremia,(1) weight gain or loss,(1) increased serum creatine kinase (CK, creatine phosphokinase, CPK) concentrations, (1) thirst,(1) and diabetes mellitus(1) have been reported in 0.1–1% of schizophrenia patients receiving oral risperidone in clinical studies.(1) In addition, decreased serum iron concentrations,(1) cachexia,(1) dehydration,(1) disorders in antidiuretic hormone,(1) hypokalemia,(1) hypoproteinemia,(1) hyperphosphatemia,(1) hypertriglyceridemia,(1) hyperuricemia,(1) and hypoglycemia(1) have been reported in fewer than 0.1% of patients.(1) Precocious puberty and pituitary adenomas also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.(104)

GI Effects

Adverse GI effects that have been reported in 5–13% of patients with schizophrenia receiving oral risperidone in clinical studies include constipation,(1) nausea,(1) dyspepsia,(1) and vomiting.(1) Abdominal pain,(1) increased salivation,(1) and toothache(1) also have been reported in 1–4% of patients receiving risperidone in clinical studies.(1) In addition, anorexia(1) and reduced salivation(1) were reported in 1% or more of patients receiving risperidone in clinical trials.(1) Flatulence,(1) diarrhea,(1) increased appetite,(1) stomatitis,(1) melena,(1) dysphagia,(1) hemorrhoids,(1) and gastritis(1) have also been reported in 0.1–1% of patients.(1) In addition, fecal incontinence,(1) eructation,(1) gastroesophageal reflux,(1) gastroenteritis,(1) esophagitis,(1) lingual discoloration,(1) cholelithiasis,(1) lingual edema,(1) diverticulitis,(1) gingivitis,(1) discolored feces,(1) GI hemorrhage,(1) and hematemesis(1) have been reported in fewer than 0.1% of patients receiving the drug in clinical trials.(1) Although a causal relationship to risperidone has not been established, intestinal obstruction(1) has been reported during postmarketing surveillance.(1)

Respiratory Effects

Rhinitis has been reported in 8–10% of patients with schizophrenia receiving oral risperidone and was the most common adverse respiratory effect reported during clinical

studies.(1) In addition, cough,(1) sinusitis,(1) pharyngitis,(1) upper respiratory infections,(1) and dyspnea(1) have been reported in 1–3% of patients receiving risperidone in clinical studies.(1) Hyperventilation,(1) bronchospasm,(1) pneumonia,(1) and stridor(1) also have been reported in 0.1–1% of patients receiving risperidone in clinical studies.(1) Asthma,(1) increased sputum,(1) and aspiration(1) have been rarely reported in fewer than 0.1% of patients.(1) Although a causal relationship to the drug has not been established, apnea also has been reported during postmarketing surveillance.(1)

Dermatologic Effects and Sensitivity Reactions

Rash(1) and dry skin(1) have been reported in about 2–5% of patients with schizophrenia receiving oral risperidone in clinical studies.(1) In addition, adverse dermatologic effects that have been reported in 1% or more of patients receiving risperidone include seborrhea(1) and increased pigmentation.(1) Increased or decreased sweating,(1) acne,(1) alopecia,(1) hyperkeratosis,(1) pruritus,(1) and skin exfoliation(1) were reported in 0.1–1% of patients in clinical trials.(1) Bullous eruption,(1) skin ulceration,(1) aggravated psoriasis,(1) furunculosis,(1) verruca,(1) dermatitis lichenoid,(1) hypertrichosis,(1) genital pruritus,(1) and urticaria(1) have been rarely reported.(1)

Although a causal relationship has not been established, hypersensitivity reactions, including anaphylaxis,(1) angioedema,(1) and photosensitivity(1) have been reported in patients receiving risperidone.(1)

Genitourinary Effects

Adverse genitourinary effects reported in 1% or more of patients with schizophrenia receiving oral risperidone include polyuria,(1) polydipsia,(1) menorrhagia,(1) orgasmic dysfunction,(1) and vaginal dryness.(1) In addition, urinary incontinence,(1) hematuria,(1) dysuria,(1) nonpuerperal lactation,(1) amenorrhea,(1) breast or perineal pain in females,(1) leukorrhea,(1) mastitis,(1) dysmenorrhea,(1) intermenstrual bleeding,(1) and vaginal hemorrhage(1) have been reported in 0.1–1% of patients receiving risperidone in clinical studies.(1) Urinary retention,(1) cystitis,(1) and renal insufficiency(1) also have been reported in fewer than 0.1% of patients.(1)

In male patients, erectile dysfunction and ejaculation failure were reported in up to 1% of schizophrenia patients receiving oral risperidone in clinical studies.(1) In addition, rare cases of priapism have been reported.(1) While a causal relationship to risperidone use has not been established, other drugs with α-adrenergic blocking effects have been reported to cause priapism, and it is possible that risperidone may share this capacity.(1) Severe priapism may require surgical intervention.(1)

Musculoskeletal Effects

Back or chest pain and arthralgia have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies.(1) In addition, myalgia has been reported in 0.1–1% of patients.(1) Arthrosis, synostosis, bursitis, arthritis, and skeletal pain also have occurred in fewer than 0.1% of patients.(1)

Hematologic Effects

Anemia,(1) hypochromic anemia,(1) epistaxis,(1) and purpura have been reported in 0.1–1% of adult patients with schizophrenia(1) and granulocytopenia has been reported in 0.1–1% of children and adolescents with autistic disorder(104) receiving oral risperidone in clinical studies.(1)(104) Normocytic anemia,(1) leukocytosis,(1) lymphadenopathy,(1) leukopenia,(1) Pelger-Huet anomaly,(1) hemorrhage,(1) superficial phlebitis,(1) thrombophlebitis,(1) and thrombocytopenia(1) also have been reported in fewer than 0.1% of patients.(1) In addition, thrombotic thrombocytopenic purpura occurred in at least one patient (a 28 year-old female patient) receiving risperidone in a large, open-labeled study.(1) This patient experienced jaundice, fever, and bruising but eventually recovered after receiving plasmapheresis.(1) The relationship of this adverse event to risperidone therapy is unknown.(1)

Hepatic Effects

Increased SGOT(1) and increased SGPT have been reported in 0.1–1% of patients with schizophrenia receiving oral risperidone in clinical studies.(1) In addition, hepatic failure,(1) cholestatic hepatitis,(1) cholecystitis,(1) cholelithiasis,(1) hepatitis,(1) and hepatocellular damage(1) have been reported in fewer than 0.1% of patients.(1) Although a causal relationship to the drug has not been established, jaundice also has been reported during postmarketing surveillance.(1)

Ocular and Otic Effects

Abnormal vision has been reported in 1–2% of patients with schizophrenia receiving oral risperidone in clinical studies.(1) Abnormal accommodation(1) and xerophthalmia(1) also have been reported in 0.1–1% of patients receiving risperidone in clinical studies.(1) In addition, diplopia,(1) ocular pain,(1) blepharitis,(1) photopsia,(1) photophobia,(1) abnormal lacrimation,(1) tinnitus,(1) hyperacusis,(1) and decreased hearing have been reported in fewer than 0.1% of patients.(1)

Other Adverse Effects

Chest pain and fever have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies.(1) Although a causal relationship to the drug has not been established, pancreatitis and aggravated parkinsonian syndrome has been reported during postmarketing surveillance.(1)

Precautions and Contraindications

Risperidone shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed.(1)(See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone,(1)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56)(57)(71)(72)(73)(74)(78)(97) the manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g.,

obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment.(1)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56) (See Cautions: Endocrine and Metabolic Effects.) Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing.(1)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56) In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the antipsychotic; in other cases hyperglycemia resolved with discontinuance of the suspect drug.(1)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56) (78) For further information on the management of diabetes risks in patients receiving atypical antipsychotics, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Because of the possibility of orthostatic hypotension, caution should be observed in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease (see Cautions: Geriatric Precautions), conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia), and patients receiving antihypertensive agents.(1) Since patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies, clinicians should be aware that risperidone has not been evaluated or used to any appreciable extent in such patients.(1) Patients receiving risperidone should be advised of the risk of orthostatic hypotension, especially during the period of initial dosage titration.(1) (See Cautions: Cardiovascular Effects.)

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including risperidone, reportedly have an increased sensitivity to antipsychotic agents.(104) Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with more frequent falling, extrapyramidal adverse effects, and clinical features consistent with neuroleptic malignant syndrome.(104) (For additional information on extrapyramidal adverse effects and neuroleptic malignant syndrome, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Plasma concentrations of risperidone and its principal active metabolite, 9-hydroxyrisperidone, are increased in patients with severe renal impairment (creatinine clearance less than 30 mL/minute per1.73 m^2), and an increased free fraction of risperidone occurs in patients with severe hepatic impairment.(1) Therefore, lower initial dosages should be used in such patients.(1) (See Dosage and Administration.)

