CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

Trade Name:	Risperdal Tablets 0.25, 0.5, 1, 2, 3 and 4 mg & Risperdal Oral Solution 1 mg/mL
Generic Name:	risperidone
Sponsor:	Janssen Pharmaceutica
Approval Date:	03/03/2002
Indications:	For the treatment of schizophrenia.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272/S-008
NDA 20-588/S-004

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Edward G. Brann
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Mr. Brann:

Please refer to your supplemental new drug applications dated March 12, 1997, received March 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) tablets and oral solution.

We acknowledge receipt of your submission dated January 28, 2002, which constituted a complete response to our January 11, 2002 action letter.

These supplemental new drug applications provide for the longer-term efficacy for risperidone in the treatment of schizophrenia.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. We note that modifications of labeling text to more clearly state that this agent is indicated for the treatment of schizophrenia (requested in our letter of September 25, 2000) have been effected. Accordingly, these supplemental applications are approved effective on the date of this letter.

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

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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, these submissions should be designated "FPL for approved supplement NDA 20-272/S-008, 20-588/S-004." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless FDA waives or defers the requirement (63 *FR* 66632) [21 CFR 314.55]. The Agency has not made a determination if a health

benefit would be gained by studying risperidone in pediatric patients for its approved indication. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations until February 1, 2005.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Description of revisions to Risperdal (risperidone) Labeling

Section of Labeling	Description of Revision(s)
DESCRIPTION	Paragraph 1, sentence 1: changed from "an antipsychotic agent" to "a psychotropic agent"
CLINICAL PHARMACOLOGY: Pharmacodynamics	Paragraph 1, sentence 1: changed "antipsychotic drugs" to "drugs used to treat schizophrenia" and "antipsychotic activity" to "therapeutic activity in schizophrenia"
CLINICAL PHARMACOLOGY: Clinical Trials	Before paragraph 1, added subheading "Short-Term Efficacy". Paragraph 1, changed "management of the manifestations of psychotic disorders" to "treatment of schizophrenia" Paragraph 2, sentence 1: changed "effects of drug treatment in psychosis" to "effects of drug treatment in schizophrenia"
CLINICAL PHARMACOLOGY: Clinical Trials	Added subheading "Long-Term Efficacy" and paragraph to describe RIS-USA-79 study design and results
INDICATIONS AND USAGE	Paragraph 1: changed "management of the manifestations of psychotic disorders" to "treatment of schizophrenia" Paragraph 2, changed "antipsychotic efficacy of RISPERDAL®" to "efficacy of RISPERDAL® in schizophrenia" Paragraph 3: replaced first sentence with FDA statement on use of Risperdal in long-term treatment; last sentence: changed "Therefore" to Nevertheless"
DOSAGE AND ADMINISTRATION: Usual Initial Dose	Paragraph 1: added "short-term" twice as descriptor of clinical trials and sentence on titration schedule from long-term study Paragraph 2, sentence 1: changed "Antipsychotic efficacy" to Efficacy in schizophrenia" for consistency with the intent of FDA 9/25/00 letter and added "short-term" as descriptor for clinical trials
DOSAGE AND ADMINISTRATION: Maintenance Therapy	Repositioned subsection to follow "Usual Initial Dose" subsection Revised paragraph to provide description and titration schedule from long-term study and to incorporate FDA's changes Added the word "schizophrenic" to describe patients in the first sentence.
DOSAGE AND ADMINISTRATION: Switching from Other Antipsychotics	Added "schizophrenic" as a descriptor for "patients" in three places and changed "other patients" to "others"

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

/s/

Russell Katz
3/3/02 11:33:45 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272/S-008
NDA 20-588/S-004

Janssen Research Foundation
Attention: Edward G. Brann
Assistant Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O.Box 200
Titusville, NJ 08560-0200

Dear Mr. Brann:

Please refer to your supplemental new drug applications dated March 12, 1997, received March 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) tablets and oral solution.

Your submissions of July 25, 2001, constituted a complete response to our action letter of January 13, 1998.

These supplemental new drug applications provide for the longer-term efficacy for risperidone in the treatment of schizophrenia.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit revised draft labeling. We have made revisions to the four sections of labeling for which you have proposed changes. Specifically:

- Under **CLINICAL TRIALS, Long-Term Efficacy.** We request that you replace your suggested paragraph under this heading with the following:

  "In a longer-term trial, 365 adult outpatients predominantly meeting /DSM-IV/ criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to Risperdal (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving Risperdal experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator."

  - In keeping with the current focus in Risperdal labeling on schizophrenia as an indication, and the predominance of schizophrenia in the sample for study 79, we have included mention only of schizophrenia, in order to avoid confusion among prescribers.

  - [redacted]

[

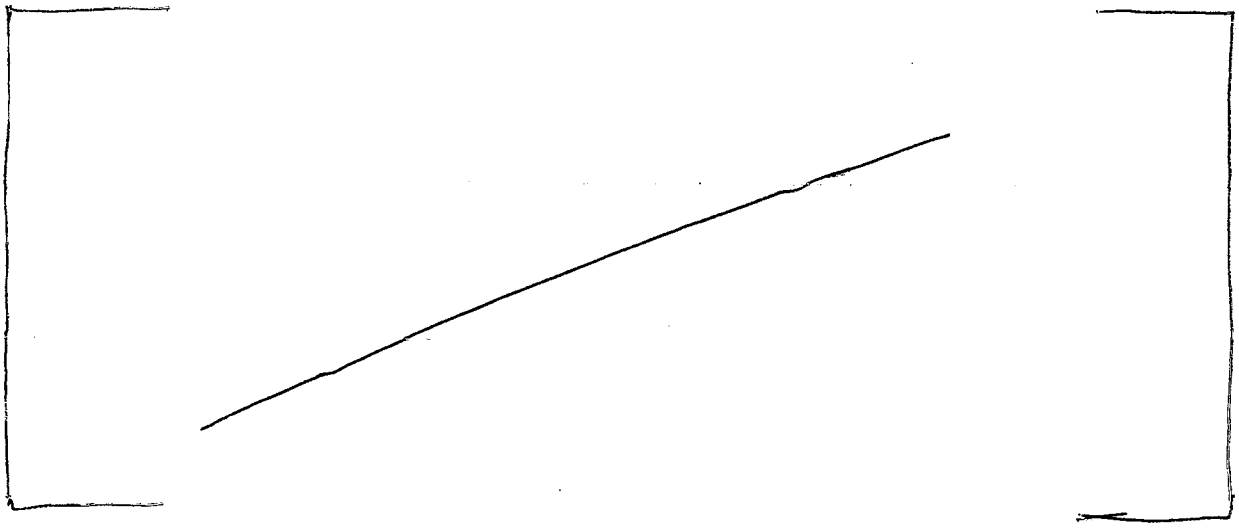
]

- We have [ ] time to relapse, the one outcome designated prospectively as the primary outcome for study 79.

- We have also made other editorial changes to bring the language into consistency with standard language for the longer-term claim.]

- Under **INDICATIONS AND USAGE.** The following paragraph should be inserted as the final paragraph in this subsection:

"The efficacy of Risperdal in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with Risperdal or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see clinical Trials, under Clinical Pharmacology). Nevertheless, the physician who elects to use Risperdal for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration)."

- 

- Under **DOSAGE AND ADMINISTRATION.** The following paragraphs should be inserted to replace the current language under the subsections entitled Usual Initial Dose and Maintenance Therapy. We have not removed the language explaining the basis for weekly dose adjustments, and we have made other editorial changes.

"Usual Initial Dose: RISPERDAL ® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL ® was generally administered at 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. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term

controlled trial in stable patients, RISPERDAL was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, Regardless of which regimen is employed, in some patients a 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 1-2 mg are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in short-term 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 for BID dosing 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. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

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 RISPERDAL 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (see Clinical Trials, under Clinical Pharmacology). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose."

The labeling should be identical in content to the enclosed labeling (text for the package insert), and all previous revisions as reflected in the most recently approved labeling must be included. Further, the labeling changes as requested in our letter of September 25, 2000, must be effected in your response to this action letter. Specifically, modifications of labeling text to more clearly state that this agent is indicated for the treatment of schizophrenia should be made.

To facilitate review of your submission, please submit a highlighted or marked-up copy of labeling that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Russell Katz
1/11/02 08:02:17 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

LABELING

NDA 20-272/20-588
RISPERDAL® (risperidone) Tablets/Oral Solution
Part No. 7503220
Physicians Insert

ORIGINAL

20588 - SE8004 (FA)

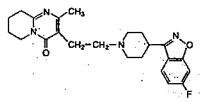
Labeling: SE8-008 (FA)

NDA No. 20-272 Rcd. 4-23-02

Reviewed by:

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro- 2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H, 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 $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-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 $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg 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 was 70% (CV=25%).

JAN 14 2003

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% 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 risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three

Clinical Trials

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8-weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (See Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® 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

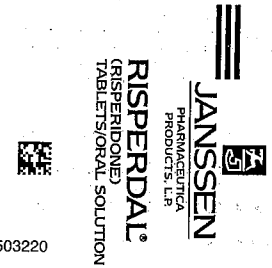
Neuroleptic Malignant Syndrome (NMS)

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 (irregular pulse or blood pressure, tachycardia, diaphoresis and 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.



7503220

20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, 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 $P_{450}IID_6$ 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 favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-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 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-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 60% compared to young healthy subjects. RISPERDAL® 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 α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See 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.

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 highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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

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

Given these considerations, 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 (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

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

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 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). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 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 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 tumorigenesis 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 ascertained 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 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse 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 28 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 overdosage with certain drugs or of 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 Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of 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.

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

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 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 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.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxy-risperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, 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-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 P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. 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 to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a 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 (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m² (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 *(9.4)*	0.2 *(2.4)*
Endocrine pancreas adenomas	rat	male	1.5 *(9.4)*	0.4 *(2.4)*
Mammary gland adenocarcinomas	mouse	female	0.2 *(2.4)*	none
	rat	female	0.4 *(2.4)*	none
	rat	male	6 *(37.5)*	1.5 *(9.4)*
Mammary gland neoplasms, Total	rat	male	1.5 *(9.4)*	0.4 *(2.4)*

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 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 study) 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

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 III 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

In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human 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. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) 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. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% 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 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled 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 5% 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 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 orgastic 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 treated 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. Reported adverse events were classified using the World Health Organization preferred terms.

well. 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, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (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., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 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 2607 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

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 prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: **Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials[1]**

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as

listed in the tabulated results from placebo-controlled [illegible]

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 libidc amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequen* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongu edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-lik symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

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

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increase sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullou eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis genital pruritus, urticaria.

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

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

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinas increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequen* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perinea pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficia phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

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 (bu not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reactior angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, dia betes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancre atitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden deat 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 psychoti 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 c humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reve

any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia 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 Overdosage: In case of acute overdosage, 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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of 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 antidote to 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 medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 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. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a 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 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in short-term 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 for BID dosing 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. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (See Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

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

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). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be [illegible] for 0.5 days at the target dose. Subsequent switches to a once-a-day

titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

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 schizophrenic patients 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 schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, 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 either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

7503220
US Patent 4,804,663
February 2002

RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® tablets and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

MEDICAL REVIEW(S)

CLINICAL REVIEW

NDA 20-272/S-008
Cross reference NDA 20-588/S-004

Clinical Review Cover Sheet

Appears This Way
On Original

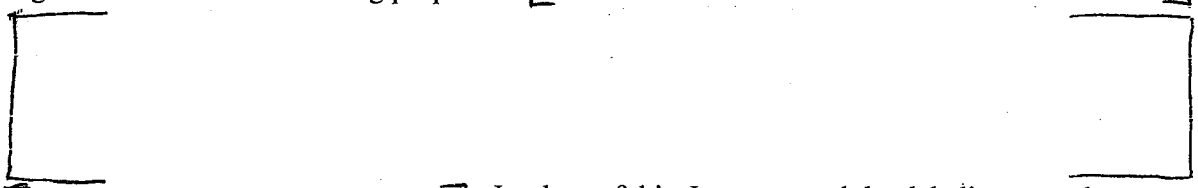
Table of Contents

Clinical Review for NDA 20-272/ S-008

Executive Summary

I. Recommendations

I recommend that the Division make an approvable action on supplement 008. I do not, however, agree with some draft labeling proposals. [ ]



[ ]. In place of this, I recommend that labeling state the risperidone was superior to "[ ]active[ ]".

II. Summary of Clinical Findings

A. Brief Overview of Submission

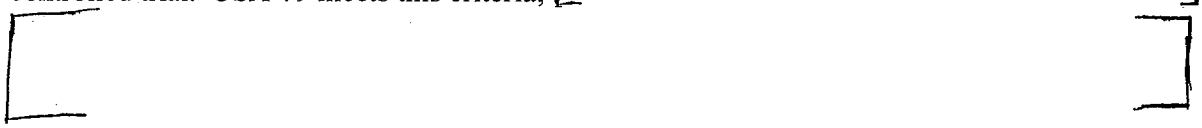
This submission comprises a complete response to the Division's not-approved letter to supplement 8 dated January 13, 1998. The sponsor proposes new labeling that describes risperidone as being effective in the treatment of patients with schizophrenia [ ] [ ]for up to[ ]-months.The sponsor submits one efficacy study RIS-USA-79 in support of a claim of extended efficacy in the treatment of schizophrenia[ ] for up to[ ]-months. The sponsor also submits a pooled analysis of nine uncontrolled studies and a pooled analysis of RIS-USA-79 and RIS-INT-6.

B. Efficacy

Study USA-79 supports the claim that Risperdal is effective in maintaining a positive treatment response for the symptoms of schizophrenia. [ ]

[ ]

[ ] It has been customary to allow claims of extended efficacy based on the results of one positive, well designed, appropriately controlled trial. USA-79 meets this criteria; [ ]



	Risperidone	Haloperidol	P- value
All diagnoses	N= 177	N= 188	0.001 b
Number (%) relapsed	45 (25.4%)	75 (39.9%)	
Mean (SE) time to relapse	452.2 (17.7)	391.3 (21.8)	
Relapse rate at 6 month a	19%	30%	
Relapse rate at 1 year a	29%	45%	
Relapse rate at end of trial a	34%	60%	
Schizophrenia	N= 144	N= 156	0.007 b
Number relapsed	36 (25.0%)	62 (39.7%)	
Relapse rate at 6 month a	19%	32%	
Relapse rate at 1 year a	28%	47%	
Relapse rate at end of trial a	34%	59%	

a: Kaplan-Meier estimates of relapse rate (probability of relapse).
b: Stratified log-rank test controlling for investigator and sex.

D. Efficacy Conclusions

Study USA-79 supports the sponsor's claim that Risperdal is effective in maintaining treatment response for schizophrenia. It has been customary to allow claims of extended efficacy based on the results of one positive, well designed, appropriately controlled trial. USA-79 meets this criteria;

In Study INT-6, a similarly designed study that was previously submitted, Risperdal was compared to haloperidol and no treatment difference was observed. USA-79 had twice the number of patients in each group. This increase in statistical power is a possible explanation for the difference between USA-79 being a positive study and INT-6 showing no difference.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

These pooled long term controlled studies were not designed to establish long-term safety. Since both INT-6 and USA-79 had haloperidol as an active control with no placebo comparator, long-term risperidone safety could only be compared to haloperidol. Even then the studies were too small to detect differences of less than 1%.

C. Safety

This review focused on the long-term, controlled clinical trials. Risperdal has been on the market in the US since 1993. The open label trials did not reveal uncommon, unexpected, unreported, serious adverse events that were likely to be drug related. Studies USA-79 and INT-6 were pooled for safety analysis. These studies were not designed to establish long-term safety. Since both INT-6 and USA-79 had haloperidol as an active control with no placebo comparator, long-term risperidone safety could only be compared to haloperidol. Even then the pooled studies were too small to detect differences of less than 1%.

These two pooled studies detected only minimal differences between the two drugs' safety profiles with the exception of the mean change in prolactin levels and weight gain. The mean prolactin level increased in the RIS group from 25.7 ng/ml at baseline to 40.2 ng/ml at end point, whereas it decreased in the HAL groups from 28.6 ng/ml to 22.6 ng/ml. Roughly twice the number of risperidone treated patients (58/241) gained >7% of their baseline body weight when compared to haloperidol treated patients (31/261).

D. Dosing

The sponsor makes changes in the DOSAGE AND ADMINISTRATION section of labeling that reflect the dosing regimen in the long-term controlled trials USA-79 and INT-6. They are accurate and acceptable from a clinical standpoint.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This submission comprises a complete response to the Division's not-approved letter dated January 13, 1998.

RISPERDAL® (risperidone) is an antipsychotic agent belonging to the benzisoxazole derivatives. Risperdal® (risperidone) tablets and oral solutions are approved for the management of the manifestations of psychotic disorders in adults.

The clinical trials in which the effectiveness of risperidone was established primarily studied adult patients with schizophrenia for up to 8 weeks. The safety and effectiveness of risperidone has not been established in any pediatric patient population. Risperidone may be given in QD or BID dose schedules. Clinical trials initiated dosing at 1-mg PO BID but subsequent trials established 8-mg QD dosing as effective. The safety of doses exceeding 16-mg/day has not been established.

The sponsor proposes new labeling that describes risperidone as being effective in the treatment of patients with schizophrenia[ ] for up to[ ]-months.

B. State of Armamentarium for Indication(s)

Risperidone is one of four approved drugs that are considered "atypical Antipsychotics". Other members of this class include clozapine, olanzapine, and ziprasidone. Atypical antipsychotic agents are so named for their $5HT_2$ and D_2 antagonist effects. "Typical" antipsychotics are believed to exert their primary clinical effect through D_2 blockade alone though neither of these theories of efficacy are established as fact.

C. Important Milestones in Product Development

Risperidone was first registered in the UK in December 1992 and launched in May 1993 for the treatment of schizophrenia and other psychotic conditions. Risperidone was marketed in 1994 in the United States and has been used widely since then. It is now licensed world-wide in more than 90 countries.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no chemistry, animal pharmacology/toxicology, or biopharmaceutical issues in this submission.

III. Description of Clinical Data and Sources

A. Overall Data

The sponsor submits one efficacy study RIS-USA-79 in support of a claim of extended efficacy in the treatment of schizophrenia [ ] for up to [ ]-months. The sponsor also submits a pooled analysis of nine uncontrolled studies and a pooled analysis of RIS-USA-79 and RIS-INT-6 in support of safety information in draft labeling. Additionally one uncontrolled study (RIS-INT-23) of elderly patients is summarized in the ISS.

B. Tables Listing the Clinical Trials

Trials Included in the ISS for NDA 20-252/Supplement 008			
Trial	**Design**	**Number of Subjects (RIS/HAL)**	**Dose/Duation**
USA-79	DB, HAL controlled, PG	192/203 excluding Site 8 177/188	RIS: 2-8 mg/day HAL: 5-20 mg/day Up to 2-years
INT-6	DB, HAL controlled, PG	91/99	RIS and HAL 5-20 mg/day; 1 year
USA-5	Open-label	7	RIS 1-16 mg/day; 1-year
USA-6	Open-label	265	RIS 2-16 mg/day; 1- year
USA-7	Open-label	105	RIS 2-16 mg/day; 34-months
USA-9	Open-label	107	RIS 2-16 mg/day; 1 year
INT-4	Open-label	386	RIS 2-16 mg/day; 57-weeks
INT-8 NED-2 BEL-17	Open-label 3 studies pooled	264	RIS 2-20 mg/day; 1-year
INT-12	Open-label	483	RIS 2-16 mg/day; 7-months
INT23	Open-label Elderly	180	RIS 0.5-8 mg/day; 1-year

C. Postmarketing Experience

Risperidone has been extensively used for a number of years. In April 2001, Janssen estimates the cumulative exposure at [ ] treatment months, corresponding to more than [ ] [ ] patient years. There have been nine periodic safety update reports on risperidone. During the time period from June 1, 1993 to May 31, 2000, 2065 verified reports became available at JRF from various sources.

D. Literature Review

The sponsor provides a literature review that summarizes clinical data on the efficacy and safety of risperidone long-term use in subjects with schizophrenia [ ] as reported in 116 articles identified in literature searches covering the period up to 25 January 2001. Safety results of risperidone were reported in 79 articles. Most of the articles were case reports. The sponsor discovered three double-blind, reference-controlled and 11 reference-controlled, open studies emerged from this search. There were 32 open, non-controlled studies. The number of subjects comprised in these articles who received risperidone amounted to a total of 4,053 subjects. There were no unexpected adverse events.

V. Clinical Review Methods

A. How the Review was Conducted

This submission contained one efficacy study and a summary of multiple studies to review safety parameters. Study USA-79 was the focus of the efficacy review. It has been customary in the Division to allow claims of extended efficacy based on positive results in one well designed and adequately controlled study.

B. Overview of Materials Consulted in Review

Supplement 008 was an electronic submission. This submission represents a complete response to a not approved action on supplement 008. No materials outside of the submission were consulted in this particular review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Raw data was submitted to the Division of Biometrics via SAS transport files and analyzed according to the methods described in the sponsor's protocol. These results were compared to the analyses in the submission. The submission was also examined for internal consistency.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was performed in accordance with the declaration of Helsinki and its subsequent revisions and the FDA Guideline 21 CFR Parts 50, 56, and 312.

E. Evaluation of Financial Disclosure

A financial disclosure and certification statement was included. This certified that Janssen Research Foundation had not entered into any financial agreement with the clinical investigators whereby the value of the compensation would be effected by the outcome of the study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The data support the claim that Risperdal is effective in maintaining a positive treatment response for the symptoms of schizophrenia. [ ] It has been customary to allow claims of extended efficacy based on the results of one positive, well designed, appropriately controlled trial. USA-79 meets this criteria; [ ]

[ ]

B. General Approach to Review of the Efficacy of the Drug

This submission contained one efficacy study and multiple studies to review safety parameters. Study USA-79 was the focus of the efficacy review. It has been customary to allow claims of extended efficacy based on positive results in one well designed and adequately controlled study.

C. Detailed Review of Trials[ ]

Study RIS-USA-79: A comparison of risperidone and haloperidol for prevention of relapse in subjects with schizophrenia and schizoaffective disorders- is submitted to support the indication of "[ ]schizophrenia[ ]long-term [ ]"

C-1 Investigators and Sites

A listing of the investigators and sites may be found in Table C-1 in the appendix.

C-2 Objectives

The primary objective of the study was to evaluate the efficacy of risperidone and haloperidol in the prevention of relapse during maintenance treatment of stable outpatients with schizophrenia or schizoaffective disorder by treating them with risperidone or haloperidol for a minimum of 1 year.

C-3 Study Population

This was a trial in outpatient men and women aged 18-65 years with chronic schizophrenia or schizoaffective disorder classified by Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Patients were clinically stable (as judged by the investigator) for 1 month prior to enrollment into the trial. Stable was defined as receiving the same dosage of antipsychotic medication for 30 days and living in the same residence for 30 days. Inclusion and exclusion criteria may be found in Table C-2. In the appendix

C-4 Design

This was a one-year double-blind, active (haloperidol), parallel group study of stable medically treated outpatients. Double blind treatment began after stratification by sex and randomization. Patients discontinued their current antipsychotic medications gradually over the first 7 days of double blind treatment. The trial used a parallel-group design with 2 treatment arms: risperidone and haloperidol. Trial medication was escalated over the first 3 days of double-blind treatment to a dosage of 4 mg/day risperidone or 10 mg/day haloperidol. For the first month of therapy, assessments were made at 1-week intervals to allow adjustment of medication to within the range of 2 mg to 8 mg/day for risperidone and 5 mg to 20 mg/day for haloperidol. Thereafter, trial visits were scheduled every 4 weeks. Additional visits were to be scheduled as needed. Patients were to be followed until the last patient enrolled into the trial had completed 1 year of double-blind treatment. After the initial 1-year double blind treatment period, patients could continue on double blind treatment up to 112-weeks.

Relapse did not require discontinuation of trial medication. Double-blind conditions remained for patients who relapsed and continued trial medication. A relapsed patient could receive otherwise disallowed psychotropic medication (e.g. neuroleptics other than risperidone and haloperidol, thymoleptics, or antidepressants) and were to have all routine assessments. A relapsed patient who had continued on trial medication and relapsed a second time was to be discontinued. Every patient who received trial medication and withdrew from the trial was to have a final set of trial assessments. Patients who were withdrawn because of trial medication-related events were to be followed until the event resolved or was no longer considered clinically significant.

C-5 Assessments

The primary efficacy parameter was the time to relapse. Relapse was defined as any 1 of the following occurrences:

- psychiatric hospitalization,
- clinical judgment that an increase in level of care was necessary and increase in PANSS score of 25% compared with Baseline, or an increase of ten points if the Baseline score was ≤40, (The increases in level of care and in PANSS score had to occur within 2 weeks of each other in order to qualify a patient's relapse.)
- deliberate self injury, in the investigator's opinion,
- emergence of clinically significant suicidal or homicidal ideation,
- violent behavior resulting in significant injury to another person or significant property damage, in the investigator's opinion, or
- significant clinical deterioration in the investigator's judgment (a CGI-C score of 6, "much worse").
- When the investigator rated the patient's CGI-C at 6, the patient was counted Analysis Plan

Secondary efficacy variables and safety assessments may be found in tables C-5.1 and C-5.2 in the appendix.

C-6 Patient Disposition

The disposition of patients in study YSA-79 follows in table C-6.

Table C-6 Patient Disposition in Study USA-79

	RIS N = 192		HAL N = 203	
	n	**%**	**n**	**%**
Total number of patients discontinued	114	59.4	157	77.3
Reason for discontinuation				
Chose to discontinue	35	18.2	36	17.7
Relapse	28	14.6	47	23.2
Adverse event	24	12.5	30	14.8
Lost to follow- up	10	5.2	10	4. 9
Poor compliance	6	3. 1	15	7.4
Administrative	6	3. 1	2	1. 0
Other	3	1. 6	4	2. 0
Inadequate response	2	1. 1	7	3. 4
Ineligible	0	0	3	1. 5
Intercurrent illness	0	0	2	1. 0
Abnormal clinical laboratory result	0	0	1	0. 5

Upon visual inspection, one sees a disparity in the percentage of patients discontinuing due to relapse and poor compliance, but other reasons appear roughly equivalent. It is difficult to explain the disparate numbers of patients who dropped out due to poor compliance since the dropout rate due to adverse events was only slightly higher in the haloperidol group. Poor antipsychotic medical compliance is linked to adverse treatment events. Since the primary efficacy variable is time to relapse (a category of discontinuation) it appears that patients

discontinuing for other reasons did not skew the results in favor of Risperdal for inappropriate reasons.

C-7 Baseline Demographics/Severity of Illness

The distribution of age, race, sex weight and height were similar between treatment groups.

Table C-7.1 Patient Demographics in Study USA-79

		RIS N = 192		HAL N = 203	
		n	%	n	%
Sex	**Female**	57	29.7	66	32.5
	Male	135	70.3	137	67.5
Race	**White**	91	47.4	97	47.8
	Black	72	37.5	72	35.5
	Hispanic	24	12.5	29	14.3
	Other	3	1. 5	2	1. 0
	Oriental	2	1. 0	3	1. 5
		Mean	SD	Mean	SD
Age	**years**	40.8	10.72	40.1	10.43
Weight	**kg**	82.0	19.62	83.6	19.87
Height	**cm**	171.3	11.75	171.3	10.18

The distribution of diagnostic types were also reasonably similar.

