DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR - 9 1999

TRANSMITTED VIA FACSIMILE

[redacted]
[redacted] Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Rd.
Titusville, NJ 08560-0200

RE: NDA #20-272, 20-588
Risperdal (risperidone) Tablets
Risperdal (risperidone) Oral Solution
MACMIS #6908

Dear [redacted]:

Reference is made to the Division of Drug Marketing, Advertising and Communications' (DDMAC) January 5, 1999, letter regarding promotional materials for Risperdal that were determined to be false, misleading, or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act. These materials included a campaign directed towards the use of Risperdal specifically for geriatric patients (i.e., "Hostile Outside, Fragile Inside").

We also refer to Janssen Research Foundation's (Janssen) response dated January 18, 1999, and a follow-up communication dated February 16, 1999. In its response, Janssen stated that identified materials, as well as materials with the same or similar violative issues, would be immediately discontinued. Janssen requested an extension in DDMAC's imposed deadline for action because it was completing a comprehensive review of all materials that were not in compliance with DDMAC's notification. The results of Janssen's completed review were submitted in the follow-up communication.

We finally refer to Janssen's February 16, 1999, request to meet with DDMAC and members of the Division of Neuropharmacologic Drug Products (DNDP) to discuss issues in the untitled letter with which Janssen disagrees or for which Janssen requests further explanation.

Janssen has presented arguments to support the continuation of the geriatric campaign for Risperdal. DDMAC has considered Janssen's arguments and is not persuaded. DDMAC is aware that Risperdal may be used in the geriatric population, and that the approved product labeling (PI) includes instructions for dosage and administration in

[redacted]
Janssen
NDA 20-272 (MACMIS 6908)

this population. DDMAC has consulted DNDP on the geriatric campaign, as well as all other aspects of the untitled letter. Our concern is three-fold. First, the materials cited in our untitled letter are materials that focus on the geriatric population when, in fact, there is limited data on the use of Risperdal in the elderly and the group was not specifically studied in the clinical trials for the drug. Second, the campaign "Hostile Outside, Fragile Inside" implies, without adequate substantiation, that Risperdal has been specifically shown to be effective in treating psychotic elderly patients with hostility. Finally, the safety and efficacy of Risperdal in the elderly was not particularly examined in "fragile" individuals (i.e., individuals with particular hepatic or renal concerns, or other concomitant illnesses). In its January 18, 1999, letter Janssen notes that practitioners prescribe Risperdal to elderly patients "in the absence of controlled clinical trials."

Janssen argues that schizophreniform disorder, schizoaffective disorder, bipolar disorder, and elderly psychosis are all approved indications for Risperdal because DNDP has authorized "relatively broad indications for this particular class of drugs." DDMAC and DNDP disagree with Janssen's interpretation of Risperdal's indication. The Indications and Usage section of the PI for Risperdal states that Risperdal is indicated for the management of the manifestations of psychotic disorders...established in short-term (6 to 8-weeks) controlled trials of schizophrenic patients." The clinical trials for Risperdal were not designed to examine bipolar disorder. The clinical trials for Risperdal were not designed to examine efficacy for specific disorders, therefore it would be misleading to claim that Risperdal is effective in any of these particularly.

DDMAC has reviewed Janssen's discussion and arguments concerning fair balance and is not persuaded. Janssen has requested a specific list of promotional pieces that DDMAC finds lacking in prominence and readability. It was not DDMAC's intent to give an exhaustive list of citations for each violation to Janssen, however examples of poor prominence and readability would include journal ads JPI-RS-470-1, JPI-RS-470-1R, JPI-RS-470-1RB, JPI-RS-470-1-C, and JPI-RS-450-2. With regard to fair balance in letters, DDMAC maintains that letters with the risk information confined to the area after the closing are considered to lack fair balance.

