DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

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TRANSMITTED VIA FACSIMILE

Todd McIntyre, Ph.D.
Director, 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 Dr. McIntyre:

This letter concerns Janssen Research Foundation's (Janssen) promotional materials and activities for the marketing of Risperdal (risperidone) Tablets that have been reviewed by the Division of Drug Marketing, Advertising and Communications (DDMAC) as part of its monitoring and surveillance program. In particular, DDMAC is concerned with a campaign that markets Risperdal for geriatric patients. These materials include, but are not limited to sales aids (ID# RS-420, RS-422, RS-473, RS-494), journal ads (ID# RS-470-1, RS-470-1-C, RS-470-1RB, RS-470-2, RS-470-2RB), a display panel (ID# RS-468), brochures (ID# RS-459, RS-469), and a letter (ID #RS-308). Other recent materials include journal ads (ID # RS-450-2, RS-451-2, RS-451-2A, RS-451-C, RS-470-1R, RS-470-2R), letters (ID # RS-462S, RS-477-1, RS-477-1R), a flashcard (ID # RS-518), a calendar (ID #RS-474), and a computer program (ID #RS-463). DDMAC has concluded that these materials are false, misleading, and/or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Specifically, DDMAC has the following objections:

Geriatric Campaign

1. Janssen is disseminating materials that state or imply that Risperdal has been determined to be safe and effective for the elderly population in particular. There is limited data on the use of Risperdal in the elderly, and the elderly population was not specifically studied in the clinical trials for Risperdal. Thus, presentations that focus on this population are

misleading in that they imply that the drug has been found to be specifically effective in the elderly population.

Also, according to the approved product labeling (PI), there are safety considerations for Risperdal in the elderly population. In healthy elderly subjects, the clearance of both risperidone and its active metabolite was decreased, and the elimination half-lives were prolonged. Hepatic impairment would further increase the mean free fraction of plasma risperidone. Risperdal should be used cautiously in healthy elderly individuals because of the potential for decreased clearance of drug, potential drug interactions, hepatic and renal dysfunction, and cardiovascular sensitivity. The safety of Risperdal in "fragile" individuals or individuals with concomitant illnesses has not been evaluated in adequate and well-controlled studies.

2. Risperdal is indicated for the management of the manifestations of psychotic disorders. However, Janssen is disseminating materials that imply, without adequate substantiation, that Risperdal is safe and effective in specifically treating hostility in the elderly.

Efficacy

Materials that claim that Risperdal is indicated "for psychotic symptoms associated with a broad range of disorders," including schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, and elderly psychosis, are false or misleading because the adequate and well-controlled clinical studies for Risperdal were not designed to examine the efficacy of Risperdal in this broad range of disorders.

Fair Balance

1. Janssen is disseminating materials that are lacking in fair balance because the risk information appears in pale and tiny font at the bottom or back of a journal ad or other presentation, or after the closing of a letter. Thus, the risk information is not presented with a prominence and readability that is reasonably comparable to the presentation of efficacy information.

2. Janssen is disseminating materials that are lacking in fair balance because they emphasize that Risperdal has a low incidence of certain side effects while minimizing or ignoring important risk information for Risperdal. For example, the sales aid ID# RS-420 has bolded headlines that state that Risperdal has a "low incidence of excessive sedation" and "low incidence of anticholinergic side effects," but the precaution concerning orthostatic hypertension is located in plain text in the "Dosing/Formulations" section, the ninth page of the ten-page piece. Further, the warning regarding tardive dyskinesia is minimized and the common adverse events, which occurred up to 34% of the time, have been reduced to a small paragraph with no quantification beneath a half-page table of common events associated with discontinuation (showing discontinuations were infrequent). Treatment-emergent extrapyramidal symptoms occurred 17-34% of patients on Risperdal (16% placebo). The dose-relationship of extrapyramidal symptoms is important risk information that is not included in many of the materials including this sales aid.

3. Materials that state or imply that Risperdal has a low incidence of movement disorders are false or misleading. According to the PI for Risperdal, adverse events that would cause movement disorders were common in the clinical studies for Risperdal and were often dose-related, as in the treatment-emergent extrapyramidal symptoms.

4. Materials that state or imply Risperdal has a low incidence of excessive sedation are false or misleading. According to the PI, the incidence of somnolence was 3% for 10 mg/day and 8% for 16 mg/day Risperdal (placebo = 1%). Sleepiness, increased duration of sleep, accommodation disturbances, asthenia, lassitude, and increased fatigability were all dose-related adverse events.

5. Materials that state or imply that Risperdal has a low incidence of anticholinergic effects are false or misleading. According to the PI, the incidence of constipation was 7% for the 10 mg/day and 13% for the 16 mg/day dose of Risperdal (placebo = 3%), and cognitive impairment (Precautions section of the PI) and reduced salivation are frequent adverse events. Furthermore, this claim is lacking in fair balance because there is no similar emphasis on adverse events that do occur with Risperdal.

6. Claims of low incidence of adverse events coupled with presentations of adverse events associated with discontinuation are false or misleading

because it implies that the events associated with discontinuation were the extent of the adverse events experienced with Risperdal.

Comparative Claims

1. Materials that state or imply that Risperdal has superior safety or efficacy to other antipsychotics due to its receptor antagonist profile are false or misleading because the mechanism of action of Risperdal is unknown, as is the correlation of the specific receptor antagonism to the clinical effectiveness and safety of the drug.

2. Presentations that compare the efficacy or safety of Risperdal to an active control make false and misleading superiority claims in the absence of substantiation from adequate and well-controlled comparative data (see for example, sales aid #RS-422).

Quality of Life Claims

1. Materials that claim that Risperdal can "enhance daily living" or that it offers "quality control of symptoms for daily living" are considered to be false or misleading in the absence of adequate and well-controlled studies using validated instruments to determine benefit to health-related quality of life.

2. The tagline "Quality control" is false or misleading because it is used out of context and can be interpreted to mean, without adequate substantiation, that Risperdal can control health-related quality of life.

The materials and promotional messages Janssen has disseminated contain false and/or misleading information about the safety and effectiveness of Risperdal. The violations discussed above do not necessarily constitute an exhaustive list. Accordingly, Janssen should immediately discontinue the use of all materials that state, suggest, or imply false, misleading, or unbalanced claims of the type discussed in this letter. Janssen should provide a written response to DDMAC stating its intent to comply with this request. The letter should also include a complete listing of the materials that Janssen will discontinue as a result of this letter, including the dates that the materials were discontinued, as well as a list of those materials that will remain in use.

Dr. Tod McIntyre
Janssen
NDA 20-272 (MACMIS 6908)

Janssen's response should be received no later than January 19, 1999. 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