Table C-7.2 Distribution of Diagnoses by treatment groups for Study USA79

		RIS N = 192		HAL N = 203	
		n	%	n	%
DSM- IV	**Schizophrenia**	155	80.7	169	83.3
diagnosis	**Schizoaffective disorder**	37	19.3	34	16.7
Diagnosis	**Paranoid**	94	49.0	114	56.2
type	**Undifferentiated**	55	28.6	45	22.2
	Depressive	19	9.9	21	10.3
	Bipolar	18	9.4	13	6. 4
	Residual	5	2. 6	7	3. 4
	Disorganized	1	0. 5	3	1. 5

C-8 Concomitant Medications

Anti-Parkinson drugs were taken by 48% of risperidone patients versus 60% haloperidol patients. This difference was mainly in patients using cogentin (risperidone group 38% versus haloperidol group 49%) while other anti-Parkinson drugs were used equally between the two groups (e.g. akineton, artane, benztropine, kemadrin).

C-9 Efficacy Results

Two analyses were performed. During the audit of RIS-USA-79, it was determined that the data from 1 site did not meet the Jansen Pharmaceutia quality standard. Therefore, the analyses were performed with and without Site #8. Time to relapse was the primary efficacy variable.

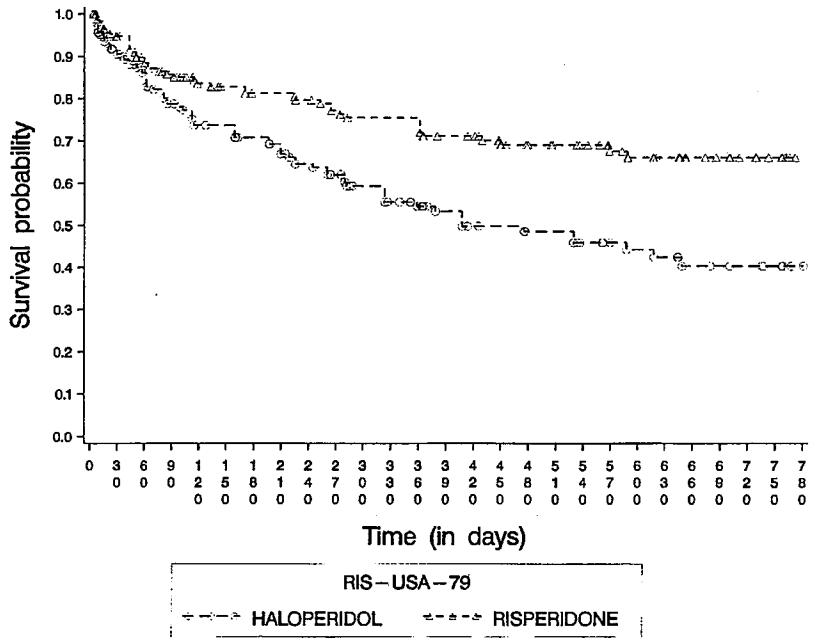
Percentage of patients experiencing relapse (by criteria definition and treatment group) are listed in table C-9.1.

Table C-9.1 Percentage of Patients Experiencing Relapse in Study USA-79

	RIS		HAL	
Criteria for relapse	**N = 177**		**N = 188**	
Entire Trial	**n**	**%**	**n**	**%**
Psychiatric hospitalization	20	44. 4	36	48. 0
Significant clinical deterioration (a CGI- C score of 6)	16	35.6	22	29.3
Increase in level of care was necessary and increase in PANSS score of 25% compared with Baseline, or an increase of 10 points if the Baseline score was 40	8	17.8	14	18.7
Emergence of clinically significant suicidal or homicidal ideation	1	2. 2	3	4. 0
TOTALS	45		75	

Figure 1 displays the Kaplan-Meier survival probability plot of time to relapse in USA-79.

Figure 1: Kaplan-Meier survival probability plot of time to relapse



Patients in the risperidone treatment group had a longer mean time to relapse (452.2 days) than the patients in the haloperidol treatment group (391.3 days). Among the patients with diagnosis of schizophrenia, there was a statistically significant difference between the two treatments, in favor of risperidone, in the survival curves ($p = 0.007$). In the risperidone group, the Kaplan-Meier estimates of relapse rates, i.e. the probability of relapse, were 19%, 29%, and 34%, at 6 months, 1 year and at the end of the trial, respectively.

Table C-9.2 Time to Relapse in Study USA-79 by Diagnosis

These two pooled studies detected only minimal differences between the two drugs safety profiles with the exception of the mean change in prolactin levels and weight gain. The mean prolactin level increased in the RIS group from 25.7 ng/ml at baseline to 40.2 ng/ml at end point, whereas it decreased in the HAL groups from 28.6 ng/ml to 22.6 ng/ml. Roughly twice the number of risperidone treated patients (58/241) gained >7% of their baseline body weight when compared to haloperidol treated patients (31/261).

B. Description of Patient Exposure

This review of safety focuses on the long-term controlled trials-USA-79 and INT-6. The following table reflects drug exposure in the long-term controlled studies.

Table VII-B.1 Estimated Risperidone Exposure in Long-term Controlled Trials

Duration of treatment (days)	RIS <4 mg	RIS 4 – 6 mg	RIS >6 mg	Total RIS
Total no. of subjects	29	156	98	283
1- 90 days, n (%)	11 (37.9)	46 (29.5)	27 (27.6)	84 (29.7)
91- 180 days, n (%)	5 (17. 2)	14 (9. 0)	10 (10.2)	29 (10.2)
181- 270 days, n (%)	2 (6.9)	10 (6. 4)	6 (6.1)	18 (6. 4)
271- 360 days, n (%)	1 (3.4)	10 (6. 4)	8 (8.2)	19 (6. 7)
>360 days, n (%)	10 (34.5)	76 (48.7)	47 (48.0)	133 (47.0)
Mean duration of treatment (days)	269 (50.7)	328 (20.5)	290 (21.2)	309 (14.5)
Total duration of exposure (patient- years)	21	140	78	239

C. Methods and Specific Findings of Safety Review

This review focuses on the long-term, controlled clinical trials. Risperdal has been on the market in the US since 1994. Open label experience is valuable as a screen for very rare, unreported, serious adverse events. Further open label experience did not reveal this type of new information.

D. Adequacy of Safety Testing

These studies were not designed to establish long-term safety. Since both INT-6 and USA-79 had haloperidol as an active control with no placebo comparator, longer-term exposure to risperidone could only be compared to haloperidol. The studies were too small to detect differences in events that occur at a rate of less than 1%.

There is a vast clinical experience with risperidone. The numbers of patients exposed in long-term controlled studies allowed for a reasonable estimate for an incidence rate for tardive dyskinesia of 1% or greater. [ ]

E. Summary of Critical Safety Findings and Limitations of Data

E-1 Deaths in controlled trials

There were two deaths in the risperidone treated patients and no deaths in the haloperidol treated patients. Neither risperidone treated patients' death was likely to be related to drug treatment. One patient completed suicide and the other died of multiple pulmonary emboli secondary to deep venous thrombosis of the both legs. Case summaries of these patients may be found in the appendix.

E-2 Serious Adverse Events

There were no serious adverse events that were unexpected and considered likely to be drug related. The numbers and distribution of types of serious adverse events was roughly equal between the two treatment groups. Most of the serious adverse events were psychiatric in nature and likely to be related to the disease of schizophrenia as opposed to drug treatment. A table of the types of serious adverse events that occurred at least twice in one, or both treatment groups is listed in table E-2.1 in the appendix.

E-3 Discontinuations Due to Adverse Events

The total number of discontinuations due to adverse events were greater in the haloperidol treated patients versus risperidone treated patients. If one considers only adverse events that are likely to be drug related as opposed to those that are likely to be incident to the disease, then the two treatment groups are less different. Nineteen versus 11 patients dropped out due to adverse events that could be considered likely to be drug related. Hyperkinesia (potentially akathisia) occurred in 10 (3.3%) haloperidol treated patients versus 4 (1.4%) risperidone treated patients. The drop out rate for "extrapyramidal disorder" was slightly higher in the risperidone treated patients [5 (1.8%) risperidone versus 3(1.0% haloperidol)].

There are discrepancies between some tables of discontinuation data in the submission. There are discrepancies in the total number of discontinuations due to adverse events between the sponsor's Table 4-3 and Table 4-9. The sponsor states that Table 4-3 is based on the trial termination form and Table 4-9 is based on the adverse event form with action taken "permanent stop" regarding trial medication. In trial RIS-USA-79, a substantial number of subjects had "relapse" as reason for trial termination but also had an adverse event for which the treatment was permanently stopped. On the trial termination form, however, only "relapse" (which was converted into "insufficient response") was recorded. There are therefore more discontinuations due to adverse events than in the trial termination table. This coding difference does not appear to effect the rates at which patients dropped out due to adverse events.

Sponsor's Table 4-3 Reasons for trial discontinuation –controlled long-term trials

Reason for discontinuation, n (%)	RIS <4 mg	RIS 4 – 6 mg	RIS > 6 mg	Total RIS	HAL
Total number of subjects	29	156	98	283	302
Completed	6 (20. 7)	71 (45.5)	45 (45.9)	122 (43.1)	83 (27.5)
Discontinued	23 (79.3)	85 (54.5)	53 (54.1)	161 (56.9)	219 (72.5)
Discontinuation reason:					
_ Insufficient response	3 (10. 3)	23 (14.7)	22 (22.4)	48 (17.0)	83 (27.5)
_ Adverse event	8 (27. 6)	17 (10.9)	11 (11.2)	36 (12.7)	47 (15.6)
_ Withdrawal of consent	10 (34.5)	21 (13.5)	4 (4.1)	35 (12.4)	36 (11.9)
_ Non compliance	0	7 (4.5)	11 (11.2)	18 (6. 4)	27 (8. 9)
_ Lost to follow- up	0	13 (8. 3)	0	13 (4. 6)	17 (5. 6)
_ Other	2 (6.9)	4 (2.6)	5 (5.1)	11 (3. 9)	6 (2.0)
_ Ineligibility	0	0	0	0	3 (1. 0)

The types and numbers of adverse events leading to discontinuation are listed in the following sponsor's table 4-9. To be listed in the table at least two patients in one of the treatment groups had to discontinue for that reason.

Sponsor's Table 4-9 Adverse events that led to treatment discontinuation in 0.5% of the total RIS and HAL subjects – controlled long-term trials

WHO system/ organ class	RIS <4 mg	RIS 4 – 6 mg	RIS >6 mg	Total RIS	HAL
WHO preferred term					
Total no. of subjects	29	156	98	283	302
Total no. of discontinuations due to AE , n (%) a)	9 (31. 0)	29 (18.6)	18 (18.4)	56 (19.8)	83 (27.5)
Psychiatric disorders	**3 (10. 3)**	**21 (13.5)**	**14 (14.3)**	**38 (13.4)**	**56 (18.5)**
Psychosis	0	11 (7. 1)	3 (3.1)	14 (4. 9)	32 (10.6)
Depression	1 (3.4)	4 (2.6)	4 (4.1)	9 (3.2)	4 (1.3)
Suicide attempt	0	2 (1.3)	4 (4.1)	6 (2.1)	2 (0.7)
Hallucination	0	0	3 (3.1)	3 (1.1)	1 (0.3)
Agitation	0	0	0	0	4 (1. 3)
Delusion	0	0	0	0	3 (1. 0)
Somnolence	0	0	0	0	3 (1. 0)
Anxiety	0	2 (1.3)	0	2 (0.7)	3 (1.0)
Schizophrenic reaction	0	1 (0.6)	1 (1.0)	2 (0.7)	2 (0.7)
Nervousness	0	1 (0.6)	0	1 (0.4)	2 (0.7)
Aggressive reaction	0	0	0	0	2 (0. 7)
Central & peripheral nervous system disorders	**2 (6.9)**	**6 (3.8)**	**3 (3.1)**	**11 (3. 9)**	**19 (6. 3)**
Extrapyramidal disorder	1 (3.4)	3 (1.9)	1 (1.0)	5 (1.8)	3 (1.0)
Hyperkinesia	1 (3.4)	3 (1.9)	0	4 (1.4)	10 (3. 3)
Dystonia	0	2 (1.3)	0	2 (0.7)	1 (0.3)
Tremor	0	0	2 (2.0)	2 (0.7)	2 (0.7)
Oculogyric crisis	1 (3.4)	0	0	1 (0.4)	2 (0.7)
Speech disorder	0	1 (0.6)	0	1 (0.4)	2 (0.7)
Hypokinesia	0	0	0	0	2 (0. 7)
Gastro- intestinal system disorders	**3 (10. 3)**	**0**	**0**	**3 (1.1)**	**4 (1.3)**
Nausea	2 (6.9)	0	0	2 (0.7)	1 (0.3)
Vomiting	2 (6.9)	0	0	2 (0.7)	1 (0.3)
Body as a whole – general disorders	**0**	**1 (0.6)**	**0**	**1 (0.4)**	**9 (3.0)**
Asthenia	0	0	0	0	2 (0. 7)
Fatigue	0	0	0	0	2 (0. 7)
Myo endo pericardial & valve disorders	**0**	**0**	0	0	2 (0. 7)
Myocardial infarction	0	0	0	0	2 (0. 7)

Drop outs in the long-term studies reflected roughly the dropout rate from risperidone short term trials in current labeling.

E-4 Adverse Events

Common and drug related adverse events associated with long term use could not be elucidated since this was an active controlled trial. In the ISS the sponsor suggests that the incidence rate of common adverse events decreases with time. Whether this is actually representative of

individual patients feeling fewer or decreased intensity of adverse events or a reflection of patients dropping out who poorly tolerate the drug is difficult to tell. [ ]

[ ]

E-5 Laboratory

Central Tendency

The sponsor reported that mean laboratory values did not change over time with the exception of prolactin The mean prolactin level increased in the RIS group from 25.7 ng/ml at baseline to 40.2 ng/ml at end point, whereas it decreased in the HAL groups from 28.6 ng/ml to 22.6 ng/ml. Visual inspection of the mean change tables confirmed this assertion.