DDMAC is not persuaded by Janssen's arguments regarding materials that emphasize that Risperdal has a low incidence of certain side effects (i.e., excessive sedation and anticholinergic side effects) while minimizing the side effects that Risperdal does have (i.e., orthostatic hypotension, tardive dyskinesia, treatment-emergent extrapyramidal symptoms). This is an issue of prominence and appropriate emphasis. For example, tardive dyskinesia is a warning and orthostatic hypotension is a precaution. These side effects require more prominence than a list of other adverse events. Balance for claims of reduced incidence of a particular side effect belongs on the same page as the claim,

[redacted]

Janssen
NDA 20-272 (MACMIS 6908)

and requires comparable prominence and readability in order to put the claim in the appropriate context. (e.g., claims of low incidence of excessive sedation require balance, with sleep/fatigue related adverse events and the rate of their occurrence; claims of low incidence of movement disorders requires balance with disclosure of the incidence of movement disorders and the fact that this is dose-related).

Janssen argues that audited IMS data indicate that the average daily dose of Risperdal, over a four-year period, was 4.6-4.8 mg/day. Moreover, Janssen argues that the FDA recommended dose is 4-6 mg/day, thus is "beyond the spirit of the fair balance requirements...[and] counterproductive" to require Risperdal promotional materials to disclose adverse events rates for doses above 6 mg/day (i.e., incidence rates for 16 mg/day Risperdal). DDMAC has considered Janssen's argument and is not convinced. DDMAC agrees that the Dosage and Administration section of the PI does not "generally recommend" doses 6 mg/day. However, the PI also states that "antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day," and stresses the dose-dependence of adverse events. Adverse events such as sedation, movement disorders, and anticholinergic effects are all dose-related, and, with the exception of extrapyramidal symptoms, are found to be 2-3 times greater than placebo even for Risperdal doses of ≤10 mg/day. For example, somnolence for Risperdal was 3% (vs. 1% for placebo), and constipation was 7% (vs. 3% for placebo). Extrapyramidal symptoms have a high incidence overall (even placebo), but are particularly problematic and were the symptoms most associated with discontinuation. Thus, it is important to stress these adverse events and provide their incidence. It is also important to disclose that these are dose-related risks. DDMAC also notes that the Adverse Reactions section of the PI lists adverse events at ≤10 mg/day and 16 mg/day Risperdal compared to placebo.

DDMAC notes Janssen's discussion of comparative claims. Whether or not Janssen believes that "the mechanism-of-action of most psychotropics have been fairly well established over the years," the correlation of specific receptor antagonism to the clinical effectiveness and safety of Risperdal has not been established in adequate and well-controlled trials. Furthermore, promotional materials for Risperdal must be consistent with its PI that states that the mechanism of action for Risperdal is unknown.

DDMAC notes Janssen's acknowledgement that DNDP did not consider comparative trials against the standard of therapy to be adequately designed. Accordingly, Janssen has agreed to discontinue the use of such comparative claims.

DDMAC also notes that Janssen will discontinue promotional claims implying that Risperdal can improve health-related quality of life in the absence of adequate and well-controlled studies using validated instruments.

Janssen has agreed to discontinue all promotional materials cited by DDMAC in our January 18, 1999, letter, including materials with the same or similar presentations and messages. Thus, DDMAC has no further objections and considers this matter closed.

DDMAC acknowledges Janssen's request to meet with DDMAC and DRUDP for clarification and discussion regarding future promotional materials for Risperdal. Janssen's letter has enumerated its concerns and views regarding DDMAC's untitled letter. In this letter, DDMAC has considered Janssen's arguments, and has provided further clarification and discussion on issues raised by Janssen. DDMAC believes that this clarification should make a meeting unnecessary. If Janssen wishes to request a meeting for further clarification, it should submit a written request of unresolved issues to DDMAC for consideration. The written request should include a proposed agenda, a listing of planned attendees representing Janssen, a listing of requested participants from CDER, and the appropriate time for which supporting documentation will be sent to DDMAC.

If Janssen has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm.17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS 6908 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications