CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-272/S-004

Trade Name: Risperdal Tablets

Generic Name: risperidone

Sponsor: Janssen Pharmaceutica

Approval Date: February 28, 1996

Indications: For the management of the manifestations of psychotic disorders.
# Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Reviews / Information</th>
<th>X</th>
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</thead>
<tbody>
<tr>
<td>Approval Letter</td>
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<td>Approvable Letter</td>
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<tr>
<td>Labeling</td>
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<tr>
<td>Medical Review(s)</td>
<td>X</td>
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<tr>
<td>Chemistry Review(s)</td>
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<tr>
<td>Pharmacology Review(s)</td>
<td></td>
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<tr>
<td>Statistical Review(s)</td>
<td>X</td>
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<tr>
<td>Microbiology Review(s)</td>
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<tr>
<td>Clinical Pharmacology/ Biopharmaceutics Review(s)</td>
<td></td>
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<tr>
<td>Administrative and Correspondence Document(s)</td>
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</tbody>
</table>
APPLICATION NUMBER:
20-272/S-004

APPROVAL LETTER
Dear Dr. McIntyre:

Please refer to your October 12, 1995, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) tablets.

Refer also to the telephone conversation of February 12, 1996, between Steven D. Hardeman, of this Division, yourself and Wayne K. Geller, M.D. of your firm. In that conversation, you verified that the omission of Apnea from the Postintroduction Reports was inadvertent and should have been included in your October 12, 1995, submission.

Supplemental application SLR-004 provides for draft labeling submitted in response to the Division’s letters of April 12, 1995, and July 17, 1995. Specifically, changes to the labeling are listed below by section (deletions in strikeout and additions in redline):

1. Under PRECAUTIONS, General, Orthostatic Hypotension:

...conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications): e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of Risperdal and antihypertensive medication.

2. Under PRECAUTIONS, Body Temperature Regulation:

...antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with Risperdal use. Caution is...

3. Under Postintroduction Reports:

a. Apnea

b. Cerebrovascular disease disorder

c. including diabetic ketoacidosis

d. Hypothermia
e. pancreatitis

f. sudden death

g. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving Risperdal. A causal relationship with Risperdal has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients, whether they remain untreated or whether they are treated with other antipsychotic drugs.

4. Under OVERDOSAGE, Human Experience:

a. Experience with RISPERDAL (risperidone) in acute overdosage was limited in the premarketing database (8 reports). Premarketing experience included eight reports of acute Risperdal overdosage.

b. 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, orthostatic hypotension, Other adverse events reported since market introduction which were temporally but not necessarily causally related to Risperdal overdosage include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatalities associated with multiple drug overdose.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated October 12, 1995. Accordingly, the supplemental application is approved effective on the date of this letter. Additionally, we have the following requests for additional information:

1. Please supply details of your review which concluded that granulocytopenia is not causally related to risperidone.

2. Please supply data regarding your observations of hypotension with concomitant antihypertensives other than beta blockers.

3. Please provide the clinical data supporting your revision of the Overdosage section.

4. Please justify your conclusion that risperidone, unlike other neuroleptics, has not been associated with \( \text{\textsuperscript{1}} \), \( \text{\textsuperscript{2}} \), particularly since there are postmarketing spontaneous reports involving aspiration.
NDA 20-272 / SLR-004

The final printed labeling (FPL) must be identical to the draft labeling submitted on October 12, 1995 (with the addition of the term "Apnea" under Postintroduction Reports).

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING for approved supplement SLR-004". Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Regulatory Management Officer at (301) 594-2777.

Sincerely yours,

[Signature]

2/27/96

Paul D. Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc:  
Original NDA 20-272  
HFD-120/Div. files  
HFD-120/CSO/S.Hardeman  
HFD-120/Laughren/Mosholder  
HFD-101/L.Carter (with labeling)  
DISTRICT OFFICE  
HF-2/medwatch (with labeling)  
HFD-80 (with labeling)  
HFD-40/DDMAC (with labeling)  
HFD-613 (with labeling - Only for applications with labeling.)  
HFD-735/D.Baresh (with labeling-for adverse reaction changes only)  

Final: February 23, 1996  

APPROVAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-272/S-004

LABELING
DESCRIPTION
RISPERDAL® (risperidone) is an atypical antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-(2-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl (8,7,5,3- tetrahydro-2-methyl-4-pyrrolidin-1-yl) 2-pyrimidinone-1-one. Its molecular formula is C20H23FN2O5, and its molecular weight is 410.48. 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® for oral use is available in tablets of 1 mg (white, scored), 2 mg (orange), 3 mg (yellow), and 4 mg (green). Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 2, 3, and 4 mg also contain talc and titanium dioxide. The 2 mg tablets contain D&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.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The mechanism of action of RISPERDAL® (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki) of 0.12 to 7.9 nM for the serotonin type 2 (5HT2), dopamine type 2 (D2), D4, and D5, adrenergic, and H1 histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1a, 5HT1b, and 5HT2 receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10 µM) for cholinergic muscarinic or 5, and 6, adrenergic receptors.

Pharmacokinetics
Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of [14C]-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 65%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome P450 to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating species, and appears approximately equipotent with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is dealkylation.) Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone is 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P450, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants,
III

Risperdal®
(Risperidone)
Tablets

FEB 26 1997
antiarrhythmics, and other drugs. Cytotoxic P450D, is subject to genetic polymorphism (about 8-18% of caucasians, and a very low percent 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 metabolizers convert riperidone rapidly into 9-hydroxyriperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower riperidone and higher 9-hydroxyriperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyriperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of riperidone was three hours (CV=30%) in extensive metabolizers and 23 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyriperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of riperidone 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-hydroxyriperidone are reached in 5-6 days (measured in extensive metabolizers).

Because riperidone and 9-hydroxyriperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of riperidone and 9-hydroxyriperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome P450,
could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The limited and adverse effects of risperidone in patients receiving quinidine have not been evaluated for observations in a modest number (n=10) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism in other pharmacologically active agents like buspirone (P450) and carbamazepine (10 μg/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.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 90% compared to young healthy subjects. Risperidone doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 9-hydroxyrisperidone. Risperidone doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In 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 DOSAGE AND ADMINISTRATION).