Outlier Analysis

Upon visual inspection there were not differences in the incidence of outliers between haloperidol and risperidone patients with potentially clinically significantly high or low clinical laboratory values. Table E-5.1 in the appendix displays this data.

E-6 ECG

There were no relevant changes in ECG parameters. QTc mean values using four correction methods were unremarkable. The incidence of patients with QTc values increases was comparable between treatment groups as seen in table E-6.1 where Bazett's (B) and Fridericia (F) corrections are displayed.

Table E-6.1 Distribution of corrected QTc increases at end point relative to baseline - controlled long-term trials

Corrected QTc increases	RIS <4 mg	RIS 4 – 6 mg	RIS _ 6 mg	Total RIS	HAL
QTcB			n/ N assessed (%)		
_ 0- 30 ms	22/ 26 (84.6)	112/ 128 (87.5)	75/ 88 (85.2)	209/ 242 (86.4)	231/ 263 (87.8)
_ 31- 60 ms	3/ 26 (11.5)	13/ 128 (10.2)	10/ 88 (11.4)	26/ 242 (10.7)	25/ 263 (9.5)
_ >60 ms	1/ 26 (3. 8)	3/ 128 (2.3)	3/ 88 (3. 4)	7/ 242 (2.9)	7/ 263 (2.7)
QTcF					
_ 0- 30 ms	24/ 26 (92.3)	114/ 128 (89.1)	76/ 88 (86.4)	214/ 242 (88.4)	241/ 263 (91.6)
_ 31- 60 ms	2/ 26 (7. 7)	12/ 128 (9.4)	10/ 88 (11.4)	24/ 242 (9.9)	19/ 263 (7.2)
_ >60 ms	0/ 26 (0)	2/ 128 (1.6)	2/ 88 (2. 3)	4/ 242 (1.7)	3/ 263 (1.1)

E-7 Weight and Vital Signs

There were more risperidone patients who gained >7% of their baseline body weight than haloperidol treated patients. There was, however, no dose dependency for risperidone with respect to weight gain.

Table E-7.1 Incidence of Body Weight Increase >7% at end point- controlled long-term trials

% change from baseline at end point	RIS <4 mg	RIS 4 – 6 mg	RIS > 6 mg	Total RIS	HAL
			n/ N assessed		
Increase > 7%	11/ 25	31/ 128	16/ 88	58/ 241	31/ 261

Mean weight change was significantly different from haloperidol.

Table E-7.2 Mean Weight Change in Controlled Clinical Trials

		RIS			HAL			
		n	mean	SE	n	mean	SE	p- value
Weight	BL	166	82.48		182	84.20		0.590
(kg)	Year 1	99	2.49*	0.60	71	-0. 20	0. 89	0. 016
	Endpoint	166	2.36*	0.60	182	-0. 56	0. 52	<0.001

E-10 Special Searches

Tardive Dyskinesia

The Extrapyramidal Symptom Rating Scale (ESRS) was used to determine the presence and severity of tardive dyskinesia in Study USA-79. Emergence or worsening of dyskinetic symptoms were assessed using the following criteria: an increase from Baseline of ≥3 points in 1 item, or an increase of 2 points in 2 or more items in the dyskinetic movement subscale on 2 or more consecutive days. Patients were considered to have emergent or worsening dyskinetic symptoms if they met the criteria at any time during the trial. The existence of Baseline dyskinetic movement was also assessed with the following criteria: ≥ 3 points in 1 item, or 2 points in 2 items of the dyskinetic subscale for ESRS.

Eleven patients (3 RIS and 8 HAL) developed emergent or worsened tardive dyskinesia (TD) over the trial course. Of the patients with no symptoms at Baseline, 171 (98.3%) risperidone patients and 177 (96.2%) haloperidol patients remained symptom-free throughout the trial. Three (1.7%) risperidone treatment group patients and 7 (3.8%) haloperidol treatment group patients developed emergent, persistent TD during the trial. Of the 37 patients (18 RIS, 19 HAL), who had dyskinetic symptoms at Baseline, 0 of the risperidone treatment group and 1 (5.3%) of the haloperidol treatment group patients developed worsening symptoms by Endpoint.

[redacted] USA-79 produces an incidence of 1.7% (per year) if one uses the mean duration of exposure (351 days) as the denominator.

The ISS reports that there were only 2 risperidone patients who developed tardive dyskinesia in the controlled trial database. This number is manifestly smaller than the number reported for the single USA-79 trial. [redacted]

VIII. Dosing, Regimen, and Administration Issues

The sponsor makes changes in the DOSAGE AND ADMINISTRATION section of labeling that reflect the dosing regimen in the long-term controlled trials USA-79 and INT-6. They are accurate and acceptable from a clinical standpoint.

IX. Conclusions and Recommendations

A. Conclusions

Study USA-79 supports the sponsor's claim that Risperdal is effective in maintaining treatment response for schizophrenia. It has been customary to allow claims of extended efficacy based on the results of one positive, well designed, appropriately controlled trial. USA-79 meets this criteria [redacted]

In Study INT-6, a similarly designed study that was previously submitted, Risperdal was compared to haloperidol and no treatment difference was observed. USA-79 had twice the number of patients in each group. This increase in statistical power might explain the difference between USA-79 being a positive study and INT-6 showing no difference.

These studies were not designed to establish long-term safety. Since both INT-6 and USA-79 had haloperidol as an active control with no placebo comparator, long-term risperidone safety could only be compared to haloperidol. Even then the studies were too small to detect adverse events that occurred at a rate of less than 1%.

These two pooled studies detected only minimal differences between the two drugs safety profiles with the exception of the mean change in prolactin levels and weight gain. The mean prolactin level increased in the RIS group from 25.7 ng/ml at baseline to 40.2 ng/ml at end point, whereas it decreased in the HAL groups from 28.6 ng/ml to 22.6 ng/ml. Roughly twice the number of risperidone treated patients (58/241) gained >7% of their baseline body weight when compared to haloperidol treated patients (31/261).

[redacted] USA-79 produces an incidence of 1.7% (per year) if one uses the mean duration of exposure (351 days) as the denominator. The ISS reports that there were only 2 risperidone patients who developed tardive dyskinesia in the controlled trial database. This number is manifestly smaller than the number reported for the single USA-79 trial. [redacted]

B. Recommendations

I recommend that the Division make an approvable action on supplement 008. [redacted]

[ ] I recommend that labeling state the risperidone was superior to "[ ]active[ ]".

Paul J. Andreason, MD
Clinical Reviewer, HFD-120

XI. Appendix

Table C-1 Listing of Investigators Sites for USA-79

Investigator Site	No. of Patients
Site #02 Ronald Brenner, M. D. St. John's Episcopal Hospital 327 Beach 19th Street Far Rockaway, NY 11691	Entered =33 Randomized 30
Site# 03 David Brown, M. D. 4411 Medical Parkway Drive Austin, TX 78756	Entered 15 Randomized= 15
Site #04 Wayne K. Goodman, MD /Matthew Byerly, M. D. Department of Psychiatry University of Florida PSB 11- 430 1600 SW Archer Road Gainesville, FL 32610- 0256	Entered= 10 Randomized= 8
Site #06 James Chou, M. D. Room 20N11 Department of Psychiatry Bellevue Hospital Center 550 First Avenue New York, NY 10016	Entered= 24 Randomized= 19
Site #07 Barry Cole, M. D./ Michael De Priest, MD Southern Nevada Adult Mental Health Services 6161 W. Charleston Blvd. Las Vegas, NV 89102	Entered= 17 Randomized- 14

Table C-1 Listing of Investigators Sites for USA-79

Investigator Site	No. of Patients
Site #08 Cal Cohn, M. D. The Cohn Center, Psychiatry 7777 SW Freeway Suite 1036 Houston, TX 77074	Entered= 35 Randomized= 30
Site #09 John Csernansky, M. D. Washington University 4940 Children's Place Box 8134 St. Louis, MO 63110	Entered= 17 Randomized= 13
Site # 10 John Davis, M. D. 1601 West Taylor Street Chicago, IL 60612	Entered= 0 Randomized= 0
Site # 11 Lawrence A. Dunn, M. D. Durham VA Medical Hospital 508 Fulton Durham, NC 27705	Entered= 4 Randomized= 4
Site # 12 Alan Green, M. D. David A. Klegon, MD Commonwealth Research Center Harvard Medical Center 74 Fenwood Road Boston, MA 02115	Entered= 9 Randomized= 9
Site # 13 Alex Kopelowicz, M. D. (PI) 15535 San Fernando Mission Blvd. Mission Hills, CA 91345	Entered= 27 Randomized= 27

Table C-1 Listing of Investigators Sites for USA-79

Investigator Site	No. of Patients
Site # 15 Mark Hamner, M. D. VAMC - 116A Department of Psychiatry 109 Bee Street Charleston, SC 29401	Entered= 9 Randomized= 7
Site # 16 Harold Harsch, M. D. General Hospital, Psychiatry –175 8700 W. Wisconsin Ave Milwaukee, WI 53226	Entered= 8 Randomized= 7
Site # 17 Federico Adan, M. D Dominion Tower (D- 79) 1400 NW 10 th Avenue Suite 307A Miami, FL 33136	Entered= 9 Randomized= 7
Site #18 George G. Jaskiw, M. D. Chief, Schizophrenia Section Psychiatry Services 116- A (B) Cleveland VAMC 10,000 Brecksville Road Brecksville, OH 44141	Entered= 8 Randomized= 6
Site # 19 Bankole Johnson, M. D. The Mental Sciences Institute 1300 Moursund Houston, TX 77030	Entered= 32 Randomized= 30
Site # 20 Ari Kiev, M. D. Social Psychiatry Research Institute 75 Booth Avenue Englewood, NJ 07063	Entered= 13 Randomized= 9
Site # 21	Entered= 18

Table C-1 Listing of Investigators Sites for USA-79

Investigator Site	No. of Patients
Mary Ann Knesevich, M. D. St. Paul Medical Center Southwestern Medical Center 5959 Harry Hines Suite 924 Dallas, TX 75235	Randomized= 10
Site # 22 Douglas Levinson, M. D. Medical College of Pennsylvania & Hahnemann Univ. Hospital 3200 Henry Avenue Room 206A Philadelphia, PA 19129	Entered= 8 Randomized= 6
Site 23 H. E. Logue, M. D. Birmingham Psychiatry Pharmaceutical Studies, Inc. 3490 Independence Drive Birmingham, AL 35209	Entered= 32 Randomized= 27
Site #24 Robert M. Hamer Ph. D (PI) Matthew Menza, M. D.(CO- PI) RWJ Medical School 675 Hoes Lane Piscataway, NJ 08854	Entered= 5 Randomized= 5
Site #26 Raj Nakra, M. D. 16216 Baxter Road Chesterfield, MO 63017	Entered= 24 Randomized= 21
Site # 28 Charles Nemeroff, M. D. Emory University School of Medicine 1639 Pierce Drive Suite 4000 Atlanta GA 30322	Entered= 1 Randomized= 0
Site # 29	Entered= 2

Table C-1 Listing of Investigators Sites for USA-79

Investigator Site	No. of Patients
Vernon Neppe, M. D. NorthWest Outpatient Med. Ctr. 10330 Meridian Ave. Seattle, WA 98133 Budget/ Contract: 6808 44th Avenue, NE Seattle, WA 98115	Randomized= 0
Site # 30 Sheldon Preskorn, M. D. 1100 N. St. Francis Suite 200 Wichita, KS 67214- 2878	Entered= 16 Randomized= 13
Site #31 Michael Plopper, M. D. Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123	Entered= 32 Randomized= 27
Site # 33 George Simpson, M. D. Professor of Psychiatry USC School of Medicine 1937 Hospital Place Grad Hall Los Angeles, CA 90033	Entered= 2 Randomized= 1
Site # 34 Stephen Strakowski, M. D. Department of Psychiatry University of Cincinnati ML 559 231 Bethesda Avenue Cincinnati, OH 45267- 0559	Entered= 7 Randomized= 5
Site # 35 Marshall Thomas, M. D. University of Colorado 4455 E. 12th Avenue Denver, CO 80220	Entered= 3 Randomized= 2
Site # 36	Entered= 16

Table C-1 Listing of Investigators Sites for USA-79

Investigator Site	No. of Patients
Jose Yaryura- Tobias, M. D. Institute for Bio- Behavioral Therapy and Research 935 Northern Blvd. Great Neck, NY 11021	Randomized= 14
Site # 39 Scott A. West, M. D. Psychiatric Institute of Florida, PA 77 W. Underwood Street 3rd Floor Orlando, FL 32806	Entered= 11 Randomized= 9
Site # 40 Irving S. Kolin, M. D. 1065 Morse Blvd. Suite 202 Winter Park, FL 32789	Entered= 4 Randomized= 4
Site # 42 Marvin J. Miller, M. D. Larue Carter Hospital 2601 Cold Springs Road Indianapolis, IN 46222	Entered= 1 Randomized= 1
Site # 43 George Pahl, M. D. 13301 North Meridian Suite 101 Oklahoma City, OK 73120	Entered= 11 Randomized= 16
Site # 44 Tai P. Yoo, MD Mercy Hospital Behavioral Medicine Services 5555 Conner Detroit, MI 48213	Entered= 5 Randomized= 5

Table C-2 Inclusion and Exclusion Criteria for Study USA-79

INCLUSION CRITERIA

Patients who met the following criteria were eligible for this trial:

- patient or legal guardian signed an approved informed consent

- male or female between 18 and 65 years of age
- met DSM-IV criteria of schizophrenia or schizoaffective disorder
- had a documented 1-year history of schizophrenia or schizoaffective disorder since the first pharmacological treatment for psychotic symptoms
- within the past 24 months was discharged from an inpatient psychiatric unit, had a partial hospitalization, completed crisis management intervention, or stayed in a psychiatric hospital emergency room holding area for at least 12 hours
- received a stable dosage of antipsychotic medication for the 30 days prior to entering the trial (Stable was calculated by dividing the minimum dosage by the maximum dosage and defined as a ratio $\geq$ 0.75.)
- domiciled at the same address for at least 30 days preceding trial entry
- was able to discontinue current antipsychotic medication, in the opinion of the investigator
- was clinically stable, in the opinion of the investigator
- had negative urine drug screens for cocaine, opiates, barbiturates, amphetamines, phencyclidine, lysergic diethylamide acid, and methadone
- females had a negative pregnancy test
- agreed to refrain from using illicit drugs and abusing alcohol