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that risperidone 0.5-, 1-, 2-, 3-. or 4-mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®) which is metabolized in the GI tract to provide about 0.14, 0.28, or 0.-42, 0.63, or 0.84 mg of phenylalanine, respectively, following oral administration.(39)(40)(41)(42)(43)(104)

Because seizures have occurred in 0.3% of patients receiving risperidone in clinical studies, the drug should be administered with caution to patients with a history of seizures.(1)

Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including risperidone.(1) Because aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced dementia of the Alzheimer's type, risperidone and other antipsychotic drugs should be used with caution in patients at risk for aspiration pneumonia.(1)

Because both hypothermia and hyperthermia have been associated with risperidone therapy, the drug should be administered with caution in patients who will be exposed to temperature extremes.(1)

Because risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including driving automobiles, until they are reasonably certain that risperidone therapy does not adversely affect them.(1)

Risperidone has an antiemetic effect in animals; this effect also may occur in humans, and may mask manifestations of overdosage with certain drugs or may obscure the cause of vomiting in various disorders such as intestinal obstruction, Reye's syndrome or brain tumor.(1)

Patients should be advised to inform their clinician if they are taking, or plan to take, any prescription or nonprescription drugs, or have any concomitant illnesses (e.g., diabetes mellitus).(1) Patients also should be advised to avoid alcohol while taking risperidone.(1)

Risperidone is contraindicated in patients with known hypersensitivity to the drug.(1)

Pediatric Precautions

The manufacturer states that safety and effectiveness of risperidone in children with schizophrenia or acute mania associated with bipolar I disorder have not been established.(104) However, efficacy and safety of the drug in the treatment of irritability associated with autistic disorder have been established in 2 placebo-controlled trials of 8 weeks' duration in 156 children and adolescents aged from 5–16 years.(31)(33)(104)(105) (See Uses: Autistic Disorder.) Additional safety information also was assessed from a long-term study in patients with autistic disorder and from short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight and who received similar risperidone dosages as patients treated for irritability associated with autistic disorder.(104)(107) Safety and effectiveness of risperidone in pediatric patients with autistic disorder younger than 5 years of age have not been established.(104)

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 patients (0.1%) reportedly developed tardive dyskinesia, which resolved upon discontinuance of therapy.(104) In addition, approximately 15% of children and adolescents receiving 0.5–2.5 mg daily dosages of risperidone developed withdrawal dyskinesia during the discontinuance phase of one long-term (6 month), open-label study.(33)

In long-term, open-label trials in patients with autistic disorder or other psychiatric disorders, a mean body weight gain of 7.5 kg after 12 months of risperidone therapy was reported, which was higher than the normal expected weight gain (i.e., 3–3.5 kg per year adjusted for age, based on the Centers for Disease Control and Prevention normative data).(104) The majority of the weight increase occurred within the first 6 months of drug exposure.(104) Average percentiles at baseline and at 12 months were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index, respectively.(104) When treating pediatric patients with risperidone, the manufacturer recommends that weight gain should be assessed against that expected with normal growth.(104)

Somnolence frequently occurred in placebo-controlled trials in pediatric patients with autistic disorder.(104) Most cases were mild to moderate in severity, occurred early during therapy (peak incidence during the first 2 weeks of therapy), and were transient (median

duration of 16 days).(104) Patients experiencing persistent somnolence may benefit from a change in dosage regimen.(104)

Risperidone has been shown to elevate prolactin concentrations in children and adolescents as well as adults.(104) In double-blind, placebo-controlled, 8-week trials in children and adolescents aged from 5–17 years, 49% of risperidone-treated patients had elevated prolactin concentrations compared with 2% of those receiving placebo.(104)

In clinical trials conducted in 1885 children and adolescents with autistic disorder or other psychiatric disorders, galactorrhea and gynecomastia reportedly occurred in 0.8 and 2.3% of risperidone-treated patients, respectively.(104)

The manufacturer states that the long-term effects of risperidone on growth and maturation have not been fully evaluated.(104)

Geriatric Precautions

Clinical studies of risperidone for the management of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients.(104) However, serious adverse effects, including an increased risk of death, have been reported in geriatric patients receiving risperidone or other atypical antipsychotic agents in clinical trials in patients with dementia-related psychosis.(104)(14)(35)(38)(98) Risperidone is not approved for the treatment of dementia-related psychosis.(98)(104) (See Geriatric Considerations in Uses: Psychotic Disorders.)

Adverse cerebrovascular events (e.g., stroke, transient ischemic attack), some of which resulted in fatalities, have been reported in clinical studies of risperidone for the management of psychosis in geriatric patients (mean age 85 years; range 73–97) with dementia.(14)(35)(38)(104) Analysis of pooled data from 4 randomized, placebo-controlled studies indicates that adverse cerebrovascular events occurred in approximately 4% of geriatric patients with dementia of the Alzheimer's type, vascular dementia, or mixed dementia receiving risperidone compared with 2% of those receiving placebo.(14)(38) Although many of the patients who experienced adverse cerebrovascular events during the course of these studies had at least one risk factor for cerebrovascular events (e.g., arrhythmia, atherosclerosis, atrial fibrillation, diabetes, heart failure, hypertension, prior history of stroke or transient ischemic attack),(14)(35) the total number of such patients was too small to permit definitive conclusions about the relationship between known risk factors for cerebrovascular events and risperidone therapy.(14) An increased risk of adverse cerebrovascular events has not been identified to date in clinical studies of risperidone for the management of schizophrenia.(14)

An increased risk of death has been reported among geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs compared with that among patients receiving placebo.(98)(104) Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., risperidone, aripiprazole, olanzapine, quetiapine) compared with that in patients receiving placebo.(98)(104) Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group.(104)(98) Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.(98)(104)

A higher incidence of mortality also was observed in geriatric patients with dementia-related psychosis receiving risperidone and furosemide concurrently in placebo-controlled trials when compared with that in patients receiving risperidone alone or placebo and

furosemide concurrently.(104) The increase in mortality in patients receiving risperidone and furosemide concurrently was observed in 2 out of 4 clinical trials.(104) The pathological mechanism for this finding remains to be established and no consistent pattern for the cause of death was observed.(104) An increased incidence of mortality in geriatric patients with dementia-related psychosis was observed with risperidone regardless of concurrent furosemide administration.(104)

Risperidone dosage generally should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range.(1) The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered.(1) Although geriatric patients exhibit a greater tendency to orthostatic hypotension, the manufacturer states that its risk may be minimized by limiting the initial oral dosage to 0.5 mg twice daily followed by careful titration and close monitoring of orthostatic vital signs in patients for whom this is of concern.(1) More recent evidence however, indicates that even lower initial dosages and slower dosage titration are better tolerated in these patients.(30) Therefore, some clinicians recommend initiating oral risperidone therapy at 0.25 mg daily, and gradually increasing dosages, as tolerated, to a dosage of 2 mg daily in these patients.(30) Higher oral dosages (e.g., 3 or 4 mg daily) may be required in some patients, but are usually associated with greater incidence of extrapyramidal reactions.(30) Most geriatric patients should *not* be maintained at an oral risperidone dosage exceeding 3 mg daily.(15) (See Geriatric Patients and Others at Risk of Orthostatic Hypotension under Dosage and Administration: Dosage.)

Mutagenicity and Carcinogenicity

Risperidone did not exhibit mutagenic potential in in vitro chromosomal aberration studies in human lymphocytes or Chinese hamster cells, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or in microbial (Ames) test systems.(1)

Statistically significant increases in pituitary gland adenomas and mammary gland adenocarcinomas were observed in female mice receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 18 months.(1)(104) In addition, statistically significant increases were observed in mammary gland adenocarcinomas in both male and female rats, and mammary gland neoplasms and endocrine pancreas adenomas in male rats receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 0.4, 1.5, and 6 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 25 months.(1)(104)

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of prolactin-stimulating drugs and mammary tumorigenesis in humans.(1) Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents.(1) Since in vitro tests indicate that approximately one-third of human breast cancers are prolactin-dependent, risperidone should be used with caution in patients with previously detected breast cancer.(1)

Pregnancy, Fertility, and Lactation

Pregnancy

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Reproductive studies in rats and rabbits using risperidone dosages of 0.4–6 times the maximum recommended human dosage on a mg/m^2basis have not revealed evidence of fetal malformation.(1) However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m^2basis.(1) In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m^2 basis.(1) It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams.(1) In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m^2 basis.(1) Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.(1)

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown.(1) Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy.(104) Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.(1) The effect of risperidone on labor and delivery in humans is unknown.(1)

Fertility

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m^2 basis.(1) The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated.(1) Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m^2 basis.(1) Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued.(1) A no-effect dosage was not found in these studies in either rats or dogs.(1)

Lactation

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk.(1) The manufacturer states that women receiving risperidone should avoid nursing.(1)

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents.(1) While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines).(1)(2)(3)(5)(6)(7)(8)(9)(10)(11)(12)(13)(60) The exact mechanism of

antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic ($5\text{-}HT_2$) receptors and central dopamine D_2 receptors.(1)(2)(3)(8)(10)(12)(13)(15)

Additional Information

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatchnotification at the beginning of this monograph.

Risperidone				
Routes	**Dosage Forms**	**Strengths**	**Brand Names**	**Manufacturer**
Oral	Solution	1 mg/mL	Risperdal®,	Janssen
	Tablets	0.25 mg	Risperdal®, (scored)	Janssen
		0.5 mg	Risperdal®, (scored)	Janssen
		1 mg	Risperdal®, (scored)	Janssen
		2 mg	Risperdal®, (scored)	Janssen
		3 mg	Risperdal®, (scored)	Janssen
		4 mg	Risperdal®, (scored)	Janssen
	Tablets, orally disintegrating	0.5 mg	Risperdal® M-TAB®,	Janssen
		1 mg	Risperdal® M-TAB®,	Janssen
		2 mg	Risperdal® M-TAB®,	Janssen
		3 mg	Risperdal® M-TAB®,	Janssen
		4 mg	Risperdal® M-TAB®,	Janssen
Parenteral	For injectable suspension, extended-release, for IM use	25 mg	Risperdal®Consta®, (available as dose pack containing a SmartSite®needle-free vial access device, a Needle-Pro®safety needle, and with 2-mL prefilled syringe diluent)	Janssen
		37.5 mg	Risperdal®Consta®, (available as dose pack containing a SmartSite®needle-free vial access device, a Needle-Pro®safety needle, and with 2-mL prefilled syringe diluent)	Janssen
		50 mg	Risperdal®Consta®, (available as	Janssen

Risperidone				
Routes	**Dosage Forms**	**Strengths**	**Brand Names**	**Manufacturer**
			dose pack containing a SmartSite®needle-free vial access device, a Needle-Pro®safety needle, and with 2-mL prefilled syringe diluent)	

Comparative Pricing

This pricing information is subject to change at the sole discretion of DS Pharmacy. This pricing information was updated 07/2011. For the most current and up-to-date pricing information, please visithttp://www.drugstore.com. Actual costs to patients will vary depending on the use of specific retail or mail-order locations and health insurance copays.