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.

Clinical Trials

The efficacy of Risperidone® in adults in the management of the manifestations of psychotic disorders was investigated in three short-term (6- to 8-week) controlled trials of psychotic patients who met DSM III-R criteria for schizophrenia.

Several instruments were used to 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 psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered as a particularity of other drugs metabolized by cytochrome P450. Relative weak binding of risperidone to the enzyme suggests this is unlikely. (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 30% over the in vivo concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfinpyrazone (100 μg/mL), warfarin (10 μg/mL) and contraceptive (10 μg/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.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=16) involving titration of Risperidone® in doses up to 10 mg/day (30 mg/mL), Risperidone® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the PANSS.

(2) In a 6-week, placebo-controlled trial (n=513) involving 4 fixed doses of Risperidone® (2, 6, 10, and 16 mg/day, on a 30 mg/mL), all 4 Risperidone® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest Risperidone® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive response 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 6 fixed doses of Risperidone® (1, 4, 8, 12, and 16 mg/day, on a 30 mg/mL), the four highest Risperidone® dose groups were generally superior to the 1 mg Risperidone® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg dose group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

INDICATIONS AND Usage

Risperidone® (risperidone) is indicated for the management of the manifestations of psychotic disorders. The efficacy of Risperidone® was established in short-term (6 to 8 weeks) controlled trials of psychotic patients (See CLINICAL PHARMACOLOGY).

The effects of Risperidone® in long-term use, that is, more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Risperidone® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).
CONTRAINDICATIONS
RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS
Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (pupil dilated or fixed, mydriasis, diaphoresis, palpitation, diaphoresis, palpitation, acute narrow-angle glaucoma, tachycardia, diaphoresis, cardiac dysrhythmia). Additional signs may include elevated creatine 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 identify 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 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.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be higher 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, RISPERDAL® (risperidone) 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 is known to respond to antipsychotic drugs, and (2) 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 RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Pneumothorax Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients; although there is no clear 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.

PRECAUTIONS
General
Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, lightheadedness, 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% (6/2907) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be mitigated by limiting the initial dose to 1 mg BID in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). 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 concurrent use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/3,007) of RISPERDAL®-treated patients, two in association with hypovolemia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the persistence of these drugs is contemplated in a patient with previously detected breast cancer. 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. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorgenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertainled by direct questioning of patients. This adverse event 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 10% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 6% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. 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.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 29-year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdose with certain drugs or conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Organic Coma or Coma Due to 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® was not 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 premarketing testing. The electrocardiograms of approximately 360 patients who received RISPERDAL® and 129 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 intervals were less than 450 ms were observed to have QTc intervals greater than 450 ms 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 <20 mL/min/1.73 m²) and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).
Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL.
Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.
Interference With Cognitive and Motor Performance: 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.
Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
Lactation: Patients should be advised not to breast-feed an infant if they are taking RISPERDAL.
Concomitant Medications: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.
Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL.
Laboratory Tests
No specific laboratory tests are recommended.
Drug Interactions
The interactions of RISPERDAL and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL is taken in combination with other centrally acting drugs and alcohol.
Because of its potential for inducing hypotenstion, RISPERDAL may enhance the hypotensive effects of other therapeutic agents with this potential.
RISPERDAL may antagonize the effects of levodopa and dopamine agonists.
Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.
Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.
Drugs that inhibit Cytocrome P-450 and Other P-450 isoymes: Risperidone is metabolized to 9-hydroxylrisperidone by cytochrome P-450, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs. (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxylrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxylrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=30) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.
In vitro studies showed that drugs metabolized by other P-450 isoymes, including 1A1, 1A2, 1C9, 3A, and 2C, are only weak inhibitors of risperidone metabolism.
Drugs Metabolized by Cytocrome P-450: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P-450. Therefore, RISPERDAL is not expected to substantially inhibit the clearance of drugs that are metabolized by the enzymatic pathway. However, clinical data to confirm this expectation are not available.
Carcinogenesis and Impairment of Fertility
Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months in mice and for 25 months in rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum human dose (16 mg/day) on a mg/m² basis or 0.2, 0.76, and 3.1 times the maximum human dose (mg) at 0.4, 1.5, and 6 times the maximum human dose (mg/kg) 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 following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

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</tbody>
</table>
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 to 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 Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, 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 the chromosomal aberration test in human lymphocytes or Chinese hamster 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) at doses 0.1 to 3 times the maximum recommended human dose 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. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² 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. No no-effect doses were noted in either rat or dog.

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment II and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m² 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 1.5 times higher than the human dose on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, 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. Risperdal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of Risperdal on labor and delivery in humans is unknown.

Nursing Mothers: It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving Risperdal should not breast feed.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Clinical studies of Risperdal did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, the higher 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 a greater tendency to postural hypotension (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment: Approximately 5 percent (244/4000) of Risperdal (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. For any condition events (≥ 0.5%) associated with discontinuation and considered to be possibly or probably drug-related included:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Risperdal</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal symptoms</td>
<td>2.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Suicide attempt was associated with discontinuation in 1.2% of Risperdal treated patients compared to 0.5% of placebo patients, but, given the almost 40-fold greater exposure time in Risperdal compared to placebo patients, it is unlikely that suicide attempt is a Risperdal-related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.6% in active-control patients in the phase 2-3 trials.
Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 3% or greater in at least one of the Risperdal® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing Risperdal® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and organic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among Risperdal® Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among Risperdal® treated patients at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received Risperdal® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reports of adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescriber with a basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

<table>
<thead>
<tr>
<th>Table 1: Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Controlled Clinical Trials*</th>
<th>Risperdal®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body System/Preferred Term</td>
<td>≤10 mg/day (N=254)</td>
<td>10 mg/day (N=177)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Agitation</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>17%</td>
<td>34%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Saliva increased</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Toothache</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Coughing</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Body System/ Preferred Term</td>
<td>RISPERDAL® ≤ (N=224)</td>
<td>Placebo (N=142)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Black pain</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Dermatological</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Rash</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Infections</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculo-Skeletal</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day and placebo are provided. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, anxiety, and other infections.