EXCLUSION CRITERIA

Patients who met 1 or more of the following criteria were not eligible for this trial:

- females who were pregnant or nursing
- had another current DSM-IV Axis-I diagnosis (except caffeine or nicotine dependence) or Axis-II diagnosis of borderline personality disorder or antisocial personality disorder (A history of substance dependence or substance abuse must be in remission for at least 3 months at the time of Screening.)
- had clinically significant neurological disorder or other condition with neurological manifestations, with the exception of DSM-IV defined medication-induced movement disorders
- had history or the presence of gastrointestinal, liver, or kidney diseases, or other conditions of sufficient severity to interfere with the absorption, distribution, metabolism, or excretion of trial medication
- had clinically significant medical disease which would prohibit treatment with risperidone or haloperidol
- had unstable medical illness, ie, unstable angina, labile hypertension, poorly controlled diabetes
- received concomitant medication, other than OTC medications or antibiotics, for fewer than 14 days at the time of Screening (Doses of concomitant medications should be stable for 14 days, that is, minor variations of up to 25% are permitted.)
- had carcinoma during the previous 5 years (History of treated basal cell skin carcinoma is allowed.)
- was HIV-positive
- received current treatment with the antipsychotic clozapine or known o be refractory to antipsychotics
- was acutely psychotic and showed no response or minimal response to risperidone at dosages >8 mg/day or haloperidol at a dosage of >20 g/day when given for 4 weeks minimum
- was currently being treated with >10 mg/day risperidone or >25 mg/day haloperidol

- required treatment with antidepressants, lithium, carbamazepine, or valproic acid within the 30 days preceding trial entry
- had history of neuroleptic malignant syndrome
- had known hypersensitivity to risperidone or haloperidol
- had history of seizures requiring medication
- received depot neuroleptic injections within 1 treatment cycle of Screening
- received an investigational medication within 30 days before Screening
- had history of attempted suicide in the previous 6 months or current suicidal ideation
- was currently at risk for violent behavior against others
- was considered by the investigator as potentially noncompliant

Table C-5.1 Secondary Efficacy Variables in Study USA-79

- relapse rates, 1-year and Endpoint
- total and subscales of PANSS,
- 1-year relapse rate,
- clinical improvement measured by a 20% decline in total PANSS score,
- CGI and CGI-C,
- QOLI,
- Drug Attitude Inventory,
- cognitive function tests (Wechsler Memory Scale, California VerbalLearning Test, Continuous Performance Task, Verbal Fluency, Digit Symbol, and Wisconsin Card Sort), and
- Health Care Resource Utilization

Table C-5.2 Safety Assessments in Study USA-79

- adverse events
- clinical laboratory tests: blood chemistry profile: sodium, potassium, chloride, bicarbonate, glucose, urea nitrogen, creatinine, calcium, phosphorus, uric acid, total bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, gamma glutamyl transpeptidase, lactic dehydrogenase, total serum protein, albumin, and prolactin complete blood count with differential and platelet count urinalysis by dip stick; if abnormal, a microscopic examination urine drug screen serum pregnancy test (females of childbearing potential)
- ECG
- vital signs: pulse, respiration, temperature, blood pressure
- physical examination
- ESRS

Summaries of Deaths in Long-term Controlled Trials that were not Considered Drug Related

Subject 0152, a 41-year old Caucasian male in RIS-USA-79, was taking RIS 4 mg and was admitted to hospital on Day 97 of the trial for dyspnea and chest pain. The physician felt that the symptoms were due to chest inflammation. One day later the subject was seen again by the physician for the same symptoms and he recovered the same day. Eight days later the subject

complained of difficulty breathing and pain in his left arm. He became pale, diaphoretic and collapsed. He was pronounced dead when the emergency squad arrived. Autopsy revealed the cause of death as bilateral deep vein thrombosis with multiple pulmonary emboli. The investigator considered this event unrelated to the trial medication.

Subject 435, a 39-year old Caucasian female who was taking RIS 12.5 mg in trial RIS-INT-6. Twenty-five days after the start of treatment, she committed suicide. There was no relation to the trial medication according to the investigator. Listing AE.4 gives details about the events leading to death.

Table E-2.1 Serious adverse events in ≥ 0.5% of the total RIS and HAL subjects – controlled long-term trials

WHO organ system class	**RIS**	**RIS**	**RIS**	**Total RIS**	**HAL**
WHO preferred term	<4 mg	4 – 6 mg	> 6 mg		
Total no. of subjects	29	156	98	283	302
No. of subjects with SAE, n (%)	4 (13.8)	38 (24. 4)	18 (18. 4)	60 (21. 2)	69 (22. 8)
Psychiatric disorders	**3 (10.3)**	**24 (15. 4)**	**13 (13. 3)**	**40 (14. 1)**	**52 (17. 2)**
Psychosis	0	18 (11. 5)	9 (9. 2)	27 (9. 5)	38 (12. 6)
Suicide attempt	0	3 (1. 9)	4 (4. 1)	7 (2. 5)	4 (1. 3)
Depression	1 (3. 4)	2 (1. 3)	2 (2. 0)	5 (1. 8)	0
Hallucination	1 (3. 4)	0	2 (2. 0)	3 (1. 1)	1 (0. 3)
Agitation	0	1 (0. 6)	1 (1. 0)	2 (0. 7)	5 (1. 7)
Drug abuse	1 (3. 4)	1 (0. 6)	0	2 (0. 7)	1 (0. 3)
Paranoid reaction	0	1 (0. 6)	1 (1. 0)	2 (0. 7)	0
Schizophrenic reaction	0	1 (0. 6)	1 (1. 0)	2 (0. 7)	3 (1. 0)
Aggressive reaction	0	0	0	0	2 (0. 7)
Anxiety	0	0	0	0	3 (1. 0)
Delusion	0	0	0	0	3 (1. 0)
Body as a whole – general disorders	**0**	**6 (3. 8)**	**3 (3. 1)**	**9 (3. 2)**	**15 (5. 0)**
Injury	0	2 (1. 3)	2 (2. 0)	4 (1. 4)	4 (1. 3)
Chest pain	0	2 (1. 3)	1 (1. 0)	3 (1. 1)	1 (0. 3)
Syncope	0	1 (0. 6)	0	1 (0. 4)	2 (0. 7)
Therapeutic response increased	0	1 (0. 6)	0	1 (0. 4)	3 (1. 0)
Condition aggravated	0	0	0	0	2 (0. 7)
Metabolic and nutritional disorders	**1 (3. 4)**	**2 (1. 3)**	**1 (1. 0)**	**4 (1. 4)**	**5 (1. 7)**
Dehydration	1 (3. 4)	0	1 (1. 0)	2 (0. 7)	0
Diabetes mellitus	0	2 (1. 3)	0	2 (0. 7)	1 (0. 3)
Hyponatraemia	0	0	0	0	2 (0. 7)
Central & peripheral nervous system disorders	**0**	**2 (1. 3)**	**1 (1. 0)**	**3 (1. 1)**	**4 (1. 3)**
Convulsions	0	0	0	0	2 (0. 7)
Myo endo pericardial & valve disorders	**0**	**0**	**0**	**0**	**2 (0. 7)**
Myocardial infarction	0	0	0	0	2 (0. 7)

Table E-5.1 Laboratory value changes beyond the predefined limits in >2% of the total RIS and HAL subjects with normal baseline values – controlled long-term trials

Variable	RIS <4 mg	RIS 4 – 6 mg	RIS > 6 mg	Total RIS	HAL
Hematology			n/ N assessed (%)		
Hematocrit					
_ Abnormally low	0/ 22 (0)	3/ 115 (2.6)	0/ 38 (0)	3/ 175 (1.7)	1/ 188 (0.5)
_ Abnormally high	0/ 22 (0)	1/ 115 (0.9)	0/ 38 (0)	1/ 175 (0.6)	4/ 188 (2.1)
WBC					
_ Abnormally high	0/ 2 (0)	0/ 25 (0)	3/ 55 (5. 5)	3/ 82 (3. 7)	1/ 85 (1. 2)
Blood chemistry			n/ N assessed (%)		
Chloride					
_ Abnormally low	0/ 25 (0)	2/ 115 (1.7)	2/ 38 (5. 3)	4/ 178 (2.2)	3/ 187 (1.6)
_ Abnormally high	0/ 25 (0)	1/ 115 (0.9)	0/ 38 (0)	1/ 178 (0.6)	2/ 187 (1.1)
GGT					
_ Abnormally high	1/ 26 (3. 8)	4/ 137 (2.9)	2/ 91 (2. 2)	7/ 254 (2.8)	7/ 263 (2.7)
Glucose					
_ Abnormally low	0/ 27 (0)	1/ 141 (0.7)	0/ 92 (0)	1/ 260 (0.4)	0/ 272 (0)
_ Abnormally high	0/ 27 (0)	9/ 141 (6.4)	0/ 92 (0)	9/ 260 (3.5)	8/ 272 (2.9)
SGPT (ALT)					
_ Abnormally high	1/ 26 (3. 8)	4/ 140 (2.9)	0/ 92 (0)	5/ 258 (1.9)	6/ 270 (2.2)
Total protein					
_ Abnormally low	0/ 26 (0)	0/ 137 (0)	0/ 89 (0)	0/ 252 (0)	0/ 270 (0)
_ Abnormally high	0/ 26 (0)	1/ 137 (0.7)	0/ 89 (0)	1/ 252 (0.4)	6/ 270 (2.2)

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/s/

Paul Andreason
11/5/01 03:16:17 PM
MEDICAL OFFICER

Thomas Laughren
12/15/01 11:55:03 AM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approvable action for
Risperdal tablets and solution (risperidone) for the longer-term treatment of schizophrenia

TO: File NDA 20-272/S-008 & NDA 20-588/S-004
[**Note:** This overview should be filed with the 7-25-01
original submission.]

1.0 BACKGROUND

Risperdal is currently approved and marketed for the treatment of schizophrenia, in an immediate release tablet (NDA 20-272) and in an oral solution (NDA 20-588). These supplements provide data in support of a new claim for these same formulations in the longer-term treatment of schizophrenia, in a dose range of [ ] mg/day.

These supplements were originally submitted 3-12-97, and a nonapproval letter was issued 1-13-98. The 3-12-97 submission included efficacy date from 4 trials, only 1 of which was a controlled trial (INT-6), and that study, a 1 year comparison of risperidone and haloperidol, demonstrated no difference between these 2 active drugs in relapse, and thus, was considered uninterpretable. We also considered longer-term safety data submitted in 3-12-97 to be uninterpretable. However, we did invite the sponsor to submit labeling language to note the apparent lack of a 2D6 inhibitory effect for risperidone, as demonstrated in data submitted with these original supplements. We also, in the 1-13-98 letter, asked the sponsor to add language in labeling to describe the results of a cross-fostering study that showed a direct toxic effect on the fetus, and supported, in our view, the continuation of a Category C for pregnancy. Both of these changes were finally approved in a 7-19-01 letter.

Since the proposal is to use the currently approved Risperdal formulations for this expanded indication, there was no need for chemistry, pharmacology, or biopharmaceutic reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Paul Andreason, M.D., from the clinical group. Yeh-Fong Chen, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The study supporting this supplement was conducted under IND 31,931. The original supplements for this expanded indication (S-008 & S-004) were submitted 7-25-01.

We decided not to take these supplements to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

As Risperdal tablets and solution are already marketed, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Risperdal tablets and solution are already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Risperdal tablets and solution are already marketed, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Study 79

Results from study 79 were submitted in support of this claim for the longer-term efficacy of Risperdal in schizophrenia. This 35 center, US, outpatient, parallel group study enrolled patients with either schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be stable by the investigator for at least 1 month prior to randomization. "Stable" was defined as receiving the same dosage of antipsychotic

medication and living in the same residence for 30 days. Patients meeting these criteria were randomized (n=395) to either risperidone 4 mg/day (n=192) or haloperidol 10 mg/day (n=203) for a minimum period of 1 year, during which time they were observed for relapse. Medication was titrated up to these initial target doses over the first 3 days. During the first month of the trial, adjustments in medication could be made weekly, within a range of 2 to 8 mg/day for risperidone and 5 to 20 mg/day for haloperidol. Thereafter, patients were seen monthly, some for periods of up to 2 years. The study ended when the last randomized patient reached the 1 year point.
Relapse was defined as any 1 of the following:
-psychiatric hospitalization
-clinical judgement that an increase in level of care was necessary and an increase in PANSS total score of 25% compared to baseline, or an increase of 10 if the baseline score was ≤ 40 (both had to occur within a 2 week period)
-deliberate self injury
-emergence of clinically significant suicidal or homicidal ideation
-violent behavior resulting in significant injury to another person or significant property damage
-CGI-C score of 6 or 7

The primary outcome was time to relapse. Secondary outcomes included relapse rate, and PANSS total and subscales, among others.

The primary analysis was the log-rank test for time to relapse.

Patients in study 79 were roughly 2/3 male, roughly ½ Caucasian and 1/3 African American, and the mean age was roughly 41 years. Roughly 82% of patients were schizophrenic.

Forty-one % of risperidone patients completed to 1 year, compared to 23% of haloperidol patients. Patients in the risperidone group had a longer mean time to relapse (452 days) than patients in the haloperidol group (391 days), p=0.001. Risperidone also was superior to haloperidol on this measure in the subgroup with schizophrenia (p=0.007). However, the effect sizes were similar to those for the schizophrenic patients. The crude relapse risks at 1 year were 23% for risperidone and 35% for haloperidol (p=0.009). The cumulative relapse rates at 1 year were 29% for risperidone and 45% for haloperidol.