Risperdal 0.25MG Tablets (JANSSEN): 30/$148.99 or 90/$427.97

Risperdal 0.5MG Tablets (JANSSEN): 30/$177.98 or 90/$507.98

Risperdal 1MG/ML Solution (JANSSEN): 60/$405.97 or 180/$1182.91

Risperdal 1MG Tablets (JANSSEN): 30/$189.99 or 90/$527.98

Risperdal 2MG Tablets (JANSSEN): 30/$294.99 or 90/$857.94

Risperdal 3MG Tablets (JANSSEN): 30/$377.98 or 90/$1049.01

Risperdal 4MG Tablets (JANSSEN): 30/$472.97 or 90/$1384.97

Risperdal M-TAB 0.5MG Dispersible Tablets (JANSSEN): 28/$171.98 or 84/$492.97

Risperdal M-TAB 1MG Dispersible Tablets (JANSSEN): 28/$195 or 84/$569.95

Risperidone 0.25MG Tablets (TEVA PHARMACEUTICALS USA): 60/$145.98 or 180/$399.96

Risperidone 1MG/ML Solution (TEVA PHARMACEUTICALS USA): 30/$125.98 or 90/$359.97

Risperidone 4MG Tablets (TEVA PHARMACEUTICALS USA): 60/$399.98 or 180/$1159.97

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

DRUGDEX® Consults

RECOMMENDATION, EVIDENCE AND EFFICACY RATINGS

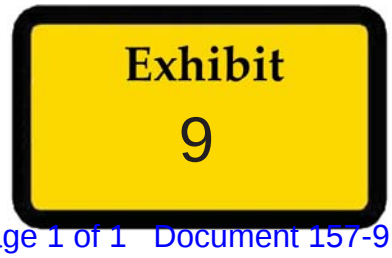
RESPONSE

The Thomson Efficacy, Strength of Evidence and Strength of Recommendation definitions are outlined below:

Table 1. Strength Of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminant	Evidence Inconclusive	

Table 2. Strength Of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No Evidence	

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.



DRUGDEX-CON 3198

MICROMEDEX
DRUGDEX® Consults
Database updated September 2013

RECOMMENDATION, EVIDENCE AND EFFICACY RATINGS

The Micromedex Efficacy, Strength of Evidence and Strength of Recommendation definitions are outlined below:

Table 1. Strength Of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminate	Evidence Inconclusive	

Table 2. Strength Of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No Evidence	

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

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END OF DOCUMENT

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Centers for Medicare & Medicaid Services

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Thomson Micromedex DrugPoints Compendium Revision Request - CAG-00390

Document Information

Date:

02/12/2008

Public Comment Period:

02/12/2008 - 03/13/2008 View Public Comments

Issue	The Social Security Act Section 1861(t)(2)(B)(ii)(I) recognizes the following compendia: American Medical Association Drug Evaluations (AMA-DE), United States Pharmacopoeia-Drug Information (USP-DI) or its successor publication [amended in Section 6001 (f)(1) of the DRA] and American Hospital Formulary Service-Drug Information (AFHS-DI) as authoritative sources for use in the determination of a "medically-accepted indication" of drugs and biologicals used off-label in an anticancer chemotherapeutic regimen. However, AFHS-DI is the only originally named compendium currently in publication. CMS received a timely complete request for the addition of the Thomson Micromedex compendium DrugPoints (designated by Thomson Micromedex as the successor publication to USP-DI) to the list of compendia for this use.
Requestor Name(s)	American Society of Clinical Oncology (ASCO) View Requestor Letter
Formal Request Accepted and Review Initiated	February 12, 2008

Exhibit 11

Expected Completion Date	June 10, 2008
Lead Analyst(s)	Kate Tillman, RN, MA Katherine.Tillman@cms.hhs.gov Brijet Burton, MS, PA-C Brijet.Burton2@cms.hhs.gov
Lead Medical Officer(s)	Lori Paserchia, MD
Actions Taken	

February 12, 2008	ASCO requested the formal addition of DrugPoints, designated by Thomson Micromedex as the successor publication to USP-DI, to the list of statutorily named compendia. The public comment period begins the date of this posting and ends after 30-calendar days. CMS considers all public comments, and is particularly interested in your feedback on the addition of DrugPoints to the list of compendia. Formal public comments may be submitted through the highlighted "comment" link located at the top of this web page. Instructions on how to submit a request to revise the list of compendia may be found at http://www.cms.hhs.gov/CoverageGenInfo/02_compendia.asp#TopOfPage
June 10, 2008	Posted decision.

To:	Administrative File: CAG #00390
From:	Steve Phurrough, MD, MPA Director, Coverage and Analysis Group Louis Jacques, MD Director, Division of Items and Devices Kate Tillman, RN, MA Analyst Brijet Burton, PA-C Analyst Lori Paserchia, MD

	Lead Medical Officer
Subject:	Thomson Micromedex DrugPoints ® - Request for addition to the list of compendia for the identification of a medically accepted indication for the off-label uses of drugs and biologicals in an anticancer chemotherapeutic regimen
Date:	June 10, 2008

Background

Section 1861(t)(2)(B)(ii)(I) of the Social Security Act (the Act) designates certain compendia as authoritative sources for use in the determination of a "medically-accepted indication" of drugs and biologicals used off-label in an anticancer chemotherapeutic regimen, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia.

Due to changes in the pharmaceutical reference industry, fewer of these statutorily-named compendia are available for our reference (*e.g.*, the AMA- DE and the USP-DI are no longer published). Consequently, CMS received requests from the stakeholder community for a process to revise the list of compendia. In the Physician Fee Schedule final rule for calendar year 2008, CMS established a process for revising the list of compendia, as authorized under section 1861(t)(2) of the Act, and also established a definition for "compendium." *See* 72 *Fed. Reg.* 66222, 66303-66306, 66404 (Nov. 27, 2007).

Under 42 C.F.R. § 414.930(a), a compendium is defined "as a comprehensive listing of FDA-approved drugs and biologicals or a comprehensive listing of a specific subset of drugs and biologicals in a specialty compendium, for example, a compendium of anti-cancer treatment." A compendium: (1) includes a summary of the pharmacologic characteristics of each drug or biological and may include information on dosage, as well as recommended or endorsed uses in specific diseases; (2) is indexed by drug or biological. See 42 C.F.R. § 414.930(a); 72 *Fed. Reg.* 66222, 66404.

In addition, CMS increased the transparency of the process by incorporating a list of desirable compendium characteristics outlined by the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) as criteria for decision-making. The list of desirable compendium characteristics was developed by the MedCAC during a public session on March 30, 2006. The goal of this session was to review the evidence and advise CMS on the desirable characteristics of compendia for use in the determination of medically-accepted indications of drugs and biologicals in anti-cancer therapy. As a result of this meeting, the MedCAC generated the following list of desirable characteristics:

- Extensive breadth of listings.
- Quick processing from application for inclusion to listing.
- Detailed description of the evidence reviewed for every individual listing.
- Use of pre-specified published criteria for weighing evidence.
- Use of prescribed published process for making recommendations.
- Publicly transparent process for evaluating therapies.
- Explicit "Not recommended" listing when validated evidence is appropriate.
- Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies.

- Explicit "Equivocal" listing when validated evidence is equivocal.
- Process for public identification and notification of potential conflicts of interest of the compendia's parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts.

We did not in regulation assign relative weights to these characteristics. Nor did we identify any characteristics as optional requirements, as we believe that all are necessary to fulfill the purpose for which this designation is made. However, as provided in regulation, CMS may consider additional reasonable factors in its decision. *See* 72 *Fed. Reg*. at 66306.

The drugs and biologicals used in the treatment of cancer are not benign agents. Boxed label “black box” warnings, a special FDA regulatory requirement, are commonly seen in many classes of agents: bevacizumab, rituximab, irinotecan, doxorubicin, busulfan, capecitabine, fludarabine, cetuximab, trastuzumab, gemtuzumab and docetaxel are but a few examples. The interests of Medicare beneficiaries who have cancer are safeguarded not only when appropriate uses of these agents are supported by Medicare payment, but equally so when inappropriate uses of these dangerous agents are discouraged by the absence of Medicare payment. Thus the explicit identification of indications that are not medically accepted is as necessary as the identification of indications that are medically accepted.

We believe the public should have access to such materials as necessary to determine if a compendium’s actions are indeed consistent with its stated policies. As Medicare beneficiaries who have cancer have the greatest personal stake in this issue, indeed their lives may hang in balance, we believe that public access is less meaningful if it is not provided broadly. Thus, as provided in regulation, we will consider broad access of the compendia to the general public as an additional reasonable factor. *See* 72 *Fed. Reg.* at 66306.

Request

A formal request submitted by the American Society of Clinical Oncology (ASCO) for the addition of Thomson Micromedex DrugPoints ® to the list of compendia for the determination of medically accepted indications for off-label uses of drugs and biologicals in an anticancer therapeutic regimen was posted on February 12, 2008 on the CMS website.

We note for the convenience of the reader that the publisher of DrugPoints ® is referred to variously by commenters and others as Thomson, Thomson Micromedex, and Thomson Healthcare. Thomson also publishes the DrugDex ® compendium.

Materials Reviewed

Requestor Letter

The application submitted by ASCO includes a detailed description of how Thomson Healthcare believes DrugPoints ® meets the CMS definition of a compendium and each of the ten MedCAC desirable characteristics.

Public Comments

As required under 42 C.F.R. § 414.930(b), CMS opened a 30 calendar day public comment period starting on the date this request was posted to receive feedback on the addition of Thomson Micromedex DrugPoints ® to the list of compendia.

CMS received a general public comment from the Biotechnology Industry Organization

(BIO) in support of the addition of all compendia for which a request to add such publication to the list of compendia for the identification of a medically accepted indication for the off-label uses of drugs and biologicals in an anticancer chemotherapeutic regimen has been submitted. BIO stated that it recognizes that the content of each compendium differs "in publication schedules, priorities, review processes, local practices and methods of describing the evidence of each listing". However, BIO believes that the addition of all these compendia is critical to the improvement of Medicare beneficiaries' access to time-sensitive cancer treatment options.