Other adverse events: Adverse events that were not included in the table include: headache, nausea, vomiting, appetite increase, diarrhea, constipation, dizziness, somnolence, and increased creatinine. (See PRECAUTIONS.)

Weight Changes: The proportions of patients treated with RISPERDAL® and placebo-treated patients meeting the weight gain criterion of 3% at baseline were compared in a pooled 6- to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (11%) compared to placebo (9%).

Laboratory Changes: A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematologic, or urinalysis parameters. Similarly, there were no statistically significant differences in the incidence of discontinuations for changes in serum chemistry, hematologic, or urinalysis parameters. However, RISPERDAL® administration was associated with increases in serum prolactin levels (See PRECAUTIONS).

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., 2 patients (1 taking RISPERDAL® and 1 taking placebo) were observed to have QTC intervals greater than 600 m sec during treatment (See WARNINGS). Changes of this type were not seen among approximately 100 placebo patients, but were seen in patients receiving placebo (19%).
Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 207 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 207 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. Infrequent: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*. Infrequent: dysarthria, vertigo, stupor, paresthesia, confusional. Rare: aphasia, akinetic syndrome, hyperesthesia, tongue paralysis, leg cramps, laryngitis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-Intestinal Disorders: Frequent: anorexia, reduced salivation*. Infrequent: flatulence, diarrhea, increased bowel evacuation, stomatitis, melena, dysphagia, hemorrhoids, gastritis. Rare: fecal incontinence, eructation, gastroesophageal reflux, gastroatresia, esophagitis, tongue discoloration, choledolithiasis, tongue edema, diverticulitis, gingivitis, dysphagia, hemorrhage, hematomas.


Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. Rare: asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*, infrequent: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. Rare: bullous eruption, skin ulceration, aggravated psoriasis, lichen planus, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, verticillar extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. Rare: diplopia, eye pain, blepharitis, photophobia, phobos, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyperpotasemia, weight increase, creatine phosphokinase increase, serum bilirubin increase, serum uric acid increase, diabetes mellitus, rare: decreased serum iron, cicaemia, dehydratation, hyperkalemia, hypoproteinemia, hyperphosphatemia, hypertension, hyperuricemia, hypoglycemia.

Musculo-skeletal System Disorders: Infrequent: myalgia. Rare: arthrosis, synostosis, bursitis, arthritis, skeletal pain.
Liver and Biliary System Disorders: Infrequent: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.
Platelets, Bleeding and clotting Disorders: Infrequent: epistaxis, purpura. Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.
Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.
Red Blood Cell Disorders: Infrequent: anemia, hypochromic anemia. Rare: normocytic anemia.
White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.
Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.
Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, zonas, atrial fibrillation, cerebrovascular disorder, diabetes melitus aggravated, including diabetic ketoacidosis, intractable obstruction, jaundice, manic, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychiatric patients whether they remain untreated or whether they are treated with another antipsychotic drug.

Drug Abuse and Dependence

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL® 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 any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of the 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).

Overdose

Human Experience: Pharmacological experience included eight reports of acute RISPERDAL® overdose 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 200 mg, was associated with hypotension, hypokalemia, prolonged QT, and widened GRVS. Another case, involving an estimated overdose of 90 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdose, 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 and hypotension. Other adverse events reported since market introduction which were temporally, but not necessarily causally, related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdose: In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiac 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 QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension. There is no specific antiserine in RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic mediation should be administered. Close medical supervision and monitoring should continue until the patient recovers.
DOSE AND ADMINISTRATION

Dosage Schedule: Risperdal® (risperidone) should be administered as a BID schedule, generally beginning with 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. In some patients, slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 mg BID are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of Risperdal®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate Risperdal® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY).

Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS).

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient treated with Risperdal® should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on Risperdal®, but at the lowest dose needed to maintain remission. 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 when restarting patients who have had 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 from other antipsychotics to Risperdal®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, the clinician may elect to discontinue, initiate Risperdal® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

Risperdal® (risperidone) tablets are imprinted "JANSSEN", and "R" and the strength "1", "2", "3", or "4".
1 mg white, scored tablet: bottles of 100 NDC 50458-900-01, blister pack of 100 NDC 50458-900-01, bottles of 500 NDC 50458-320-50.
2 mg orange tablet: bottles of 100 NDC 50458-320-01, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.
3 mg yellow tablet: bottles of 100 NDC 50458-330-01, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.
4 mg green tablet: bottles of 100 NDC 50458-350-01, blister pack of 100 NDC 50458-350-01, bottles of 500 NDC 50458-350-01.

Storage and Handling - Risperdal® should be stored at room temperature (15°-30°C). Risperdal® should be protected from light and moisture.
US Patent 4,804,603
7503210
July 1995, February 1996
APPLICATION NUMBER:
20-272/S-004

MEDICAL REVIEW
REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-272
Sponsor: Janssen
Drug: Risperidone (Risperdal)
Drug Category: Antipsychotic
Material Reviewed: Supplement 4: proposed labeling changes being effected
Correspondence Date: October 12, 1995
Date Received: October 16, 1995

I. Background

The Division issued letters dated 4/13/95 and 7/17/95 concerning revisions to the Risperdal labeling with respect to certain adverse events; the sponsor has submitted this supplement in response.

II. Material submitted

In this labeling supplement, the sponsor has made some of the changes requested in the letters noted above, and they explain their reasons for not making other requested changes. I will outline these below, along with my own assessment.

Orthostatic Hypotension--The Division requested that a statement indicating the occurrence of moderate orthostatic hypotension be added under the section Precautions-Orthostatic Hypotension. Janssen’s counter-proposal is to include a statement that clinically significant hypotension has been observed with concomitant antihypertensive medications. They state that severe hypotension has been observed with co-administration of calcium channel blockers, ACE inhibitors, and diuretics; however, no data was offered to support this.