Dr. Chen did an analysis considering all censored patients as treatment failures, and this analysis also favored Risperdal over placebo (p=0.008).

Dr. Chen conducted subgroup analyses based on gender and race. This analysis showed a superiority of risperidone over haloperidol only for the male subgroup, however, the effect sizes were similar for both subgroups. Analyses based on race showed a superiority risperidone over haloperidol for both Caucasian and African American subgroups.

Comment: Both Drs. Andreason and Chen considered this a positive study supporting a claim of longer-term efficacy for Risperdal in the treatment of schizophrenia, and I agree. I also agree with Dr. Andreason that labeling should [ ] mention that superiority was established over an active comparator in this trial.

5.1.2 Conclusions Regarding Efficacy Data

Study 79 demonstrated a benefit of risperidone over haloperidol for the maintenance of stability, or delay of relapse, in patients with schizophrenia who were stable at trial entry and were then observed for relapse during a 1 to 2 year followup period.

5.2 Safety Data

Dr. Andreason's safety review of this supplement was based on 283 patients who received Risperdal in a pool of 2 controlled long-term studies (Study 79 and INT-6). Dosing was according to the currently recommended dose range for Risperdal. There were no unexpected safety findings among these patients, and no basis for changes in the labeling for Risperdal from the standpoint of safety, [ ]

[ ]

5.3 Clinical Sections of Labeling

We have modified the language in the 4 sections of labeling in which the sponsor has proposed changes, i.e., Clinical Trials, Indications, Adverse Reactions, and Dosage and Administration. We have also added language changing the focus of the claim for this drug from "management of the manifestations of psychosis" to "schizophrenia," as part of a class action for the antipsychotic drugs.

6.0 WORLD LITERATURE

Dr. Andreason reviewed the sponsor's report on a total of 116 published papers pertaining to the longer-term use of Risperdal in schizophrenia. He concluded that there were no unexpected adverse events reported that would impact on Risperdal labeling.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Risperdal is not approved for the longer-term treatment of schizophrenia anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we did not take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

9.0 DSI INSPECTIONS

DSI did not, to my knowledge, inspect investigative sites for this supplement.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling Attached to Approvable Package

Our proposed labeling for this new claim is included in the approvable letter.

10.2 Foreign Labeling

To my knowledge, Risperdal is not approved for the longer-term treatment of shizophrenia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes our proposed labeling for this supplement.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Janssen has submitted sufficient data to support the conclusion that Risperdal is effective and acceptably safe in the longer-term treatment of schizophrenia. I recommend that we issue the attached approvable letter with our proposed labeling language for this expanded claim.

cc:
Orig NDAs 20-272/S-008 & NDA 20-588/S-004
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/SHardeman

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/s/

Thomas Laughren
12/15/01 12:11:47 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 14, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approval action for
Risperdal tablets and solution (risperidone) for the longer-term treatment of schizophrenia

TO: File NDA 20-272/S-008 & NDA 20-588/S-004
[**Note:** This overview should be filed with the 1-28-02 response to our 1-11-02 approvable letter.]

We issued an approvable letter for these supplements on 1-11-02, with proposed modifications to labeling. There were no issues other than labeling that needed resolution prior to taking a final approval action. The sponsor has in fact accepted our proposed changes verbatim. They have also made changes throughout labeling to shift the focus of the claim from "psychosis" to "schizophrenia." as we had requested in a 9-25-00 letter.

There are only two issues that require further comment:

-In the cover letter to their 1-28-02 response, the sponsor has raised a question about a statement regarding[ ] we had included within a bracketed comment to them in our proposed labeling. They express a concern about this statement but they do not, in my view, articulate any question that needs a response at this time. [ ]

[ ] however, I think they need to give us a more definitive question before we can provide a meaningful response. Therefore, I recommend that we not respond to this vague inquiry at this time.

In summary, we have reached agreement with the sponsor on final labeling and I recommend that we approve these supplements, with the agreed upon final labeling.

cc:
Orig NDAs 20-272/S-008 & NDA 20-588/S-004
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/SHardeman

DOC: MEMSCZLT.AP1

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/s/

Thomas Laughren
2/14/02 02:07:53 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Neuropharmacological Drug Products (HFD-120)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER/SERIAL NUMBER:	20-272/S-008 & 20-588/S-004
DATE RECEIVED BY CENTER:	7/25/01
DRUG NAME:	RISPERDAL® (risperidone)
INDICATION:	Schizophrenia [ ]
SPONSOR:	Janssen Research Foundation
STATISTICAL REVIEWER:	Yeh-Fong Chen, Ph.D.
STATISTICAL TEAM LEADER:	Kun Jin, Ph.D.
BIOMETRICS DIVISION DIRECTOR:	George Chi, Ph.D.
CLINICAL REVIEWER:	Paul Andreason, M.D.
PROJECT MANAGER:	Steve Hardeman, M.D.

I. TABLE OF CONTENTS

II. EXECUTIVE SUMMARY OF STATISTICAL REVIEWER'S FINDINGS

- This reviewer did not have any inconsistent findings on the values of the sponsor's statistical analysis results.
- [ ] the sponsor had statistically significant test results shown on the primary and some secondary efficacy endpoints for the whole study population on Study RIS-USA-79[ ]
[ ]
[ ]
- Except for two diagnosis groups, the sponsor did not perform any other subgroup analysis. According to this reviewer's subgroup analysis results, the risperidone was shown significantly more effective than haloperidol for male patients but not for female patients. For both white and black patient groups, there existed statistically significant differences between the risperidone and haloperidol treatments.
- After reversing the values for censoring variables in the early discontinued study patients, the robustness of the test result for the primary endpoint was confirmed.

III. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1. Introduction and Background

In response to the FDA's not approvable letter dated January 13, 1998, the sponsor submitted this amendment to the supplement S-008 to provide for the long-term treatment of patients with schizophrenia [ ]

According to the sponsor's submission, efficacy data supporting this amendment were derived from clinical studies RIS-USA-79 and RIS-INT-6. The long-term efficacy of risperidone in delaying onset to relapse of schizophrenia [ ] was established by an in depth review of data from RIS-USA-79 in which an established agent, haloperidol was used as a reference neuroleptic agent. Data from the earlier study, RIS-INT-6, comparing long-term treatment with risperidone and haloperidol in the treatment of subjects with chronic schizoprenia were used to support the findings of RIS-USA-79. Since Study RIS-INT-6 was reviewed before, this review will be only focusing on the statistical evaluation for Study RIS-USA-79 but will report the sponsor's study outlines and statistical results for both studies.

2. Summary of the Sponsor's Results and Conclusions for Study RIS-USA-79

The primary efficacy endpoint for Study RIS-USA-79 was time to relapse in stable outpatients with chronic schizophrenia or schizoaffective disorder who received risperidone or haloperidol as maintenance treatment for at least 1 year. The secondary efficacy endpoints included relapse rates at 1-year and at endpoint, total and sub scales of PANSS, CGI severity, CGI-relative to change from the baseline assessment, cognitive function, quality of life, drug attitude inventory and health care resource utilization. Table 1 shows a summary of the sponsor's efficacy results for the primary and some important secondary endpoints.

Table 1. Summary of Efficacy Results

Efficacy	Risperidone		Haloperidol		p-value
Primary Variable	N=177		N=188		
• Time to Relapse (days)	452.23 (SE 17.68)		391.33 (SE 21.83)		0.001
Secondary Variables					
• Number of patients with Psychotic Relapse					
---- at 1 year	41 (23.2%)		65 (34.6%)		0.009
---- at Endpoint	45 (25.4%)		75 (39.9%)		0.002
• PANSS, change from Baseline to Endpoint	BL	mean change	BL	mean change	
---- Total PANSS score	65.06	–3.15	67.38	1.79	p<0.001
---- Positive symptoms	18.58	–1.56	19.15	-0.24	0.005
---- Negative symptoms	16.98	–0.53	17.80	0.77	0.004
---- Disorganized thoughts	14.97	–0.79	15.38	0.17	0.014
---- Uncontrolled hostility/excitement	1.04	0.29	6.26	0.73	0.076
---- Anxiety/depression factor	1.45	-0.52	8.76	0.24	0.005
• CGI-C, change from Baseline to Endpoint					
---- Very much improvement	12 (6.9%)		8 (4.3%)		<0.001
---- Much improvement	41 (23.7%)		25 (13.4%)		
---- Minimum improvement	50 (28.9%)		35 (18.7%)		
---- Unchanged	35 (20.2%)		59 (31.6%)		

According to the sponsor's test results shown on Table 1, they concluded that risperidone was statistically significantly more effective than haloperidol in maintaining clinical efficacy over a 1- to 2- year period in stable subjects with schizophrenia or schizoaffective disorder. Log-term treatment with risperidone was associated with superior symptom improvement including statistically significantly superior efficacy against haloperidol on positive, negative and affective symptoms.

3. Description of the Sponsor's Studies and Statistical Methodologies

3.1 Study RIS-USA-79

3.1.1 Trial Objectives

The primary objective of this double-blind study is to compare the time to relapse in stable outpatient schizophrenics and subjects with schizoaffective disorder receiving risperidone or haloperidol for at least 1 year.

Secondary objectives include comparing the effects of these two drugs on the incidence of relapse, symptom measures (PANSS, CGI), extrapyramidal side effects (ESRS), compliance, cognitive function (6 item test battery), subject satisfaction, quality of life and resource use.

3.1.2 Trial Design

This was a double-blind trial in outpatients with chronic schizophrenia or schizoaffective disorder classified by Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Patients were judged by the investigator to be clinically stable for 1 month prior to enrollment into the trial, discontinued their current antipsychotic medications, and were assigned to treatment using a randomization scheme that was stratified by sex. Stable was defined as receiving the same dosage of antipsychotic medication for 30 days and living in the same residence for 30 days.

The trial used a parallel-group design with 2 treatment arms: risperidone and haloperidol. Trial medication was escalated over the first 3 days of double-blind treatment to a dosage for 4 mg/day risperidone or 10 mg/day haloperidol. For the first month of therapy, assessments were made at 1-week intervals to allow adjustment of medication to within the range of 2 mg to 8 mg/day for risperidone and 5 mg to 20 mg/day for haloperidol. Thereafter, trial visits were scheduled every 4 weeks. Additional visits were to be scheduled as needed. Patients were to be followed until the last patient enrolled into the trial had completed 1 year of double-blind treatment. Patients who relapsed a second time were to be discontinued from the trial.

3.1.3 Efficacy

Several parameters were used to evaluate the efficacy of risperidone for maintenance treatment of patients with stable schizophrenia or schizoaffective disorder.

3.1.3.1 Primary Efficacy Parameter

The primary efficacy parameter was the time to relapse. Relapse was defined as any one of the following occurrences:

- psychiatric hospitalization,
- clinical judgment that an increase in level of care was necessary and increase in PANSS score of 25% compared with Baseline, or an increase of ten points if the baseline score was ≤40, (The increases in level of care and in PANSS score had to occur within 2 weeks of each other in order to qualify a patient's relapse.)
- deliberate self injury, in the investigator's opinion,
- emergence of clinically significant suicidal or homicidal ideation,
- violent behavior resulting in significant injury to another person or significant property damage, in the investigator's opinion, or
- significant clinical deterioration in the investigator's judgment (a CGI-C score of 6, "much worse").

When the investigator rated the patient's CGI-C at 6, the patient was counted as relapsed even if the investigator did not indicate relapse.

3.1.3.2 Secondary Efficacy Parameters

The secondary efficacy parameters were:
- Relapse rates at 1-year and at Endpoint
- Total PANSS
- PANSS subscale scores
- Clinical improvement measured by a 20% decline in total PANSS score
- CGI and CGI-C
- Quality of life (the Delight-Terrible (D-T) scales in the brief Quality of Life Interview)
- Cognitive function tests
- Drug Attitude Inventory and,
- Health Care Resource Utilization

3.1.4 Statistical Methods and Analyses Planned

Assume that a projected relapse rate over a 1-year period of 25% in the risperidone group and 40% in the haloperidol group, 165 patients per treatment, or a total of 330 patients were reqired to achieve the power of 0.8. To adjust for patient discontinuations resulting from reasons other than disease relapse, the protocol specified the randomization of 414 patients from 40 sites. All statistical tests were interpreted at the 5% 2-tailed significance level, unless otherwise noted.

Trial sites were sorted by the number of patients enrolled. If too few patients were entered at a site, the site was grouped with another site accordingly by size. Sites with the fewest patients were pooled with the next smallest site. If the number of patients was not ≥ 12 after pooling, the

next smallest site was included in the pool. The process was repeated until all-sites had a minimum of 12 patients.

Two populations of patients were defined for purposes of analyses:

1. All randomized patients who received trial medication were counted in the population for safety analyses;
2. All randomized patients who received trial medication and who had at least 1 post-Baseline assessment were counted in the intent-to-treat population for the analyses of changes from Baseline.

There were 4 weekly visits numbered 3 through 6 (Week 1 to Week 4) starting the double-blind treatment. Visits could continue through 27 months of treatment and were numbered 7 through 33 (Week 8 through Week 112). Visits 3 through 6 were to be performed on specified days plus or minus 1 day (i.e., Visit 3 could be made on trial days 7, 8 or 9). Visit 7 through 33 were to be made on the specified day plus or minus 4 days from the previous visit (i.e., Visit 7 could be made on trial days 53 through 61). Any deviation from this schedule was considered a violation of the protocol.

3.1.4.1 For Baseline Demographic Characteristics

Demographic information was summarized statistically for age, with mean values, standard deviations, standard errors, median values, and minimum and maximum values provided. For patient sex and race, frequency counts were provided by treatment group. Inter-group differences were evaluated with a 2-way ANOVA model with treatment and investigator as factors. For categorical data, the Cochran-Mantel-Haenszel (CMH) test, adjusting for investigator, was used.