CMS received two public comments regarding the addition of Thomson Micromedex DrugPoints ® to the list of statutorily named compendia. The American Society of Health-System Pharmacists (ASHP) commented on the reference to DrugPoints ® as "the successor publication to USP-DI" in the formal request letter submitted by the American Society of Clinical Oncology (ASCO), dated February 11, 2008. ASHP does not believe that DrugPoints ® is a successor because it "bears little resemblance to the previous USP-DI database in content [and lacks] editorial oversight by USP's Expert Committees." In addition ASHP stated, "DrugPoints ® information is derived from Thomson Micromedex's DrugDex ® database". Thomson Micromedex, publisher of both DrugPoints ® and DrugDex ®, stated that the recommendations in the former are derived from the latter. ASHP stated that CMS should only make a determination on "the parent database", DrugDex ® since Thomson has filed a separate request for the recognition of DrugDex ®.

The other public comment February 12, 2008, was submitted the Amerihealthmercy health plan – DBA Passport Health plan, regarding the request for the addition of DrugPoints ® by ASCO. According to the commenter, ASCO's "sponsorships from internal oncology practices as well as Pharma companies" is a conflicted interest. The commenter states that ASCO should not be in the position "to set directions or approvals for medications" by requesting the recognition of a compendium.

Other Relevant Comments

CMS received a letter from the Senate Finance Committee, signed by Senator Max Baucus, Senator Charles E. Grassley, Senator John D. Rockefeller and Senator Orrin G. Hatch. They expressed a particular interest with the CMS compendia review process, specifically noting "…conflicts of interest on the part of authors who contribute to the compendia." In the correspondence, the Senators requested "…that CMS rely solely on compendia that are developed under policies of transparency and financial disclosure…."

Thomson Healthcare submitted a letter responding to the issues raised by ASHP regarding the designation of DrugPoints ® as the successor to USP-DI. In its response, Thomson stated that as of July 2007, DrugPoints ® includes "indication ratings, references, clinical teachings, toxicology information, and common synonyms". Similar to the USP Committee, Thomson stated that it has developed the Oncology Advisory Board. Thomson stated that DrugPoints ® is a summarized version of DrugDex ®. However, Thomson stated that it believes that both "DrugDex ® and DrugPoints ® independently meet the [statutory] definition of a 'compendium'…and may be independently considered for inclusion" to the list of recognized compendia.

Thomson Micromedex DrugPoints ®

As part of the compendium application submission, CMS requires access to the compendium under review. CMS had unlimited access to the Thomson Micromedex DrugPoints ® during the entire review process, which allowed CMS to navigate the compendium database in order to assess its infrastructure and content.

Analysis

1. The product known as Thomson Micromedex DrugPoints ® is a compendium as defined by CMS in the regulation because it includes a summary of the pharmacologic characteristics of each drug or biological, information on dosage, recommended or endorsed uses in specific diseases and is indexed by drug or biological rather than by disease.

2. Thomson Micromedex DrugPoints ® addresses each of the MedCAC identified desirable characteristics as noted below.

    - It provides an extensive breadth of listings by listing more than 2300 drugs and biologics including prescription, non-prescription and investigational products. FDA-approved indications and off-label uses are presented as well.
    - It is designed to provide quick processing from application for inclusion to listing by conducting an ongoing editorial review of the world's primary literature published in thousands of peer-reviewed journals, FDA-approved product labeling, clinical judgment and recommendations, regulatory standards and compliance, national healthcare trends, editorial board suggestions, external requests, and policy changes in health and disease management from professional health organizations. Online updates of the compendium are provided weekly. We note from materials provided by Thomson, the publisher, that these listings flow from its reliance on the DrugDex ® compendium rather than an independent review.
    - It provides a detailed description of the evidence reviewed for every individual listing and fully cites specific studies that are the basis for recommendations.
    - It provides on the DrugPoints ® website pre-specified published criteria for weighing evidence that focus on the efficacy, strength of recommendation and strength of evidence, which directly guide the process of decision-making leading to recommendations. We note from materials provided by Thomson, the publisher, that these recommendations flow from its reliance on the DrugDex ® compendium rather than from an independent review.
    - It uses a prescribed published process for evaluating therapies, which is available for subscribers to see on its website. When formulating recommendations, clinical staff develops drafts, which are reviewed by internal experts and the Chief Medical Officer. The draft may also be reviewed by an Oncology Advisory Board if the subject involves a new FDA-unapproved use related to oncology or a significant ratings change related to oncology. The staff then collates all comments and formulates the final document. We note from materials provided by Thomson, the publisher, that these recommendations flow from its reliance on the DrugDex ® compendium rather than an independent review.
    - It presents the process used for evaluating therapies to subscribers via its website including a listing of all involved panel members. There is an opportunity to make an external request for inclusion of information to the compendium; the policy and process regarding an external request is presented to subscribers via the website. We note that these flow from its reliance on the DrugDex ® compendium rather than an independent review.
    - It does not explicitly note when the use of a drug or biologic is not recommended (i.e., denoted with a "Class III" rating in DrugDex ®) when validated evidence is appropriate.
    - It provides information regarding the appropriate patient population and appropriate circumstance and time for the use of a drug or biologic alone or in combination and therefore provides explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies.
    - It does not explicitly note an "Equivocal" listing (i.e., denoted as "Class indeterminate" in DrugDex ®) when validated evidence is equivocal.
    - It incorporates a process for identification and notification of potential conflicts of interest of the compendia's parent and sibling organizations, internal and external reviewers and internal and external committee members, with an established procedure to manage recognized conflicts. The policy and

process are disclosed to subscribers via its website as is a listing of all potential and real conflicts of interest.

3. DrugPoints ® is available to subscribers via the internet.

4. Public comment was divided on this request. We have addressed the points raised by the commenters in the analysis above.

In summary, we have determined that Thomson Micromedex DrugPoints ® meets the definition of a compendium as defined by 42 C.F.R. § 414.930(a); 72 *Fed. Reg.* 66222, 66404 but fails to satisfactorily address several of the desirable characteristics recommended by the MedCAC and referenced in the regulation. Specifically, DrugPoints ® itself does not explicitly note when the use of a drug or biologic is not recommended, nor does it explicitly note an "Equivocal" listing when validated evidence is equivocal. The publisher notes that these issues are addressed in DrugDex ®, from which DrugPoints ® is derived. However, we note that a user of DrugPoints ® cannot access DrugDex ® from DrugPoints ®. Rather, a user would have to separately obtain access to DrugDex ® for this information.

The process as defined by 42 C.F.R. § 414.930(c)(1)(vi); 72 *Fed. Reg.* 66222, 66404 includes a provision that a request include "[a] single compendium as its subject." Thus, we consider DrugPoints ® as the subject of this request and will not credit to its application such information that must be accessed through another compendium

Conclusion

Thomson Micromedex DrugPoints ® is not an authoritative compendium for such purposes as defined and outlined in 42 C.F.R. § 414.930(a); 72 *Fed. Reg.* 66222, 66404. Therefore, we are not adding Thomson Micromedex DrugPoints ® to the list of compendia in Chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual, for use in the determination of a "medically-accepted indication" of drugs and biologicals used off-label in an anticancer chemotherapeutic regimen.

Additional Materials:

Public comment from ImClone

Contacts

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Jim Gottstein

From: Jim Gottstein <jim.gottstein@psychrights.org>
Sent: Friday, November 08, 2013 12:59 PM
To: 'Ward, Stacy G. (USAWIE)'
Cc: 'Brad Foley'; 'Mark Larson'; 'Thomas L. Storm'; tobywatson@gmail.com; 'Rebecca Gietman'; jim.gottstein@psychrights.org
Subject: RE: DrugPoints -- Not

Hi Stacy,

Gee, then can you tell me what CMS' position is or to whom I should direct the question? When we talked on the phone you said a Rule 30(b)(6) subpoena would not be helpful. Is it necessary?

I am not trying to be difficult. It is just that it seems this should be an easy question to answer. Until a few weeks ago, I was confident there was no successor publication. Since I saw something that suggested otherwise, which was basically the Medicaire cancer drug situation, I have been seeking to get a definitive answer to no avail so far.

James B. (Jim) Gottstein, Esq.
President/CEO

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The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging and electroshock. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Currently, due to massive growth in psychiatric drugging of children and youth and the current targeting of them for even more psychiatric drugging, PsychRights has made attacking this problem a priority. Children are virtually always forced to take these drugs because it is the adults in their lives who are making the decision. This is an unfolding national tragedy of immense proportions. Extensive information about all of this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.

Exhibit
12

From: Ward, Stacy G. (USAWIE) [mailto:Stacy.G.Ward@usdoj.gov]
Sent: Friday, November 08, 2013 12:51 PM
To: Jim Gottstein
Cc: 'Brad Foley'; 'Mark Larson'; 'Thomas L. Storm'; tobywatson@gmail.com; 'Rebecca Gietman'; Rebecca Gietman; Thomas L. Storm
Subject: RE: DrugPoints -- Not

Jim: It's not that CMS doesn't have an official position. I am not authorized to speak for CMS and my contacts that I referenced in my original email were not at CMS.

Stacy

From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Friday, November 08, 2013 3:48 PM
To: Ward, Stacy G. (USAWIE)
Cc: 'Brad Foley'; 'Mark Larson'; 'Thomas L. Storm'; tobywatson@gmail.com; 'Rebecca Gietman'; jim.gottstein@psychrights.org; Rebecca Gietman; Thomas L. Storm
Subject: RE: DrugPoints -- Not

Thanks Stacy,

I didn't intend to misstate what you said, when I wrote "it does not appear . . ." I don't think I did, but apologize to the extent I did. It is curious that the Centers for Medicare and Medicaid Services doesn't just know the answer. Or have an official position. In any event, at this point, I think we just have to go with the American Hospital Formulary Service and DRUGDEX as the only applicable compendia.

Thank you for your assistance.

Jim

From: Ward, Stacy G. (USAWIE) [mailto:Stacy.G.Ward@usdoj.gov]
Sent: Friday, November 08, 2013 11:18 AM
To: Jim Gottstein
Cc: Brad Foley; Mark Larson; Thomas L. Storm; tobywatson@gmail.com; Rebecca Gietman
Subject: RE: DrugPoints -- Not

Jim: as we discussed, I have checked with a couple of sources and neither of them had heard of DrugPoints being the successor to the U.S. Pharmacopeia. This is not the official position of the Centers for Medicare and Medicaid Services, nor the United States' government. I was simply trying to obtain information to get you off in the right direction.