If the sponsor has data on other such reactions with the other classes of antihypertensives, then I believe we should request it.

Sudden Death--The Division asked for a more detailed statement about sudden death in the Postintroduction Reports subsection. Janssen has agreed to do this, but has changed the wording to omit mention of moderate orthostatic hypotension.

However, there have in fact been reports of fatalities associated with aspiration (see, for example, the case of the 47 year old woman in Canada who died following colonoscopy; her autopsy showed aspiration). Further, it is my understanding that granulocytopenia has also been observed with neuroleptics other than the phenothiazines.

Respiratory Arrest--The Division requested that this be added to the listing of risperidone overdose sequelae, based on a postmarketing report. Janssen has substantially revised this section and added a description of postmarketing experience with overdosage. However, they have not submitted any supporting data; while they conceivably could make changes to this section of labeling as changes being effected without prior review, I believe that data supporting their revisions should be submitted.

Granulocytopenia--As they have stated in previous submissions, the sponsor continues to maintain that this event has not been conclusively attributed to risperidone treatment. In this
submission, only their conclusions are stated; no review of the available data is presented. Nonetheless, there are a growing number of cases being reported. Further, a definitive causal relationship to drug treatment is not a prerequisite for inclusion in the Postintroduction Reports section. I do not agree with their assertion that such an inclusion would deprive a needy population of drug therapy. There is thought to be a rare but detectable rate of blood dyscrasias with other neuroleptic drugs and thus it is not unexpected to find this with risperidone as well.

Pancreatitis--Janssen has added this to Postintroduction Reports, as per our request.

Precautions: Body Temperature Regulation--Janssen has added the requested description of hyperthermia and hypothermia (and deleted hypothermia from Postintroduction Reports).

Apnea--This supplement makes no mention of our request to add Apnea to Postintroduction Reports.

Additional changes--Janssen has added diabetic ketoacidosis under Postintroduction Reports (which currently only specifies aggravated diabetes mellitus as an event). Although no data was included to support this, I have no reason to doubt that there are reports of diabetic ketoacidosis with the drug (as of April 1995, the SRS contained one such report). Also under Postintroduction Reports, they have exchanged the term cerebrovascular disorders for the current term cerebrovascular disease.

III. Conclusions and Recommendations

1. The changes Janssen has agreed to make are acceptable.

2. Apnea should still be added to Postintroduction Reports (the submission failed to address this).

3. Janssen should be asked to supply details of their review which concluded that granulocytopenia is not causally related to risperidone.

4. Janssen should be asked to supply data regarding their observations of hypotension with concomitant antihypertensives other than beta blockers.

5. Janssen should be asked to provide the clinical data supporting their revision of the Overdosage section.

6. Janssen should be asked to justify their conclusion that risperidone, unlike other neuroleptics, has not been associated with ☐ ☐ ☐, particularly since their are postmarketing spontaneous reports involving aspiration. A search of FDA’s SRS data may be relevant on this issue.

Andrew Mosholder, M.D.
Medical Officer HFD-120

orig NDA 20-272
HFD-120 TLaughren/AMosholder/SHardeman

10-27-95

T. Laughren
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-272/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Dear Dr. McIntyre:

We acknowledge the receipt of your April 4, 1996 submission containing final printed labeling in response to our February 28, 1996 letter approving your supplemental new drug application for Risperdal (risperidone) 1 mg, 2 mg, 3 mg, and 4 mg tablets.

We have reviewed the labeling that you have submitted in accordance with our February 28, 1996 letter, and we find it acceptable.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc:
  Original NDA 20-272
  HFD-120/Div. Files
  HF-2/Medwatch (with labeling)
  HFD-101/Office Director (with labeling)
  HFD-120/CSO/Hardeman
  HFD-40/DDMAC (with labeling)
  HFD-92/DDM-DIAB (with labeling)
  HFD-613/OGD (with labeling)
  HFD-735/DPE (with labeling)

Final: February 14, 1997

c:\docs\nda\risperdal\slr-004.ar

ACKNOWLEDGE AND RETAIN (AR)
April 4, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Attn: Document Control Room 10B-40
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: NDA 20-272
RISPERDAL® (risperidone) Tablets
FINAL PRINTED LABELING for approved supplement SLR-004

Dear Dr. Leber:

Please refer to Janssen's labeling supplement (S-004) of October 12, 1995 and to the Agency's approval letter of February 28, 1996. As requested, enclosed are sixteen copies of the final printed labeling (FPL) identical to the draft labeling submitted on October 12, 1995. Ten copies are individually mounted on heavy weight paper.

If you have any questions or comments, please contact me at (69) 730-3349.

Sincerely,

[Signature]
Todd D. McIntyre, Ph.D.
Associate Director, Regulatory Affairs

www/ENC

[Stamp: APR 05 1996
HFD-120
EVALUATION AND RESEARCH]

[Handwritten note: "Comparison of approved draft labeling vs. FPL revealed no changes. labeling identical."]

[Signature]
[Date: 2/4/97]
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% HCl.

Risperidone is available for oral use in tablets of 1 mg (white, scored), 2 mg (orange), 3 mg (yellow), and 4 mg (green). Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, sodium lauryl sulfate, and starch (corn). Tablets of 0.5, 1, and 2 mg also contain talc and titanium dioxide. The 0.5 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 1 mg and 2 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of Risperidone is, as with other antipsychotics, unknown. It has been proposed that the drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of Risperidone.

Risperidone is a selective monoamine antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 (5HT2), dopamine type 2 (D2), and adrenergic (a1) receptors. It has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin type 3 (5HT3) and 5HT1A receptors, weak affinity (Ki of 220 to 800 nM) for the dopamine type 1 (D1) and histaminergic H1 receptors, and no affinity (when tested at concentrations >10-6 M) for cholinergic muscarinic or B2 and adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of [14C]-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome P450, to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating species, and appears approximately equipotent with risperidone with respect to receptor binding affinity and some effects in animals. A second minor pathway is N-dealkylation. Consequently, the clinical effect of the drug likely results from the combined contributions of risperidone plus 9-hydroxyrisperidone or dose proportional over the dosing range of 1 to 10 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P450, also called deltoxye, the enzyme responsible for metabolism of many neuroleptics, antidepressants, and beta-adrenergic.