3.1.4.2 For Primary Parameter- Time to Relapse

Kaplan-Meier survival curves were generated for each treatment group. Between treatment differences were assessed using a stratified log-rank test controlling for investigator and sex.

Relapse rate at 6 month, 1 year, and at end of the trial, were estimated by using Kaplan-Meier method.

Secondary analyses were performed on the subsets of patients who had diagnosis of schizophrenia or schizoaffective in order to assess the consistency in treatment effects across these subgroups. Whereas a similar statistical method, a stratified log-rank test controlling for investigator and sex, was applied in the analysis of the schizophrenia subgroup. For the schizoaffective subgroup, a non-stratified log-rank was used due to the small sample size.

3.1.4.3 For the Secondary Parameters

3.1.4.3.1 Relapse Rate

One-year relapse rate frequency tables were generated and CMH tests were applied controlling for investigator and sex. A similar analysis was performed for the endpoint data.

The differences in relapse rates between the two treatment groups were assessed for the subsets of patients who had diagnosis of schizophrenia or schizoaffective at baseline. Similar to the analysis on the time to relapse data, due to the small sample size, the between treatment comparison for the schizoaffective subgroup was based on the chi-square test without controlling for the investigator and sex effects.

3.1.4.3.2 Positive and Negative Symdrome Scale (PANSS)

The changes from baseline in total PANSS score and subscale scores were calculated at each assessment time point. Within-group differences were calculated using the paired t-test and inter-group comparisons were performed using an ANCOVA model with investigator, treatment, and sex as factors, and the baseline value as a covariate.

3.1.4.3.3 Cognitive Assessments

Treatment differences in each of the cognitive assessment tests were analyzed using ANCOVA with investigator, sex, and treatment as factors, and the baseline value as a covariate.

3.1.4.3.4 Drug Attitude Inventory (DAI)

Between treatment differences were evaluated with the CMH test controlling for investigator and sex. For total DAI, the sum of all items was calculated, and inter-treatment differences in the changes from baseline were analyzed using the ANOVA model with factors of treatment, sex, and investigator.

3.1.4.3.5 Quality of Life Interview (QOLI)

Descriptive statistics for the observed changes from baseline were provided for the Delight-Terrible (D-T) scales, which were added together, with total calculated scores. Treatment differences in D-T scales were examined using ANCOVA with factors for treatment, sex and investigator as factors, and baseline scores as covariates.

3.2 Study RIS-INT-6

RIS-INT-6 was the first long-term study with risperidone to be conducted under double-blind conditions. The trial was of a multicenter, multinational, double-blind, randomized design comparing the efficacy of risperidone and haloperidol over 1 year in patients with an acute exacerbation of chronic shcizophrenia at selection.

3.2.1 Efficacy Assessments

3.2.1.1 Primary Efficacy Parameter

The primary efficacy parameter was the time to discontinuation as a result of adverse events or clinical relapse. Relapse was defined as a deterioration in the subject's clinical condition that could not be managed satisfactorily after adjustment of dosage within protocol limits

3.2.1.2 Secondary Efficacy Parameters

The secondary efficacy parameters were:
- Total PANSS
- PANSS subscale scores (positive, negative, and psychopathology scales)
- CGI
- Quality of life
- Patient compliance

3.2.2 Planned Statistical Analyses

Sample size determination was based on a projected 1-year relapse rate of 25% in the risperidone group and of 55% in the haloperidol group. It was estimated that 80 subjects per treatment group, or a total of 160 subjects were would provide 90% power to detect statistically significant difference in the relapse rates at a two-tailed significance level of 0.05. To account for patient discontinuations for reasons other than disease relapse, a total of 180 subjects across 40 centers were randomized.

The primary efficacy parameter (the time to discontinuation because of adverse events or psychotic relapse) was estimated by the Kaplan-Meier product-limit method and compared between treatment groups by means of the Gehan's generalized Wilcoxon test, stratified for country.

Changes from baseline to endpoint in PANSS total and subscale scores were subjected to a two-way analysis of covariance (ANCOVA) model with factors for baseline score, treatment, and country. A clinical response was defined as a 50% or greater reduction in PANSS score. The number of responders and the CGI scores in each treatment group was compared using the Cochran-Mantel-Haenszel tests for general association. The compliance rating scale scores in each group were compared using the Van Eletern test.

4. Detailed Review of the Sponsor's Individual Study Results

4.1 Study RIS-USA-79

4.1.1 Subject Disposition

In total, 397 subjects were enrolled into RIS-USA-79 from 32 sites in the USA: 395 subject received trial medication (192 risperidone and 203 haloperidol). At the time of stopping the trial, 78 subjects were still being treated with risperidone and 46 were still receiving haloperidol.

During the audit of RIS-USA-79, the sponsor determined that the data from Site #8 did not meet the Janssen Pharmaceutical quality standards, so the analyses were performed with and without Site #8. Since the sponsor mentioned that the results from the analyses with or without this site were found generally consistent. In the sponsor's study report for efficacy analyses, the efficacy data without Site #8 were presented but with brief summaries of the all site population analyses.

After excluding data from Site #8, there were total 365 subjects in the efficacy analyses. The groups of risperidone and haloperidol had 177 subjects and 188 subjects, respectively.

4.1.2 Premature Discontinuations

As shown in Table 2, more subjects discontinued treatment with haloperidol (77.3%) than was the case for risperidone (59.4%). This was principally due to a higher rate of relapse in the haloperidol group (23.2%) than in the risperidone group (14.6%).

Table 2. Summary of Reasons for Premature Discontinuation

Reasons for Discontinuation	Risperidone N=192		Haloperidol N=203	
	n	%	n	%
Chose to discontinue	35	18.2	36	17.7
Relapse	28	14.6	47	23.2
Adverse event	24	12.5	30	14.8
Lost to follow-up	10	5.2	10	4.9
Poor compliance	6	3.1	15	7.4
Administrative	6	3.1	2	1.0
Other	3	1.6	4	2.0
Inadequate response	2	1.0	7	3.4
Ineligible	0	0	3	1.5
Intercurrent illness	0	0	2	1.0
Abnormal clinical laboratory result	0	0	1	0.5
Total Number of Subjects Discontinued	114	59.4	157	77.3

4.1.3 Demographics and Baseline Characteristics

The demographic characteristics were well balanced between the treatment groups. Overall 31.1% of the patients were female; 47.6% were white and 36.5% were black. Their mean age±SD was 40.5±10.56 years old (median age 39 years and range 20 years to 65 years old). Their mean weight±SD was 82.8±19.74 kg and their mean height±SD was 171.3±10.96 cm. Table 3 provides a by treatment summary of the demographic and Baseline characteristics for the 395 patients who were randomized and received trial medication.

Table 3. Baseline Demographic Characteristics including data from Site #8

Demographic Data		Risperidone N=192		Haloperidol N=203	
		n	%	N	%
Sex	Female	57	29.7	66	32.5
	Male	135	70.3	137	67.5
Race	White	91	47.4	97	47.8
	Black	72	37.5	72	35.5
	Hispanic	24	12.5	29	14.3
	Other	3	1.5	2	1.0
	Oriental	2	1.0	3	1.5

	Mean	SD	Mean	SD
Age (years)	40.8	10.72	40.1	10.43
Weight (kg)	82.0	19.62	83.6	19.87
Height (cm)	171.3	11.75	171.3	10.18

The without Site #8 baseline demographic characteristics by treatment groups were shown in Table 3.1. Overall 30.1% of the patients were female; 47.7% were white and 35.6% were black. The mean age±SD was 40.2±10.51 years old. Their mean weight±SD was 82.8±19.11 kg and mean height±SD was 171.3±11.01 cm and.

Table 3.1. Baseline Demographic Characteristics without data from Site #8

Demographic Data		Risperidone N=177		Haloperidol N=188	
		n	%	N	%
Sex	Female	50	28.2	60	31.9
	Male	127	71.8	128	68.1
Race	White	81	45.8	93	49.5
	Black	67	37.9	63	33.5
	Hispanic	24	13.6	27	14.4
	Other	3	1.7	2	1.0
	Oriental	2	1.1	3	1.6
		Mean	SD	Mean	SD
Age (years)		40.3	10.62	40.1	10.43
Weight (kg)		82.8	19.21	82.8	19.06
Height (cm)		171.5	11.87	171.2	10.16

4.1.4 Primary Efficacy Parameter

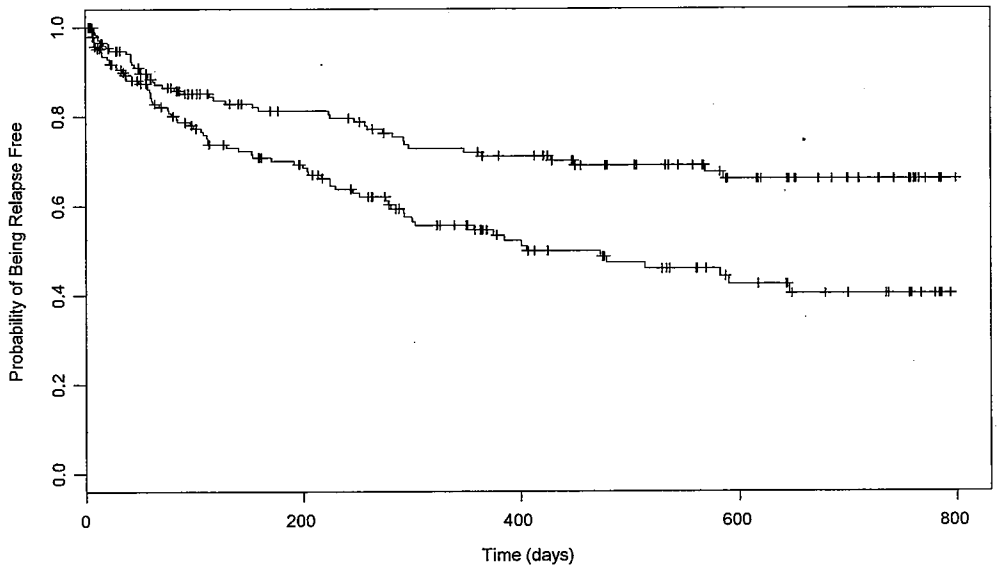
Since the sponsor determined that the data from Site #8 did not meet the Janssen Pharmaceutical quality standards, they only presented the data analyses for the primary and secondary efficacy variable excluding data provided by this site in their study report.

According to the sponsor's study report, subjects in the risperidone treatment group had a longer mean time to relapse (452.2±17.7 days) than the subjects in the haloperidol treatment group (391.3±21.8 days). However, as the last observations for both treatment groups were censored, the mean time to relapse may be underestimated.

The 25th percentile for time to relapse was 292 days for the risperidone treatment group and 113 days for the haloperidol treatment group. Median time to relapse was 406 days for subjects on haloperidol, but there were too few relapsing subjects in the risperidone group to determine a median time to relapse. There were insufficient numbers of relapse subjects in either treatment group to calculate the 75th percentile relapse rates.

Using the stratified logrank test, there was a statistically significant difference, in favor of risperidone, between the survival distribution of the 2 treatment groups (p=0.001). The Kaplan-Meier survival probability plot of time to relapse is shown in Figure 1.

Figure 1. Kaplan-Meier Survival Probability plot of time to relapse
(Note: The upper curve is for Risperidone group and the lower curve is for Haloperidol group)



The one year relapse rate (probability of relapse), based on the Kaplan-Meier estimates, were 29% and 45% for the risperidone and haloperidol groups, respectively. The Kaplan-Meier estimates for the relapse rates were consistently lower in the risperidone group than in the haloperidol group at 6 month (19% versus 30%), 1 year (29% versus 45%), and at the end of the trial timepoints (34% versus 60%).

In order to verify the results for subjects with for those with schizophrenia, the analyses were repeated in each diagnosis of the population. These results are shown in Table 4.

Among the patients with diagnosis of schizophrenia (n=200), there was a statistically significant difference between the two treatments, in favor of risperidone, in the survival curves (p=0.007). In the risperidone group, the Kaplan-Meier estimates of relapse rates, i.e., the probability of relapse, was 19%, 28% and 34%, at 6 months, 1 year and at the end of the trial, respectively. These rates were consistently lower than those in the haloperidol group (32%, 47% and 59% respectively)

Nonetheless, the Kaplan-Meier estimates of relapse rates at 6 months, 1 year and at the end of the trial were 19%, 34%, and 34%, in the risperidone group, which were consisetntly lower than the corresponding rates in the haloperidol group (21%, 37% and 62%, respectively).

Table 4. Analysis of Time to Relapse in Patients with Schizophrenia and Schizoaffective Disorders

	Risperidone	Haloperidol	P-value
All diagnoses	N=177	N=188	0.001[b]
Number (%) relapsed	45 (25.4%)	75 (39.9%)	
Mean (SE) time to relapse*	452.2 (17.7)	391.3 (21.8)	
Relapse rate at 6 month[a]	19%	30%	
Relapse rate at 1 year[a]	29%	45%	
Relapse rate at end of trial[a]	34%	60%	
25% Quartile (days)	292.0	113.0	
50% Quartile (days)	----	406	
Schizophrenia	N=144	N=156	0.007[b]
Number relapsed	36 (25.0%)	62 (39.7%)	
Relapse rate at 6 month[a]	19%	32%	
Relapse rate at 1 year[a]	28%	47%	
Relapse rate at end of trial[a]	34%	59%	
25% Quartile (days)	293.0	109.0	
50% Quartile (days)	----	385	

*The estimated means were biased, since the last observations were censored.
[a]Kaplan-Meier estimates of relapse rate (probability of relapse).
[b]Stratified log-rank test controlling for investigator and sex.

4.1.5 Secondary Efficacy Parameters

4.1.5.1 Relapse Rates (The Crude Rates)

Of 365 patients in the trial, 41 patients (23.2%) in the risperidone treatment group and 65 patients (34.6%) in the haloperidol treatment group relapsed by the end of the first year (p=0.009). At Endpoint, 45 patients (25.4%) on risperidone treatment and 75 patients (39.9%) on haloperidol had relapsed (p=0.002).