Stacy Gerber Ward
Assistant United States Attorney
E.D. Wisconsin

From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Friday, November 08, 2013 1:59 PM
To: Ward, Stacy G. (USAWIE)
Cc: jim.gottstein@psychrights.org; Brad Foley; Mark Larson; Thomas L. Storm; tobywatson@gmail.com; Rebecca Gietman
Subject: DrugPoints -- Not

Hi Stacy,

Thanks for following up on my question and advising me that it does not appear DrugPoints or any other publication is the successor to United States Pharmacopeia–Drug Information, leaving just the American Hospital Formulary Service Drug Information, and DRUGDEX as the compendia incorporated by reference into 42 U.S.C. § 1396r–8(k)(6), § 1396r–8(g)(1)(B)(i). *See, U.S. v. King-Vassel*, 728 F.3d 707, 716 (2013*)*

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The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging and electroshock. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Currently, due to massive growth in psychiatric drugging of children and youth and the current targeting of them for even more psychiatric drugging, PsychRights has made attacking this problem a priority. Children are virtually always forced to take these drugs because it is the adults in their lives who are making the decision. This is an unfolding national tragedy of immense proportions. Extensive information about all of this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.

DRUGPOINT D926134

MICROMEDEX

DrugPoints® System
Database updated September 2013

Ziprasidone Hydrochloride

Name Info:

US Trade Names
- Geodon

Class
- Antipsychotic
- Benzisothiazoyl

Regulatory Status
- RX

Generic Availability
- Yes

Black Box WARNING:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in clinical trials were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that antipsychotic drugs may increase mortality. It is unclear from these studies to what extent the mortality findings may be attributed to the antipsychotic drug as opposed to patient characteristics. Ziprasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis .

Contraindications:/Warnings

Contraindications
- concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class IA and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect
- heart failure, uncompensated
- hypersensitivity to ziprasidone
- myocardial infarction, acute and recent
- QT prolongation, including congenital long QT syndrome, known history of

Precautions
- elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported when antipsychotics were used to treat behavioral disorders associated with dementia
- agranulocytosis, including fatal cases, has been reported
- aspiration pneumonia, patients at risk for; esophageal dysmotility and aspiration have been reported with antipsychotic drug use
- conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with

antipsychotic agents
- diabetes mellitus or risk factors for diabetes mellitus (eg, obesity, family history); increased risk of worsening of glucose control or severe hyperglycemia; monitoring recommended
- hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) has been reported with atypical antipsychotic use; monitoring recommended
- hyperprolactinemia may occur and may result in galactorrhea, amenorrhea, gynecomastia, impotence, and decreased bone density
- hypotension, orthostatic, may occur; especially during initial dose titration and in patients with known cardiovascular disease (eg, history of myocardial infarction or ischemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or at risk for hypotension (eg, dehydration, hypovolemia, and antihypertensive therapy)
- leukopenia/neutropenia has been reported; increased risk with history of drug-induced leukopenia/neutropenia or preexisting low WBC; monitoring recommended; discontinue use if suspected
- metabolic changes (ie, dyslipidemia, body weight gain, and hyperglycemia) have been reported with atypical antipsychotic use; monitoring of weight and blood glucose recommended
- neuroleptic malignant syndrome (NMS), potentially fatal, has been reported; immediately discontinue therapy if NMS is suspected
- priapism has been reported; severe cases may require surgical intervention
- QT prolongation, possibly resulting in torsade de pointes and sudden death, has been reported; risk increased in patients with bradycardia, hypokalemia, hypomagnesemia, and congenital QTc prolongation, and with concomitant use of other drugs that prolong the QTc interval; monitoring recommended; discontinue with persistent QTc measurements of greater than 300 milliseconds
- seizure disorder, history, or conditions that lower the seizure threshold (eg, Alzheimer dementia), particularly in the elderly
- suicide risk; close monitoring of high-risk patients recommended
- tardive dyskinesia, potentially irreversible, may occur; increased risk in elderly, especially elderly women, and patients receiving higher cumulative doses and/or longer duration of therapy; discontinue treatment if appropriate
- report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

Pregnancy Category
- Ziprasidone: C (FDA)
- Ziprasidone: B3 (AUS)

Breast Feeding
- Ziprasidone: Micromedex: Infant risk cannot be ruled out.

Drug Interactions:

Contraindicated
Major
Moderate

Adverse Effects:

COMMON
SERIOUS

Dosing & Indications

Adult Dose
- Bipolar I disorder, Acute manic or mixed episodes, monotherapy: day 1, 40 mg twice daily with food; day 2, 60 or 80 mg twice daily; then adjust to 40 to 80 mg twice daily
- Bipolar I disorder, to lithium or valproate; Adjunct: 40 mg to 80 mg twice a day as an adjunct to lithium or valproate
- Schizophrenia: initial, 20 mg ORALLY twice a day with food; may increase dosage every 2 days up to 80 mg twice a day
- Schizophrenia: maintenance, 20 to 80 mg ORALLY twice a day (MAX recommended dose is 80 mg twice a day); to ensure use of the lowest effective dose, observe for improvement for several weeks before upward dosage adjustment

Pediatric Dose

- safety and effectiveness in pediatric patients have not been established

Dose Adjustments

- geriatrics: no dose adjustment needed
- hepatic impairment: no dose adjustment needed
- renal impairment: no dose adjustment needed

FDA Labeled Indications

- Bipolar I disorder, Acute manic or mixed episodes, monotherapy
- Bipolar I disorder, to lithium or valproate; Adjunct
- Schizophrenia

Non-FDA Labeled Indications

- Schizoaffective disorder

Mechanism of Action/Pharmacokinetics

Mechanism of Action

- Ziprasidone hydrochloride is a psychotropic agent and its efficacy in schizophrenia is postulated to be from antagonism of both dopamine type 2 (D2) and serotonin type 2 (5HT2) receptors. It also exhibits high antagonistic binding affinity to alpha(1)-adrenergic receptors and other dopamine and serotonin receptors as well as moderate affinity for histamine H(1) receptor. The exact mechanism in bipolar disorder is unknown .

Pharmacokinetics

Absorption

Distribution

Metabolism

Excretion

Elimination Half Life

Administration/Monitoring

Administration

- Oral

Monitoring

- improvement in signs and symptoms of schizophrenia or manic or mixed episodes associated with bipolar disorder are indicative of efficacy
- personal and family history of obesity, diabetes mellitus, and cardiovascular disease; baseline, and updated annually
- CBC with differential; frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia or neutropenia
- fasting blood glucose test; baseline, at week 12, and annually in all patients; more frequently for patients with risk factors for diabetes mellitus; diabetic patients should be closely monitored for worsening glucose control
- fasting lipid profile; baseline, at week 12, and every 5 years thereafter
- serum potassium and magnesium, especially in patients prone to electrolyte disturbances; baseline, and periodically
- blood pressure; baseline, at week 12, and annually thereafter; more frequently in patients with risk factors for hypertension
- waist circumference; baseline, and annually thereafter
- weight and BMI; baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter
- tardive dyskinesia; prior to treatment and annually thereafter; every 6 months in patients with higher risk (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects)
- suicide risk; patients at high-risk for suicide should be closely supervised during therapy

How Supplied

- Generic
- Geodon

Toxicology

Clinical Effects
- ZIPRASIDONE

Treatment of Exposure
- ZIPRASIDONE

Range of Toxicity
- ZIPRASIDONE

Clinical Teaching

- Patient should avoid activities requiring mental alertness or coordination, as this medicine may cause dizziness and somnolence.
- Drug may impair heat regulation. Advise patient to use caution with activities leading to an increased core temperature, such as strenuous exercise, exposure to extreme heat, or dehydration.
- Instruct patient to rise slowly from a sitting/supine position, as drug may cause orthostatic hypotension.
- This drug may cause nausea or headache.
- Instruct patient to report signs/symptoms of bradycardia, arrhythmia, tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities), or neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).
- Advise diabetic patients to report worsening of glycemic control.
- Patient should not drink alcohol while taking this drug.

End of Document

DRUGPOINT D922222

MICROMEDEX
DrugPoints® System
Database updated 20130901

Risperidone

Name Info:
US Trade Names Risperdal
Risperdal Consta
Risperdal M-Tab
RisperiDONE M-Tab **Class** Antipsychotic
Benzisoxazole **Regulatory Status** RX **Generic Availability** Yes

Black Box WARNING:

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in clinical trials were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that antipsychotic drugs may increase mortality. It is unclear from the observational studies to what extent these mortality findings may be attributed to the antipsychotic drug as opposed to patient characteristics. Risperidone is not approved for the treatment of patients with dementia-related psychosis .Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risperidone is not approved for the treatment of patients with dementia-related psychosis .

Contraindications:/Warnings
Contraindications hypersensitivity to risperidone , paliperidone (an active metabolite of risperidone) or to any product component **Precautions** elderly patients with dementia-related psychosis (unapproved use); increased risk of death and increased risk of cerebrovascular events (cerebrovascular accidents and TIA, some fatal); most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia)
agranulocytosis, leukopenia, and neutropenia have been reported; risk factors include preexisting low WBC and history of drug-induced leukopenia or neutropenia; monitoring recommended; discontinue if significant WBC decline with no other causative factors or if patient has severe neutropenia (ie, absolute neutrophil count less than 1000/mm(3))
cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension
conditions that may contribute to elevated body temperature; disruption of body temperature regulation has been

reported with antipsychotic agents
diabetes mellitus or risk factors for diabetes mellitus (eg, obesity, family history); increased risk of worsening of glucose control or severe hyperglycemia; monitoring recommended
dyslipidemia, which may increase cardiovascular or cerebrovascular risk has been reported
elderly patients, especially elderly women; increased risk of tardive dyskinesia
elderly patients; increased risk of orthostatic hypotension, especially during the initial dose-titration period (oral)
esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia
hepatic impairment; increase in the free fraction of risperidone reported with severe impairment; dosage adjustment recommended
hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) has been reported with atypical antipsychotic use; monitoring recommended
hyperprolactinemia; may result in galactorrhea, amenorrhea, gynecomastia, impotence, hypogonadism, and decreased bone density; incidence of hyperprolactinemia appears to be higher with risperidone relative to other antipsychotic agents
increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia
neuroleptic malignant syndrome (NMS), potentially fatal, has been reported in association with antipsychotic drugs; immediately discontinue drug if NMS is suspected
patients with phenylketonuria; contains phenylalanine, a component of aspartame (oral disintegrating tablet)
Parkinson disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications
priapism has been reported; severe cases may require surgical intervention
renal impairment; increased plasma concentrations reported with severe impairment (CrCl less than 30 mL/min/1.73 m(2)); dosage adjustment recommended
seizure disorder, history, or conditions that lower seizure threshold
suicide risk; close monitoring of high-risk patients recommended
tardive dyskinesia, potentially irreversible; discontinue treatment if appropriate
weight gain, which may increase cardiovascular or cerebrovascular risk has been reported; monitoring recommended
report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch **Pregnancy Category** C (FDA)
B3 (AUS) **Breast Feeding** Micromedex: Infant risk cannot be ruled out.