INTERACTIONS

Risperidone can interfere with conversion of risperidone to 9-hydroxyrisperidone. This in turn can convert quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The influence of this effect on risperidone in patients receiving quinidine has not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences in blood levels or pharmacological effects. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome P450. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (see PRECAUTIONS and DRUG INTERACTIONS).

Special Populations

Risperidone is not indicated for patients with moderate or severe renal impairment. The plasma half-life of risperidone was 77% or the parent or metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μg/mL, warfarin (10 μg/mL) and carbamazepine (10 μg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL, and 9-hydroxyrisperide at 50 ng/mL, changes of unknown clinical significance.

CLINICAL TRIALS

The efficacy of Risperidone in the management of the manifestations of psychotic disorders was established in three short-term (6 to 8 weeks) placebo-controlled trials of psychotic patients who met DSM-III criteria for schizophrenia.

In one 6-week, double-blind, placebo-controlled trial (n=186) involving 4 fixed doses of Risperidone (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 Risperidone groups were generally superior to placebo on the BPRS total score, CGI severity score, and BPRS positive and negative subscales. 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.

In an 8-week, double-blind, placebo-controlled trial (n=135) involving 5 fixed doses of Risperidone (2, 6, 10, and 16 mg/day, on a BID schedule), the four highest Risperidone dose groups were generally superior to the 1 mg Risperidone dose group on the BPRS total score, BPRS pyridine cluster, and CGI severity score. None of these dose groups were superior to the 1 mg dose group on the BPRS negative subscale. The most consistently positive responses were seen for the 6 mg dose group.

INDICATIONS AND USAGE

Risperidone is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of Risperidone was established in short-term (6 to 8 weeks) placebo-controlled trials of schizophrenic patients (see CLINICAL PHARMACOLOGY).

The effectiveness of Risperidone in long-term use, that is, more than 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Risperidone for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Risperidone is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscular rigidity, altered mental status and in some cases, autonomic instability (e.g., tachycardia, tachycardia, and changes in blood pressure), lactic acidosis, 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 where the clinical presentation includes both serious medical illness (e.g., pneumonia, hypoglycemia, congestive heart failure, etc.) and other disorders with similar 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 conditions for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Enlargement of the prostate and benign prostatic hyperplasia in elderly patients: Plaque should be carefully monitored, as recurrence of NMS has been reported.

FEB 26 1997
...e.g., disorientation and hyperventilation. Clinically significant hypotension has been observed with concomitant use of RISPERIDON® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (29/907) of RISPERIDON®-treated patients, two in association with hypotension. RISPERIDON® should be used cautiously in patients with a history of seizures.

Hypersensitivity: As with other drugs that antagonize dopamine D₂ receptors, Risperidone elevates prolactin levels and the elevation persists during chronic administration. 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. Although data from such as galactophoria, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is uncertain for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatelet cell hypoplasia and/or hypogonadism was observed in the risperidone cardiotoxicity studies conducted in mice and rats (See CARCINOGENICITY). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorogenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERIDON® treatment, especially when administered by direct intramuscular patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERIDON® 16 mg/day) reported somnolence compared to 10% of placebo patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatelet cell hypoplasia and/or hypogonadism was observed in the risperidone cardiotoxicity studies conducted in mice and rats (See CARCINOGENICITY). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorogenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Pruritus: Rare cases of pruritus have been reported. While the relationship of the events to RISPERIDON® use has not been established, other drugs with a-hemodynamic blocking effects are being reported to induce pruritus, and it is possible that RISPERIDON® may share this capacity. Severe pruritus may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year old female patient receiving RISPERIDON® in a young, open premarketing experience approximately 1300 patients. She experienced jaundice, fever, and bruising, and eventually recovered after receiving plasmapheresis. The relationship to RISPERIDON® therapy is unknown.

Antimanic effect: Risperidone has an antimanic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intermittent dementia, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERIDON® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERIDON® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

In the Treatment of Schizophrenia and Concomitant Illnesses: Clinical experience with RISPERIDON® in patients with concomitant systemic illnesses is limited. Caution is advised in using RISPERIDON® in patients with disorders or conditions that could affect metabolism or hemodynamic response.

RISPERIDON® 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 premarketing testing. The electrocardiograms of approximately 380 patients who received RISPERIDON® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed no findings of potential concern, i.e., 5 patients taking RISPERIDON® 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 7 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of QT prolongation 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 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERIDON®:

Orthostatic Hypotension: Patients should be advised of the possible risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERIDON® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, while they are reasonably certain that RISPERIDON® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breastfeed an infant if they are taking RISPERIDON®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over the counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERIDON®.

Laboratory Tests: No specific laboratory tests are recommended.
Pregnancy: Caution (check) be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast-feed an infant if they are taking Risperdal.

Concomitant Medications: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking Risperdal.

Laboratory Tests:

No specific laboratory tests are recommended.

Drug Interactions:

The interactions of Risperdal and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when Risperdal is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, Risperdal may enhance the hypotensive effects of other antihypertensive agents with this potential.

Risperdal may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of cimetidine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Drugs that inhibit Cytochrome P450 and Other P450 Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P450, an enzyme that is polymorphic in distribution and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P450 enzymes, including 1A1, 1A2, 1B9, 3A4, and 2D6, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome P450: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P450. Therefore, Risperdal® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

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, 2.5, and 10 mg/kg for 18 months in mice and for 20 months in rats. These doses are extrapolated to 5.4, 9.4, and 37.4 times the maximum human dose (10 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the maximum human dose (10 mg/day) on an mg/m² 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 following table summarizes the multiples of the human dose on a mg/m² basis at which these tumors occurred.

