DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272 / SLR-025
NDA 20-588 / SLR-016
NDA 21-444 / SLR-005

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Susan Merchant
Manager, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Merchant:

Please refer to your supplemental new drug applications dated June 25, 2002, received June 26, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets and Oral Solution. We also refer to your supplemental new drug application dated September 5, 2003, received September 8, 2003 for Risperdal M-TAB (risperidone) Orally Disintegrating Tablets

We acknowledge receipt of your submissions dated May 21, 2003.

Your submission of May 21, 2003, constituted a complete response to our December 20, 2002, action letter.

These supplemental new drug applications provide for revised labeling which deletes the information on QT prolongation from the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections of the labeling as follows:

1. The following section of labeling has been removed --

   WARNINGS
   Potential for Proarrhythmic Effects
   Risperidone and/ or 9-hydroxyrisperidone appear to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/ day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life- threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

2. The following section of labeling has been edited --

PRECAUTIONS
Use in Patients with Concomitant Illness
Clinical experience with RISPERDAL ® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL ® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL ® 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 clinical studies during the product's premarket testing. ~~The electrocardiograms of approximately 380 patients who received RISPERDAL ® and 120 patients who received placebo in two double- blind, placebo- controlled trials were evaluated and the data revealed one finding of potential concern, i. e., 8 patients taking RISPERDAL ® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (see WARNINGS and PRECAUTIONS).~~

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/ min/ 1.73 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

3. The following section of labeling has been edited --

ADVERSE REACTIONS
ECG Changes
~~The electrocardiograms of approximately 380 patients who received RISPERDAL and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (see WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/ 126).~~ Between-group comparisons for pooled placebo-controlled trials 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).

4. The following section of labeling has been edited to separate pre-marketing and post-marketing experience into two paragraphs. Extrapyramidal symptoms and torsades de pointes have been added to the post-marketing experience paragraph. --

   OVERDOSAGE
   Human Experience
   Premarketing experience included eight reports of acute RISPERDAL ® (risperidone) 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 events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL ® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

We completed our review of these applications, as amended and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-272/SLR-025 and NDA 20-588/SLR-016." Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Steven D. Hardeman, Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

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