Drug Interactions:

Contraindicated

Bepridil (theoretical) Cisapride (theoretical) Levomethadyl (theoretical) Mesoridazine (theoretical) Metoclopramide (theoretical) Pimozide (theoretical) Terfenadine (theoretical) Thioridazine (theoretical)

Major

Acecainide (theoretical) Ajmaline (probable) Amiodarone (theoretical) Amisulpride (theoretical) Amitriptyline (theoretical) Amoxapine (theoretical) Aprindine (theoretical) Arsenic Trioxide (theoretical) Asenapine (theoretical) Astemizole (theoretical) Azimilide (theoretical) Bretylium (theoretical) Chloral Hydrate (theoretical) Chloroquine

(theoretical) Chlorpromazine (theoretical) Citalopram (probable) Clarithromycin (theoretical) Desipramine (theoretical) Dibenzepin (theoretical) Disopyramide (probable) Dofetilide (theoretical) Dolasetron (theoretical) Doxepin (theoretical) Droperidol (theoretical) Encainide (theoretical) Enflurane (theoretical) Erythromycin (theoretical) Flecainide (theoretical) Fluconazole (theoretical) Foscarnet (theoretical) Gemifloxacin (theoretical) Ginkgo Biloba (probable) Halofantrine (theoretical) Haloperidol (theoretical) Halothane (theoretical) Hydromorphone (theoretical) Hydroquinidine (probable) Ibutilide (theoretical) Imipramine (theoretical) Isoflurane (theoretical) Isradipine (theoretical) Lidoflazine (theoretical) Linezolid (probable) Lithium (probable) Lorcainide (theoretical) Mefloquine (theoretical) Milnacipran (theoretical) Nortriptyline (theoretical) Octreotide (theoretical) Pentamidine (theoretical) Pirmenol (probable) Prajmaline (probable) Probucol (theoretical) Procainamide (probable) Prochlorperazine (theoretical) Propafenone (theoretical) Protriptyline (theoretical) Quetiapine (probable) Sematilide (theoretical) Sertindole (theoretical) Simvastatin (probable) Sotalol (theoretical) Spiramycin (theoretical) Sulfamethoxazole (theoretical) Sultopride (theoretical) Tedisamil (theoretical) Telithromycin (theoretical) Tetrabenazine (theoretical) Tramadol (theoretical) Trifluoperazine (theoretical) Trimethoprim (theoretical) Trimipramine (theoretical) Vasopressin (theoretical) Zolmitriptan (theoretical) Zotepine (theoretical)

Moderate

Bupropion (probable) Carbamazepine (probable) Cimetidine (probable) Fluoxetine (probable) Fosphenytoin (probable) Itraconazole (established) Ketoconazole (established) Lamotrigine (probable) Levorphanol (probable) Methadone (probable) Midodrine (probable) Paroxetine (established) Phenobarbital (probable) Phenytoin (probable) Ranitidine (probable) Ritonavir (probable) Valproic Acid (probable)

Adverse Effects:

COMMON

Dermatologic: Rash (oral, adults, 1% to 4%; pediatrics, up to 11% ; IM, less than 4%) Endocrine metabolic: Hyperprolactinemia (oral, adults, less than 1%; pediatrics, 49% to 87% ; IM, less than 4%), Weight increased (oral, adult, 8.7% to 20.9%; pediatric, 14% to 32.6% ; IM, adult, 8% to 10%) Gastrointestinal: Constipation (oral, 8% to 21% ; IM, 5% to 7%), Diarrhea (oral, 1% to 8% ; IM, less than 4%), Excessive salivation (oral, 1% to 10% ; IM, 1% to 4%), Increased appetite (oral, adult, more than 5%; pediatric, 4% to 47% ; IM, 4%), Indigestion (oral, 2% to 10% ; IM, 6%), Nausea (oral, 4% to 16% ; IM, 3% to 4%), Upper abdominal pain (oral, adult, more than 5%; pediatric, 13% to 16%), Vomiting (oral, 10% to 25% ; IM, less than 4%), Xerostomia (oral, 4% to 15% ; IM, up to 7%) Neurologic: Akathisia (oral, up to 10% ; IM, 4% to 11%), Dizziness (oral, 4% to 16% ; IM, 3% to 11%), Dystonia (oral, adult, 3% to 5%; pediatric, 2% to 6% ; IM, adult, less than 4%), Parkinsonism (oral, 6% to 28% ; IM, 8% to 15%), Sedated (oral, adult, 3% to 6%; pediatric, 8% to 29%), Tremor (oral, 2% to 12% ; IM, 3% to 24%) Ophthalmic: Blurred vision (oral, 1% to 7% ; IM, 2% to 3%) Psychiatric: Anxiety (oral, up to 16% IM, less than 4%) Respiratory: Cough (oral, adults, 2%; pediatrics, 24% ; IM, 2% to 4%), Nasal congestion (oral, adult, 4% to 6%; pediatric, 13%), Nasopharyngitis (oral, adult, 3% to 4%; pediatric, 21%), Pain in throat (oral, adult, more than 5%; pediatric, 3% to 10%), Upper respiratory infection (oral, 2% to 8% ; IM, 2% and 6%) Other: Fatigue (oral, adult, 1% to 3%; pediatric, 18% to 42% ; IM, 3% to 9%), Pain, General (IM, 1% to 4%)

SERIOUS

Cardiovascular: Prolonged QT interval, Sudden cardiac death, Syncope (oral, up to 1% ; IM, up to 2%) Endocrine metabolic: Diabetic ketoacidosis, Hypothermia Gastrointestinal: Pancreatitis Hematologic: Agranulocytosis, Leukopenia, Neutropenia, Thrombocytopenia, Thrombotic thrombocytopenic purpura Neurologic: Cerebrovascular accident (oral, less than 5% ; IM, less than 4%), Seizure (oral, 0.3% ; IM, 0.3%), Tardive dyskinesia (oral, less than 5% ; IM, less than 4%) Reproductive: Priapism Respiratory: Pulmonary embolism Other: Neuroleptic malignant syndrome (oral, adults, less than 1%; pediatrics, less than 5%)

Dosing & Indications

Adult Dose Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets

previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone long-acting injection to ensure that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun

Bipolar I disorder: (oral, monotherapy or in combination with lithium or valproate) initial, 2 to 3 mg ORALLY once a day; maintenance, dosage adjustments should be made in increments of 1 mg/day at intervals of at least 24 hours; doses higher than 6 mg/day have not been evaluated in clinical trials

Bipolar I disorder: (IM, monotherapy or in combination with lithium or valproate) establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; initial, 25 mg IM every 2 weeks; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued

Bipolar I disorder: (IM, monotherapy or in combination with lithium or valproate) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks

Schizophrenia: (oral) initial, 2 mg/day ORALLY, administered either once or twice daily; increase as tolerated in increments of 1 to 2 mg/day (or slower) at intervals not less than 24 hours, to a recommended dose of 4 to 8 mg/day; doses above 6 mg/day for twice-daily dosing were not shown to be more efficacious than lower doses; the safety of doses above 16 mg/day has not been evaluated in clinical trials

Schizophrenia: (oral) maintenance, 2 mg/day to 8 mg/day

Schizophrenia: (oral) if risperidone is discontinued, restart with the initial titration schedule

Schizophrenia: (oral) when switching from other antipsychotic agents, minimize the period of overlapping administration .

Schizophrenia: (oral) when switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection

Schizophrenia: (IM) establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; initial, 25 mg IM every 2 weeks; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued

Schizophrenia: (IM) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks **Pediatric Dose** safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients younger than 18 years

safety and effectiveness of oral risperidone in pediatric patients younger than 13 years with schizophrenia have not been established

safety and effectiveness of oral risperidone in pediatric patients younger than 10 years with bipolar mania has not been established

safety and effectiveness or oral risperidone in pediatric patients younger than 5 years with autistic disorder have not been established

Autistic disorder - Irritability: dosing individualized according to the response and tolerability, over a dose range of 0.5 to 3 mg/day

Autistic disorder - Irritability: (5 years or older; weight less than 20 kg) initial, 0.25 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 0.5 mg/day; maintenance, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days and may increase doses at 2-week intervals or longer, in increments of 0.25 mg per day to achieved sufficient clinical response; dosing data in children weighing less than 15 kg is not available

Autistic disorder - Irritability: (age 5 years or older; weight 20 kg or greater) initial, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 1 mg/day; maintenance, 1 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days; may increase doses at 2-week intervals or longer, in increments of 0.5 mg per day to achieve sufficient clinical response

Autistic disorder - Irritability: in patients with persistent somnolence, administering a once daily dose at bedtime, or half the daily dose twice daily, or a reduced dose may be beneficial

Bipolar I disorder: (10 years or older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 2.5 mg/day

Bipolar I disorder: in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial

Schizophrenia: (13 years or older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 3 mg/day

Schizophrenia: in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial

Schizophrenia: if risperidone is discontinued, restart with the initial titration schedule

Schizophrenia: when switching from other antipsychotic agents, minimize the period of overlapping administration .