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>SPECIES</th>
<th>SEX</th>
<th>MULTIPLE OF MAXIMUM HUMAN DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IN mg/kg (mg/m²)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LOWEST EFFECT LEVEL</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>mouse</td>
<td>female</td>
<td>0.75 (8.4)</td>
</tr>
<tr>
<td>Endocrine pancreas adenomas</td>
<td>rat</td>
<td>male</td>
<td>1.5 (8.4)</td>
</tr>
<tr>
<td>Mammary gland adenocarcinomas</td>
<td>mouse</td>
<td>female</td>
<td>0.2 (2.4)</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td>female</td>
<td>0.4 (2.4)</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td>male</td>
<td>6 (27.5)</td>
</tr>
<tr>
<td>Mammary gland neoplasms, Total</td>
<td>rat</td>
<td>male</td>
<td>1.5 (8.4)</td>
</tr>
</tbody>
</table>
Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone study. In two rodent and subchronic toxicity studies showed that risperidone elevated serum prolactin levels in rats. In mice and subchronic toxicity studies showed that risperidone elevated serum prolactin levels in rats. An increase in mammary, pituitary, and adrenocortical responses has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance of human risk of the binding of these antipsychotic drugs and is considered to be prolactin mediated. The relevance of human risk of the binding of these antipsychotic drugs and is considered to be prolactin mediated. The relevance of human risk of the binding of these antipsychotic drugs and is considered to be prolactin mediated. 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The relevance of human risk of the binding of these antipsychotic drugs and is considered to be prolactin mediated. The relevance of human risk of the binding of these antipsychotic drugs and is considered to be prolactin mediated.
### Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Body System</th>
<th>RISPERIDAL</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>510 mg/d</td>
<td>16 mg/d</td>
</tr>
</tbody>
</table>

### Other Adverse Events

- Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERIDAL (1, 4, 8, 12, and 16 mg/d) were explored for dose-relatedness of adverse events.
- The analysis of these data provided no evidence of a dose-response relationship for the following adverse events: psychoses, increased weight and appetite, acne, increased frequency of erections, hyperesthesia, somnolence, myalgia, increased fatigue, increased pigmentation.
- No significant relationship was found between weight gain and total daily dose of RISPERIDAL.

### ECG Changes

- The electrocardiograms of approximately 380 patients who received RISPERIDAL and 120 patients who received placebo in two double-blind clinical studies were analyzed for changes in heart rate and QT intervals.
- Changes of QT intervals were noted in about 12% of placebo patients, but were seen in over 30% of patients receiving RISPERIDAL.

### Laboratory Changes

- The most frequently occurring changes in laboratory tests were an increase in total cholesterol and triglycerides, and a decrease in HDL cholesterol.
- No clinically significant changes in other laboratory tests were noted.

### Psychiatric Disorders

- Increased appetite, increased weight, weight gain, elevated blood pressure, and body weight gain were also noted.

### Somnolence

- Somnolence was noted in about 1% of patients receiving RISPERIDAL.

### Tachycardia

- Tachycardia was noted in about 1% of patients receiving RISPERIDAL.

### Respiratory System

- Increased respiratory rate was also noted in about 1% of patients receiving RISPERIDAL.

### Skin and Appendage Disorders

- Increased pigmentation and photosensitivity were reported in about 1% of patients receiving RISPERIDAL.

### Metabolic and Nutritional Disorders

- Increased appetite, increased weight, and increased body weight were noted in about 1% of patients receiving RISPERIDAL.

### Urinary System Disorders

- No clinically significant changes in urinalysis results were noted in patients receiving RISPERIDAL.

### Other Adverse Events

- The most frequently occurring changes in laboratory tests were an increase in total cholesterol and triglycerides, and a decrease in HDL cholesterol.
- No clinically significant changes in other laboratory tests were noted.
Musculoskeletal System Disorders: Infrquent: myalgia. Rare: arthrosis, synovitis, bursitis, arthritis, skeletal pain.
Liver and Biliary System Disorders: Infrquent: increased SGOT, increased SGPT. Rare: hepatic failure.
Platelet, Bleeding and Clotting Disorders: Infrquent: epistaxis, purpura. Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytoopenia.
Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.
Red Blood Cell Disorders: Infrquent: anemia, hypochromic anemia. Rare: normocytic anemia.
Reproductive Disorders, Male: Frequent: erectile dysfunction. Infrquent: ejaculation failure.
White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly.
Endocrine Disorders: Rare: gynecomastia, male breast pain, adrenocortical hormone disorder.
Special Senses: Rare: bitter taste.

*Based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL therapy, include the following: anaphylactic reaction, diabetic ketoacidosis, intestinal obstruction, jaundice, pneumonia, pancreatitis. Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL. A causal relationship with RISPERDAL has not been established. It is important to note that sudden and unexpected death may occur in psychiatric patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

**DRUG ABUSE AND DEPENDENCE**

Controlled Substance Class: RISPERDAL (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL 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 any drug-seeking behavior, these observations were not systematic and it is not possible to predict in advance the extent to which a CNS-active drug will be misused, diverted, or abused. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of signs of RISPERDAL misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

**OVERDOSAGE**

**Human Experience**: Premarketing experience included eight reports of acute RISPERDAL overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hypoxemia, hypotension, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 30 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacologic effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events related to RISPERDAL overdose include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatalities associated with multiple drug overdose.

**Management of Overdose**: In case of acute overdose, institute and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after induction, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of aspiration with induced emesis. Cardiovascular monitoring should be monitored while the patient is monitored, and endotracheal intubation should be performed if necessary. If antiarrhythmic therapy is administered, intravenous fluids, including blood, should be used to maintain blood pressure. In deaths following overdose, the possibility of carbon monoxide poisoning or other causes of death should be considered.

There is no specific antidote to RISPERDAL. Therefore, appropriate supportive management should be administered. Treatment complications may be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical observation and monitoring should continue until the patient recovers.

**DOSEAGE AND ADMINISTRATION**

Usual Initial Dose: RISPERDAL (risperidone) should be administered on a BID schedule, generally beginning with 1 mg BID orally. If there is no response or significant improvement is achieved, the dose should be increased at weekly intervals by 1 mg BID to a target dose of 3 mg BID by the third day. In some patients, slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally be restricted to intervals of not less than 3 - 4 weeks. When dosage adjustments are necessary, small dose increments (0.5 mg BID) are recommended.
DOSAGE AND ADMINISTRATION

Initial Oral Dose: Risperidone (risperidone) should be administered in a divided dose schedule, generally beginning with 1 mg BID initially, with increases in increments of 1 mg BID on the second and third days, as appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of at least 1 week, until steady state for the active metabolite is reached. Close medical supervision and monitoring should continue until the patient recovers.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of Risperidone. However, maximal effect was generally seen in a range of 4 to 6 mg/day with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Doses in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated. Patients with severe renal or hepatic impairment, and patients either predisposed to hypotension, no more than 0.5 mg BID. Increases to doses above 0.5 mg BID should generally occur at intervals of at least 1 week, in some patients, slower titration may be medically appropriate. Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate antipsychotic drug(s), possibly resulting in an enhanced effect. Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be treated cautiously and carefully monitored. See PRECAUTIONS.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the patient should remain on it, the effectiveness of maintenance therapy of atypical antipsychotic drugs is well established for schizophrenia and other disorders treated with this class of medications. It is recommended that responding patients be continued on treatment designed to determine the need for maintenance treatment. 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 remission of treatment, it is recommended that when reinitiating treatment in patients who have had an interval of discontinuation, the initial dosage schedule be followed. Switching from Other Antipsychotics: The decision to switch from other antipsychotics to Risperidone, or from Risperidone to other antipsychotics, should be made with caution. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be more appropriate for other patients. In all cases, the decision to switch from one antipsychotic to another should be made with caution. See PRECAUTIONS.

HOW SUPPLIED
Risperidone tablets are supplied in bottles of 100 mg, NDC 5848-320-05, blister pack of 100 NDC 5848-320-01, bottles of 500 NDC 5848-320-00.
2 mg orange tablets: bottles of 60 NDC 5848-320-01, blister pack of 100 NDC 5848-320-01, bottles of 500 NDC 5848-320-00.
3 mg yellow tablets: bottles of 60 NDC 5848-320-01, blister pack of 100 NDC 5848-320-01, bottles of 500 NDC 5848-320-00.
4 mg green tablets: bottles of 60 NDC 5848-350-01, blister pack of 100 NDC 5848-350-01.
Storage and Handling - Risperidone should be stored at room temperature (59°F to 86°F/15°C to 30°C).

JANSSEN PHARMACEUTICALS
Titusville, NJ 08560

July 1989, February 1996

750310
DATE OF SUBMISSION:
October 12, 1995

Applicant's Name and Address:
Janssen Research Foundation
1125 Trenton-Harborton Road
Post Office Box 200
Titusville, New Jersey 08560-0200

Trade Name:
RISPERDAL

Generic Name:
risperidone

Dosage Form and Strength:
1,2,3, and 4mg Tablets

Pharmacological Category and/or Principal Indication:
Antipsychotic

Material Reviewed:
2. Medical Officer's Review
3. SLR-004: Draft Labeling
4. CSO Telecon of 2/15/96

RECOMMENDATIONS:
Recommend approval based on draft (with addition of Apnea).

Steven D. Hardeman, R.Ph.
Consumer Safety Officer, DNDP

Concur:
John S. Purvis
Supervisory CSO, DNDP
Review Notes

1. LABELING CHANGES
The following changes to the labeling were noted and are listed below by section (deletions
in strikeout and additions in redline):

a. Under PRECAUTIONS, General, Orthostatic Hypotension:

...conditions which would predispose patients to hypotension (dehydration,
hypovolemia, and treatment with antihypertensive medications). Concomitant
dehydration and hypovolemia. Clinically significant hypotension has been observed with
concomitant use of Risperdal and antihypertensive medication.

b. Under PRECAUTIONS, Body Temperature Regulation:

...antipsychotic agents. Both hyperthermia and hypothermia have been reported in
association with Risperdal use. Caution is...

c. Under Postintroduction Reports:

1) Apnea
2) Cerebrovascular disease disorder
3) Including diabetic ketoacidosis
4) Hypothermia
5) Pancreatitis
6) Sudden death
7) There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving Risperdal. A causal relationship with Risperdal has not
been established. It is important to note that sudden and unexpected death
may occur in psychiatric patients whether they remain untreated or whether
they are treated with other antipsychotic drugs

d. Under OVERDOSAGE, Human Experience:

1) Experience with Risperdal (risperidone) in acute overdosage was limited
in the premarketing database (8 reports); Premarketing experience included
eight reports of acute Risperdal overdosage.

2) Postmarketing experience includes reports of acute Risperdal overdosage
with reported doses up to 450 mg. In general, the most frequently
reported signs and symptoms are those resulting from an exaggeration of the
drug's known pharmacological effects, drowsiness, sedation,
extrapyramidal, and hypotension. Other adverse events reported since market
NDA 20-272 / SLR-004

Introduction which were temporally, but not necessarily causally related to Risperdal overdose, include prolonged QT interval, convulsions, cardiac pulmonary arrest, and rare fatality associated with multiple drug overdose.

There are no other changes in the text of the labeling.

2. CONCLUSIONS (SLR-004):

A. A line by line labeling comparison of last approved FPL and SLR-004 revealed no changes other than those specified by the sponsor.