Schizophrenia: when switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection **Dose Adjustments** concomitant CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital): titrate dose to desired effect

concomitant CYP2D6 inhibitors (eg, fluoxetine, paroxetine): titrate dose to desired effect

debilitated patients (oral): initial dose 0.5 mg ORALLY twice a day; dosage increases in these patients should be in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week. If a once-a-day dosing regimen is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2 to 3 days at the target dose and then switched to once-daily dosing

geriatric (oral): initial dose 0.5 mg ORALLY twice a day; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week. If a once-a-day dosing regimen is desired, initiate and titrate on a twice-a-day regimen for 2 to 3 days to the target dose; switch to a once-a-day dosing regimen can be done thereafter

geriatric (IM): 25 mg IM every 2 weeks

hepatic impairment (IM): administer titrated doses of ORAL risperidone prior to starting IM therapy in these patients; initial, 0.5 mg ORALLY twice daily for 1 week, then dose may be increased to 1 mg twice daily OR 2 mg once daily

in the second week; if a 2 mg ORAL dose is well tolerated, 12.5 mg or 25 mg of the long-acting injection may be given IM every 2 weeks

hepatic impairment, severe (oral): initial dose, 0.5 mg ORALLY twice daily; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week

hypotension (oral): patients either predisposed to hypotension or for whom hypotension would pose a risk, initial dose 0.5 mg ORALLY twice a day; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week

poor tolerability to psychotropic medications: although the efficacy has not been confirmed in clinical trials, 12.5 mg IM may be given

renal impairment, severe (oral): initial dose, 0.5 mg ORALLY twice daily; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week

renal impairment (IM): administer titrated doses of ORAL risperidone prior to starting IM therapy in these patients; initial, 0.5 mg ORALLY twice daily for one week, then dose may be increased to 1 mg twice daily OR 2 mg once daily in the second week; if a 2 mg ORAL dose is well tolerated, 12.5 mg or 25 mg of the long-acting injection may be given IM every 2 weeks **FDA Labeled Indications**

Autistic disorder - Irritability

FDA Approval: Adult, no Pediatric, yes 5 years or older, oral only
Efficacy: Pediatric, Effective
Strength of Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category B

Bipolar I disorder

FDA Approval: Adult, yes oral and IM Pediatric, yes 10 years or older, oral only
Efficacy: Adult, Effective Pediatric, Evidence favors efficacy
Strength of Recommendation: Adult, Class IIa Pediatric, Class IIb
Strength of Evidence: Adult, Category B Pediatric, Category B

Schizophrenia

FDA Approval: Adult, yes oral and IM Pediatric, yes 13 years or older, oral only
Efficacy: Adult, Effective Pediatric, Evidence favors efficacy
Strength of Recommendation: Adult, Class IIa Pediatric, Class IIb
Strength of Evidence: Adult, Category B Pediatric, Category B **Non-FDA Labeled Indications**

Behavioral syndrome - Mental retardation

FDA Approval: Adult, no Pediatric, no
Efficacy: Adult, Evidence favors efficacy Pediatric, Evidence favors efficacy
Strength of Recommendation: Adult, Class IIb Pediatric, Class IIb
Strength of Evidence: Adult, Category B Pediatric, Category B

Gilles de la Tourette's syndrome

FDA Approval: Adult, no Pediatric, no
Efficacy: Adult, Evidence favors efficacy Pediatric, Evidence favors efficacy
Strength of Recommendation: Adult, Class IIb Pediatric, Class IIb
Strength of Evidence: Adult, Category B Pediatric, Category B

Pervasive developmental disorder
FDA Approval: Adult, no Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Strength of Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

Mechanism of Action/Pharmacokinetics

Mechanism of Action The mechanism by which risperidone exerts its antipsychotic effect is unknown. Risperidone is a selective monoaminergic antagonist with a strong affinity for serotonin Type 2 (5-HT2) receptors and a slightly weaker affinity for dopamine Type 2 (D2) receptors. The antipsychotic activity of risperidone may be mediated through antagonism at a combination of these receptor sites, particularly through blockade of cortical serotonin receptors and limbic dopamine systems. Risperidone also has moderate affinity for the alpha 1-adrenergic, alpha 2-adrenergic, and H1-histaminergic receptors. The affinity of risperidone for the serotonin 5-HT1A, 5-HT1C, and 5-HT1D receptors is low to moderate, while its affinity for dopamine D1 and the haloperidol-sensitive sigma site is weak. Risperidone has negligible affinity for cholinergic-muscarinic, beta-adrenergic, and serotonin 5-HT1B and 5-HT3 receptors. **Pharmacokinetics**

Absorption

Tmax, IM: 29 to 31 days Tmax, Oral, adult: 1 hour Tmax, Oral, pediatric: 2 hours Bioavailability, oral: 70% Effects of food: none

Distribution

Vd: 1.1 L/kg (1 to 2 L/kg) Protein binding, adults: 90% (risperidone); 77% (9-hydroxyrisperidone) Protein binding, adolescents: 85.3% (risperidone), 71.9% (9-hydroxyrisperidone) Protein binding, children: 88.3% (risperidone); 75% (9-hydroxyrisperidone)

Metabolism

Hepatic: extensively via CYP2D6 pathway 9-hydroxy-risperidone: active

Excretion

Fecal: 14% (risperidone and its metabolites) Risperidone, Renal: adults, 70%; adolescents, 7.4%; children, 4.3%; 9-hydroxyrisperidone, Renal: adolescents, 26%; children, 23.9% Renal clearance: 0.96 L/hr Total body clearance: adults, 3.2 to 3.3 L/hr in poor CYP2D6 metabolizers; 13.7 L/hr (risperidone) and 5 L/hr (risperidone plus 9-hydroxyrisperidone) in extensive CYP2D6 metabolizers Total body clearance: adolescent, 18.1 L/hr; children, 13.5 L/hr

Elimination Half Life

3 to 20 hours (oral) ; 2.9 to 6 days (IM) active moiety: 8 days 9-hydroxyrisperidone: 21 to 30 hours

Administration/Monitoring

Administration

Intramuscular

Intramuscular: (long-acting injection) administer by deep IM injection into the deltoid or gluteal muscles; must be administered with only the appropriate needle supplied in the dose pack, alternating between the 2 arms or 2 buttocks; do not inject intravenously Intramuscular: (long-acting injection) do not combine different dosage strengths in a single administration Intramuscular: (long-acting injection) reconstitute only with diluent supplied in the dose pack; use immediately after reconstitution, but may be stored at room temperature (not exceeding 77 degrees F (25 degrees C)) for up to 6 hours; shake vigorously to resuspend just prior to administration

Oral

Oral: (orally disintegrating tablets) consume tablet immediately once it is removed from the blister unit; tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid Oral: (orally disintegrating tablets) do not split or chew Oral: (orally disintegrating tablets) peel back foil to expose tablet; do not push the tablet through the foil backing Oral: (solution) may be administered directly from the calibrated pipette, or can be mixed with water, coffee, orange juice, or low-fat milk; it is NOT compatible with cola or tea Oral: may be taken with or without meals **Monitoring** improvement in the signs and symptoms of bipolar disorder (manic or mixed episodes), schizophrenia, or irritability associated with autistic disorder are indicative of efficacy

personal and family history of obesity, diabetes mellitus, and cardiovascular disease, baseline, and updated annually

CBC with differential; frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia or neutropenia

fasting blood glucose test; baseline, at week 12, and annually in all patients; more frequently for patients with risk factors for diabetes mellitus; diabetic patients should be closely monitored for worsening glucose control

fasting lipid profile; baseline, at week 12, and every 5 years thereafter

blood pressure; baseline, at week 12, and annually thereafter; more frequently in patients with risk factors for hypertension

waist circumference; baseline, and annually thereafter

weight and BMI; baseline, at week 4, at week 8, at week 12, following initiation and change in therapy, and quarterly thereafter

orthostatic vital signs in patients predisposed to hypotension

tardive dyskinesia; baseline, and annually thereafter; every 6 months in patients with higher risk (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects)

suicide risk; patients at high-risk for suicide should be closely supervised during therapy

How Supplied

Generic

Oral Solution: 1 MG/ML Oral Tablet: 0.25 MG, 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG Oral Tablet, Disintegrating: 0.25 MG, 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG

Risperdal Consta
Intramuscular Powder for Suspension, Extended Release: 12.5 MG, 25 MG, 37.5 MG, 50 MG

Risperdal M-Tab
Oral Tablet, Disintegrating: 0.5 MG, 1 MG, 2 MG

Risperdal M-TAB
Oral Tablet, Disintegrating: 3 MG, 4 MG

Risperdal
Oral Solution: 1 MG/ML Oral Tablet: 0.25 MG, 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG

RisperiDONE M-Tab
Oral Tablet, Disintegrating: 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG

Toxicology

Clinical Effects

RISPERIDONE

USES: An atypical antipsychotic used to treat schizophrenia. PHARMACOLOGY: A benzisoxazole derivative with high antagonist affinity for dopamine (D2) and serotonin (5-HT2) receptors. TOXICOLOGY: Dopamine receptor blockade results in extrapyramidal symptoms, and alpha1-adrenergic effects are responsible for orthostatic hypotension. Its affinity, albeit low affinity, for histamine receptors contributes to anticholinergic effects. EPIDEMIOLOGY: Unintentional and deliberate poisonings of atypical antipsychotics are common and occasionally severe. MILD TO MODERATE TOXICITY: Tachycardia and hypotension are common. Depressed mental status, somnolence and extrapyramidal symptoms are also fairly common. In most cases, symptoms manifest mainly as mild central nervous system effects and reversible cardiovascular and neuromuscular effects. SEVERE TOXICITY: QTc prolongation, extrapyramidal symptoms likely. Respiratory depression, seizure, or coma could potentially occur, as well as neuroleptic malignant syndrome. ADVERSE EFFECTS: COMMON: Nausea, diarrhea, constipation, dizziness, somnolence, tachycardia, orthostatic hypotension, and extrapyramidal disorder. **Treatment of Exposure**