B. SLR-004 reviewed by Medical Officer and found acceptable.

END OF REVIEW
NDA 20-272 / SLR-004

cc:
ORIG NDA
DIV FILE
HFD-120/Purvis
    /Hardeman

C:\DOCS\NDA\RISPERDA\SLR-004.CSO

Final:  February 15, 1996

CSO LABELING REVIEW
Date: October 17, 1995
NDA No.: 20-272

Janssen Pharmaceutica Research Foundation
Janssen At Washington Crossing
1125 Trenton-Harbouron Road
Post Office Box 200
Titusville, NJ 08560-0200

Attention: Gregory Burkhart

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Risperdal-Tablets
NDA Number: 20-272
Supplement Number: S-004
Date of Supplement: October 12, 1995
Date of Receipt: October 16, 1995

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 10B-20
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

[Signature]

(FOR) John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research
October 12, 1995

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Attn: Document Control Room 10B-40
5600 Fishers Lane
Rockville, Maryland  20857

SUBJECT:  NDA 20-272
RISPERDAL® (risperidone) Tablets
DRAFT LABEL:  Proposed Changes

Dear Dr. Leber:

Please reference NDA 20-272, the Division’s letters of April 13, 1995 (regarding Janssen’s Periodic Reports submitted on 10/31/94 and 2/3/95) and July 17, 1995 (regarding Janssen’s Periodic Report submitted on 4/25/95, and other data which your Division received from the Division of Epidemiology and Surveillance) and the accompanying requests from the Division to modify the Risperdal® (risperidone) product label (package insert).

We note that Janssen agrees with the Division that all of the requests reflect adverse events which are serious in nature, and also note that Janssen has committed itself to the thorough monitoring and reporting of these events. Janssen has also committed itself to maintaining an open dialogue about all adverse events with both the Division of Neuropharmacological Drug Products and the Division of Epidemiology and Surveillance.

Janssen appreciates very much the insight proffered in the aforementioned letters, and agrees with much that has been suggested. Nevertheless, Janssen respectfully disagrees with certain other observations and requests delineated therein. The results of our own review of these issues, as well as additional investigations and deliberations, are described hence. We invite your concurrence on our assessments and conclusions, as well as the revised text which we propose to incorporate into the product label.

Enclosed, for your review, are four copies of the proposed revisions to the product label for NDA 20-272.

Letter of April 13, 1995

- Orthostatic Hypotension:

  The post-marketing experience of Risperdal does not support indicating ☐ ☐
However, severe hypotension has been observed with Risperdal and the co-administration of calcium-channel blockers, ACE inhibitors, and diuretics. Thus, we recommend strengthening the existing language in the label by changing the last sentence of this subsection to indicate:

"... and conditions which would predispose patients to hypotension "e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with the concomitant use of Risperdal and antihypertensive medications."

- Sudden Death:

Janssen agrees that the reports of sudden death are difficult to interpret, but nevertheless continues to discuss this periodically with the Agency's representatives (Dr. Gregory Burkhart; DES). We agree that it is reasonable to expand the mention of sudden death in the Postintroduction Reports subsection of Adverse Reactions. However, we disagree with FDA's proposed language of

Instead, we recommend utilizing language similar to that which is contained in the Haldol (haloperidol) product label:

"There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving Risperdal. A causal relationship with Risperdal use has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs."

- Respiratory Arrest:

Janssen agrees that it is reasonable to add a statement regarding post-marketing experience, to the Human Experience section of Overdosage, which would indicate:

"HUMAN EXPERIENCE: Premarketing experience included eight reports of acute Risperdal overdose 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 interval, 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 were those resulting from an exaggeration of the drug’s known pharmacological effects, i.e., drowsiness, sedation, tachycardia, and hypotension. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to Risperdal overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose."

Letter of July 17, 1995

• Granulocytopenia:

After reviewing the data regarding the issue of granulocytopenia, it is our conclusion that the extant data do not support a causal relationship between the use of Risperdal and the occurrence of granulocytopenia.

Specifically, the majority of the cases were engendered by reports in which granulocytopenia was either a preexisting condition or by reports in which baseline counts (prior to the initiation of Risperdal therapy) were either not performed or were unavailable to determine whether these were in fact drug-emergent events. Additionally, there were other confounding factors present, such as co-administration of other medications and/or co-morbidities known to cause granulocytopenia, prior to, or during, Risperdal therapy. Furthermore, the majority of these cases had either a negative de-challenge or a negative re-challenge, while in other cases granulocytopenia resolved while continuing Risperdal therapy. Finally, there have been no reports of a positive re-challenge in which granulocytopenia recurred with the re-introduction of Risperdal.

Thus, it is Janssen’s belief that including granulocytopenia in the Risperdal product label would be unwarranted at this time and could result in identifying Risperdal with other neuroleptics known to cause life-threatening granulocytopenia. This may have the unintentional consequence of depriving a needy population of an effective therapy.

• Pancreatitis:

We agree to revise the Postintroduction Reports subsection of the Adverse Events
section to include:

"...mania, pancreatitis, Parkinson's Disease aggravated..."

- Hypothermia:

We agree to revise the Body Temperature Regulation subsection of the Precautions section to indicate:

"Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with Risperdal use. Caution is advised when prescribing Risperdal for patients who will be exposed to temperature extremes."

In addition, "hypothermia" will be removed from the Postintroduction Reports subsection of the Adverse Events section.

Label Revisions Initiated by Janssen

- Diabetic Ketoacidosis:

Based upon Janssen's independent review of the data, we suggest expanding the statement in the Postintroduction Reports section regarding diabetes mellitus aggravated to indicate:

"...diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction,...".

- Cerebrovascular Disorders:

Similarly, in the same section, Janssen recommends replacing the existing term "cerebrovascular disease" with "cerebrovascular disorders" (as it is listed in the WHO-ART dictionary):

"...atrial fibrillation, cerebrovascular disorders, diabetes mellitus aggravated, including diabetic ketoacidosis...".
Should you have any questions regarding this submission, or wish to discuss its conclusions any further, please feel free to contact me (609-730-3349) at your convenience. Should you consider it useful, Janssen would welcome the opportunity to discuss our perceptions and conclusions with you and your staff.

Sincerely,

[Signature]

Todd D. McIntyre, Ph.D.
Assistant Director, Regulatory Affairs

Attachment (Draft Package Insert: 4 copies)

Desk Copy: Gregory Burkhart, Ph.D.
Steve D. Hardeman, R. Ph.
Thomas P. Laughren, M.D.
Paul D. Leber, M.D.
Andrew D. Mosholder, M.D.