RISPERIDONE

Support: MANAGEMENT OF MILD TO MODERATE TOXICITY: Management will primarily be symptomatic and supportive. Treat seizures with benzodiazepines. Manage mild hypotension with IV fluids. MANAGEMENT OF SEVERE TOXICITY: Treat seizures with benzodiazepines. Treat hypotension with IV fluids and pressors (norepinephrine preferred) if needed. Treat ventricular dysrhythmias with sodium bicarbonate, use lidocaine or amiodarone if bicarbonate unsuccessful. Manage severe extrapyramidal symptoms with anticholinergics and/or benzodiazepines. Although rare, treat neuroleptic malignant syndrome with benzodiazepines, bromocriptine, consider dantrolene, as well as cooling and supportive measures. Decontamination: PREHOSPITAL: Prehospital gastrointestinal decontamination is not recommended due to the potential for somnolence, seizures and dystonic reaction. HOSPITAL: Administer activated charcoal if the overdose is recent, the patient is not vomiting, and is able to maintain airway. Airway management: Insure adequate ventilation and perform endotracheal intubation early in patients with serious cardiac toxicity, coma or significant CNS depression. Antidote: None Seizure: Administer IV benzodi-

azepines; add propofol, or barbiturates if seizures recur or persist. Hypotensive episode: Treat hypotension with intravenous fluids, if hypotension persists administer vasopressors. Norepinephrine is preferred; the manufacturer recommends avoidance of epinephrine and dopamine since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade. Conduction disorder of the heart: Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalemia, hypocalcemia, and hypomagnesemia). Sodium bicarbonate is generally first line therapy for QRS widening and ventricular dysrhythmias, administer 1 to 2 mEq/kg, repeat as needed to maintain blood pH between 7.45 and 7.55. In patients unresponsive to bicarbonate, consider lidocaine or amiodarone. Neuroleptic malignant syndrome: Oral bromocriptine, benzodiazepines or oral or IV dantrolene in conjunction with cooling and other supportive measures. Monitoring of patient: Monitor vital signs and mental status. Obtain an ECG and institute continuous cardiac monitoring. Monitor serum electrolytes including sodium, potassium, and magnesium, as well as glucose; obtain CBC. Enhanced elimination procedure: Hemodialysis and hemoperfusion are UNLIKELY to be of value because of the high degree of protein binding. Patient disposition: HOME CRITERIA: Children less than 12 years of age who are naive to risperidone can be observed at home following an unintentional ingestion of 1 mg or less and are only experiencing mild sedation. All patients, 12 years of age or older, who are naive to risperidone, can be observed at home following an unintentional ingestion of 5 mg or less and are experiencing only mild sedation. All patients who are taking risperidone on a chronic basis can be observed at home if they have unintentionally ingested no more than 5 times their current single dose (not daily dose) of risperidone and are only experiencing mild sedation. Patients who have not developed signs or symptoms more than 6 hours after ingestion are unlikely to develop toxicity. OBSERVATION CRITERIA: Any patient with a deliberate ingestion or more than minor symptoms should be referred to a healthcare facility. Children less than 12 years of age who are naive to risperidone should be referred to a healthcare facility following an unintentional ingestion of more than 1 mg. All patients, 12 years of age or older, who are naive to risperidone should be referred to a healthcare facility following an unintentional ingestion of more than 5 mg. All patients who are taking risperidone on a chronic basis should be referred to a healthcare facility following an acute ingestion of more than 5 times their current single dose (not daily dose) of risperidone. ADMISSION CRITERIA: Patients with deliberate ingestions demonstrating cardiotoxicity, or persistent neurotoxicity should be admitted. CONSULT CRITERIA: Consult a medical toxicologist or Poison Center for assistance in managing patients with severe toxicity or in whom the diagnosis is unclear. **Range of Toxicity**

RISPERIDONE

TOXICITY: SUMMARY: CHILD: In drug naive children, an ingestion of 1 mg in a child less than 12 years of age should be considered potentially toxic, and an ingestion of more than 5 mg should be considered potentially toxic in a child 12 years or older. In children who are using risperidone on a regular basis, a does of more than 5 times their current single dose (not daily dose) should be considered potentially toxic. ADULT: Overdose of 270 mg in an adult resulted in dysrhythmias (supraventricular tachycardia, atrial flutter, prolonged QTc, bradycardia) and extrapyramidal symptoms. An adult developed tachycardia and QTc prolongation after ingesting an estimated dose of greater than 60 mg of risperidone. PEDIATRIC: A 15-year-old girl developed transient lethargy, hypotension, and tachycardia after ingesting 110 mg of risperidone. THERAPEUTIC DOSE: ADULT: 4 to 16 mg/day, with therapeutic effects usually in the range of 4 to 6 mg/day.

Clinical Teaching

Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and somnolence.

Drug may impair heat regulation. Advise patient to use caution with activities leading to an increased core temper-

ature, such as strenuous exercise, exposure to extreme heat, or dehydration.

Advise patient to rise from a sitting/lying position slowly, as drug may cause orthostatic hypotension.

This drug may cause constipation, dyspepsia, akathisia, agitation, anxiety, and weight gain.

Patient should report signs/symptoms of extrapyramidal effects, tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities), or neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).

Advise diabetic patients to monitor for signs/symptoms of hyperglycemia and to report difficulties with glucose control.

Instruct elderly patients to immediately report signs/symptoms of arrhythmia, heart failure, pneumonia, transient ischemic attack, or cerebrovascular accident.

Patient should not drink alcohol or use medicines that cause drowsiness while taking this drug.

Advise patients using injectable form to call healthcare professional if a dose is missed, as drug should be given on a regular schedule.

DRUGPOINT D922222

Appendix A. Strength of Recommendation and Evidence

Strength of Recommendation:

Class I - Recommended
The given test or treatment has been proven to be useful, and should be performed or administered.

Class IIa - Recommended, In Most Cases
The given test, or treatment is generally considered to be useful, and is indicated in most cases.

Class IIb - Recommended, In Some Cases
The given test, or treatment may be useful, and is indicated in some, but not most, cases.

Class III - Not Recommended
The given test, or treatment is not useful, and should be avoided.

Class Indeterminant - Evidence Inconclusive

Strength of Evidence:

Category A
Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.

Category B
Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).

Category C
Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.

No Evidence

- 9/30/2013 4:36:26 PM CDT (UTC -05:00)

- Date Accessed:
  - 10/9/2013 2:09:05 PM CDT (UTC -05:00)
- Electronic Address:
  - http://online.statref.com/Document.aspx?fxId=6&docId=1842
- Location In Title:
  - DRUGPOINTS® SYSTEM
    Appendices
    Appendix A. Strength of Recommendation and Evidence

Jim Gottstein

From: Jim Gottstein <jim.gottstein@psychrights.org>
Sent: Thursday, November 14, 2013 2:17 PM
To: 'Brad Foley'
Cc: jim.gottstein@psychrights.org; Rebecca Gietman; tobywatson@gmail.com; stacy.g.ward@usdoj.gov; Mark Larson
Subject: RE: Compendia

Hi Brad,

It is not United States Pharmacopeia–Drug Information. I suspect it is United States Pharmacopeia-National Formulary. It is not the statutorily incorporated compendia listed in 42 U.S.C. §1396r-8(g)(1)(B)(i)(II). Send me the cover page.

Jim

From: Brad Foley [mailto:bradley.foley@gebsc.com]
Sent: Thursday, November 14, 2013 1:25 PM
To: Jim Gottstein
Subject: RE: Compendia

Jim, we have obtained the US Pharmacopeia 2006 book and thus it is in existence.

Brad

From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Thursday, November 14, 2013 12:12 PM
To: Brad Foley
Cc: Mark Larson; jim.gottstein@psychrights.org; Rebecca Gietman; stacy.g.ward@usdoj.gov
Subject: RE: Compendia

Hi Brad,

I believe it is factually correct. What would you say is factually correct?

James B. (Jim) Gottstein, Esq.
President/CEO

Psych Rights
LAW PROJECT FOR PSYCHIATRIC RIGHTS

Law Project for Psychiatric Rights
406 G Street, Suite 206
Anchorage, Alaska 99501 USA

Exhibit
16

Phone: (907) 274-7686 Fax: (907) 274-9493
jim.gottstein@psychrights.org
http://psychrights.org/

The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging and electroshock. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Currently, due to massive growth in psychiatric drugging of children and youth and the current targeting of them for even more psychiatric drugging, PsychRights has made attacking this problem a priority. Children are virtually always forced to take these drugs because it is the adults in their lives who are making the decision. This is an unfolding national tragedy of immense proportions. Extensive information about all of this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.

From: Brad Foley [mailto:bradley.foley@gebsc.com]
Sent: Thursday, November 14, 2013 9:07 AM
To: Jim Gottstein
Cc: Mark Larson
Subject: Compendia

Jim, we will not stipulate to this. Your description is not factually accurate.

Brad

From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Thursday, November 14, 2013 6:03 AM
To: Mark Larson; Brad Foley
Cc: stacy.g.ward@usdoj.gov; Rebecca Gietman; jim.gottstein@psychrights.org; tobywatson@gmail.com
Subject: Compendia

Hi Mark and Brad,

You have been copied on correspondence between myself and Ms. Gerber Ward about the status of the compendia. Further research has not revealed any information to suggest there is a successor publication to the United States Pharmacopeia–Drug Information. However, we did find where DrugPoints was rejected as the successor publication for use in the determination of a "medically accepted indication" of drugs and biologicals off-label in an anticancer chemotherapeutic regimen under Medicare. I have (hopefully) attached that decision.

Therefore, will you stipulate that the American Hospital Formulary Service Drug and the DRUGDEX Information System are the only applicable compendia?

James B. (Jim) Gottstein, Esq.
President/CEO

Law Project for Psychiatric Rights
406 G Street, Suite 206
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http://psychrights.org/

The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging and electroshock. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Currently, due to massive growth in psychiatric drugging of children and youth and the current targeting of them for even more psychiatric drugging, PsychRights has made attacking this problem a priority. Children are virtually always forced to take these drugs because it is the adults in their lives who are making the decision. This is an unfolding national tragedy of immense proportions. Extensive information about all of this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.