Similar significant differences (p=0.011) were apparent in subgroup analyses of patients with schizophrenia.

Table 5. Relapse Rates in Subjects with Schizophrenia and Schizoaffective Disorders

Relapse Rates	Risperidone		Haloperidol		P-value
	n	%	N	%	
All diagnoses	N=177		N=188		
1 Year	41	23.2	65	34.6	0.009
Endpoint	45	25.4	75	39.9	0.002
Schizophrenia	N=144		N=156		
1 Year	32	22.2	56	35.9	0.016
Endpoint	36	25.0	62	39.7	0.011

As it was shown in Table 6, most of the patient relapses were due to the psychiatric hospitalization and clinical deterioration.

Table 6. Summary of the Number of Subjects Discontinuing due to Relapse by Criteria of Relapse

Criteria for Relapse Entire Trial	Risperidone N=177		Haloperidol N=188	
	n	%	n	%
Psychiatric hospitalization	20	44.4	36	48.0
Significant clinical deterioration (a CGI-C score of 6)	16	35.6	22	29.3
Increase in level of care was necessary and increase in PANSS score of 25% compared with Baseline, or an increase of 10 points if the Baseline score was ≤40	8	17.8	14	18.7
Emergence of clinically significant suicidal or homicidal ideation	1	2.2	3	4.0
Totals	45		75	

4.1.5.2 Positive and Negative Symptom Scale (PANSS)

There was no significant difference in baseline measures of positive, negative or affective symptoms on the PANSS (see Table 7).

The mean shift from baseline on the PANSS total score at endpoint was better in the risperidone treatment group (-3.15), compared to +1.79 in the haloperidol treatment group. At endpoint, there was a significant difference in favor of risperidone over haloperidol for the total PANSS score ($p<0.001$) and for both the positive ($p=0.005$) and negative ($p=0.004$) subscales. A similar advantage for risperidone was also seen on the anxiety/depression ($p=0.005$) and disorganized thoughts ($p=0.014$) subscales of the PANSS. The between treatment difference for uncontrolled hostility/excitement was on the borderline of significance ($p=0.076$).

Table 7. PANSS results – data from Site 8 were excluded

PANSS	Risperidone			Haloperidol			P-value
	N	Mean	SE	N	Mean	SE	
Total PANSS							
Baseline	170	65.06		184	67.38		0.162
Year 1	91	-7.13	1.40	69	-5.74	1.99	0.261
Endpoint	170	-3.15	1.42	184	1.79	1.28	<0.001
Positive Symptoms							
Baseline	171	18.58		186	19.15		0.364
Year 1	92	-2.77	0.56	69	-1.71	0.79	0.212
Endpoint	171	-1.56	0.49	186	-0.24	0.46	0.005
Negative Symptoms							
Baseline	172	16.98		186	17.80		0.172
Year 1	92	-1.59	0.54	69	-1.55	0.73	0.835
Endpoint	172	-0.53	0.41	186	0.77	0.46	0.004
Disorganized Thoughts	171	14.97		184	15.38		0.478
Baseline	93	-1.47	0.34	69	-1.26	0.48	0.322
Year 1	171	-0.79	0.36	184	0.17	0.35	0.014
Endpoint							
Uncontrolled Hostility/Excitement							
Baseline	172	6.04		186	6.26		0.321
Year 1	93	-0.43	0.22	69	-0.38	0.29	0.655
Endpoint	172	0.24	0.23	186	0.73	0.20	0.076
Anxiety/Depression							
Baseline	172	8.45		186	8.76		0.425
Year 1	93	-0.96	0.26	69	-0.84	0.40	0.167
Endpoint	172	-0.52	0.29	186	0.24	0.24	0.005

Note: 1. Mean values at Baseline are the mean score, all other means are the mean change from Baseline, non-imputed.

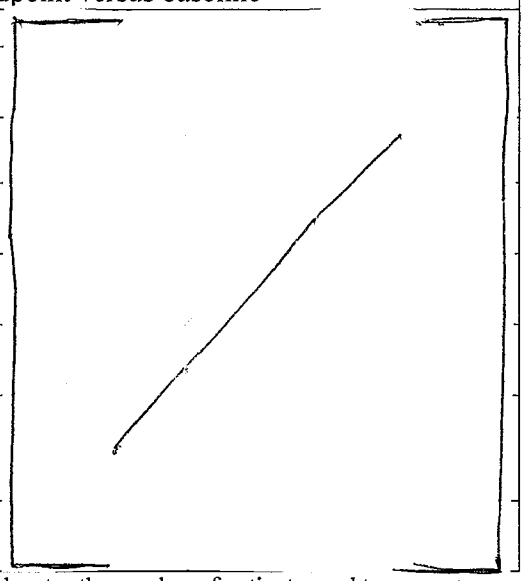
2. p-value determined by an analysis of covariance model with Baseline as a covariate and treatment, investigator, and sex as factors.

Table 8 shows us the test results for different diagnosis groups. As it was observed in Table 8, the test results obtained in the subgroup of patients diagnosed as having schizophrenia give us the same conclusions as those described for the population as a whole except the item of disorganized thoughts. The treatment of risperidone showed significantly more effective than haloperidol at reducing total PANSS scores as well as those relating to positive symptoms, negative symptoms and anxiety/depression.

[ ] risperidone was found to be significantly more effective than haloperidol at reducing the total PANSS score as well the subscale scores relating to negative symptoms and disorganized thought in this subgroup analyses.

Table 8. PANSS results in subjects with schizophrenia

PANSS	Mean change at endpoint versus baseline		
	Schizophrenia		
	Risperidone N=144	Haloperidol N=156	p-value
Total PANSS	-3.01 (n=139)	2.22 (n=152)	0.004
Positive Symptoms	-1.56 (n=140)	0.05 (n=154)	0.008
Negative Symptoms	-0.51 (n=141)	0.73 (n=154)	0.026
Disorganized Thoughts	-0.61 (n=140)	0.17 (n=152)	0.146
Uncontrolled Hostility/ Excitement	0.41 (n=141)	0.77 (n=154)	0.251
Anxiety/ Depression	-0.75 (n=141)	0.36 (n=154)	<0.001



Note: 1. N denotes the total number of patients in the group but n denotes the number of patients used to compute the mean change from Baseline to the endpoint.

2. p-values were from the analysis of covariance test of no difference between treatment groups with baseline score as covariate.

4.1.5.3 Clinical Global Impression (CGI/CGI-C)

The CGI ratings at Baseline were comparable in both groups, however, during double-blind treatment, symptoms decreased more with risperidone treatment than with haloperidol treatment. Table 9 shows that the overall CGI ratings at endpoint were significantly better with risperidone than with halopericdol ($p<0.001$), with 59.5% of risperidone-treated subjects compared with 36.4% of the haloperidol group being minimum improved, much improved or very much improved.

Table 9. CGI-C from Baseline to Year 1 and Endpoint

	Risperidone		Haloperidol		p-value
	n	%	n	%	
Year 1	N=93		N=70		
Very much improvement	7	7.5	4	5.7	0.006
Much improvement	28	30.1	14	20.0	
Minimum improvement	27	29.0	19	27.1	
Unchanged	28	30.1	27	38.6	
Endpoint	N=173		N=187		
Very much improvement	12	6.9	8	4.3	<0.001
Much improvement	41	23.7	25	13.4	
Minimum improvement	50	28.9	35	18.7	
Unchanged	35	20.2	59	31.6	

4.1.5.4 Cognitive Assessments

There were no statistically significant differences between treatment groups and no significant change from Baseline for any of the cognitive assessment scales.

4.1.5.5 Drug Attitude Inventory

The items 'Good things about medication outweigh the bad' (p=0.033) and 'medications make me feel more relaxed' (p=0.037) were statistically significantly favorable to risperidone at endpoint.

At Weeks 2 and 4, and at endpoint, statistically significantly (p=0.038, 0.044, and 0.001, respectively) greater number of haloperidol subjects rated their medication as causing 'weird like a zombie' symptoms. At the same visits, significantly more subjects receiving haloperidol than risperidone (p=0.04, <0.001, and <0.001, respectively) stated that their medication caused 'tired/sluggish' feelings.

4.1.5.6 Quality of Life

The Delight-Terrible scales of the QOLI showed a trend in favor of risperidone ($p \leq 0.10$) at Edpoint on the majority of scales. There were statistically significant differences between risperidone and haloperidol in 'general satisfaction,' 'daily activity and functioning,' 'family,' and 'social relationship' categories (Table 10).

Table 10. Changes in Quality of Life Assessments

Quality of Life	Mean change from baseline to endpoint		
	Risperidone N=177	Haloperidol N=188	P-value
General satisfaction	0.28	-0.11	0.011
Daily activity and functioning	0.93	-0.29	0.018
Family relationships	0.39	-0.50	0.005
Social relationships	0.54	-0.37	0.002

4.1.5.7 Health Care Resource Utilization

The majority of parameter were significantly different from Baseline at mose assessments. But, no comparison between treatment groups was performed.

4.1.6 Sponsor's Efficacy Conclusion

Risperidone was statistically significantly more effective than haloperidol in maintaining clinical efficacy over a 1- to 2-year period in stable subjects with schizophrenia or schizoaffective disorder. Long-term treatment with risperidone was associated with superior symptom improvement, including statistically significantly superior efficacy against haloperidol on positive, negative, and affective symptoms.

The finding that risperidone is superior to haloperidol, which has itself been shown to be effective in preventing relapses, indicates that risperidone has an important role to play in the long-term treatment of schizophrenia.

4.2 Study RIS-INT-6

4.2.1 Subject Disposition

A total of 190 subjects were recruited into the study from 48 centers in seven countries: 91 subjects were assigned to treatment with risperidone and 99 received haloperidol.

4.2.2 Premature Discontinuations

A significantly greater proportion of subjects discontinued treatment with haloperidol (62 subjects; 63%) than was the case with risperidone (47 subjects; 52%; p=0.04 CMH test).

The primary reason for discontinuing therapy was insufficient efficacy (including psychotic relapse) which accounted for 20 subjects (22%) in the risperidone group and 32 subjects (32%) in the haloperidol group.

4.2.3 Demographics and Baseline Characteristics

The subjects in the risperidone group comprised 57 male and 34 female patients with a median age of 33 year (range: 18 to 65 years). The haloperidol group included 58 male and 41 female patients with a median age of 34 years (range: 18 to 65 years).

4.2.4 Primary Efficacy Parameter: Withdrawal for Adverse Events and/or Psychotic Relapse

In total 25 subjects (27%) withdrew from risperidone and 26 (26%) withdrew from haloperidol because of adverse events and/or psychotic relapse. Regarding the time to discontinuation, 25% of the subjects in the risperidone group dropped out by Day 141 (lower 95% CI: Day 78) whereas 25% of the subjects in the haloperidol group had done so by Day 100 (lower 95% CI; Day 36). The difference between the groups was not statistically significant (p=0.457, Gehan's generalized Wilcoxon test stratified for country).

4.2.5 Secondary Efficacy Parameters

4.2.5.1 PANSS Scores

Baseline PANSS scores were found to be comparable in the two groups of subjects. However, subjects treated with risperidone tended to have a significantly greater change in total PANSS score at end point (-24.6) than those receiving haloperidol (-18.9; p=0.059 ANOVA). The corresponding changes in the total PANSS-derived BPRS scores were –14.0 for risperidone and –10.8 for haloperidol (p=0.061).

As shown in Table 11, the mean changes in total PANSS scores were progressive throughout the 52 week evaluation period in both groups of subjects.

Table 11. PANSS results

PANSS	Risperidone			Haloperidol			p-value
	N	Mean	SE	N	Mean	SE	
Total PANSS							
Baseline	91	95.8	1.91	99	96.8	1.91	0.059
Year 1	45	-39.0	3.90	36	-38.3	4.26	
Endpoint	91	-24.6	3.08	99	-18.9	2.89	
Positive Subscale							
Baseline	91	22.8	0.67	99	23.5	0.72	0.082
Year 1	45	-11.7	1.21	36	-11.9	1.37	
Endpoint	91	-7.9	0.92	99	-6.6	0.94	
Negative Subscale							
Baseline	91	26.0	0.76	99	26.5	0.76	0.103
Year 1	45	-8.7	1.19	36	-8.1	1.43	
Endpoint	91	-5.9	0.87	99	-4.6	0.77	
Thoughts Disturbances							
Baseline	91	13.4	0.43	99	14.2	0.42	0.105
Year 1	45	-6.7	0.71	36	-6.9	0.75	
Endpoint	91	-4.6	0.54	99	-4.2	0.52	
Hostility							
Baseline	91	8.5	0.32	99	8.7	0.33	0.410
Year 1	45	-3.9	0.47	36	-3.8	0.71	
Endpoint	91	-2.2	0.43	99	-1.7	0.47	
Anxiety/Depression							
Baseline	91	11.6	0.34	99	11.1	0.39	0.291
Year 1	45	-4.7	0.60	36	-4.5	0.54	
Endpoint	91	-2.5	0.47	99	-1.6	0.45	

Note: Mean values at Baseline are the mean score, all other means are the mean change from Baseline.

4.2.5.1 Clinical Global Improvement (CGI)

The mean baseline values of the CGI were 5.0 for risperidone and 5.1 for haloperidol. The corresponding mean scores at end point, were 3.8 and 4.1, respectively (p=0.103, CMH test).

The mean overall CGI change score versus baseline were also comparable in the two treatment groups at endpoint (3.1 for risperidone and 3.2 for haloperidol, p=0.357).

4.2.5.2 Quality of Life

The mean total Quality of Life score at baseline was 47.0 for risperidone and 45.4 with haloperidol. There was a significantly greater improvement in the risperidone group for the

cluster 'instrumental role functioning' (+2.3) than was apparent in the haloperidol group (+1.0; p=0.037). The changes from baseline to end point on the other subscales were similar in the two treatment groups.

4.2.5.3 Compliance Rating Scale

The majority of patients in both groups (77%) had 'good' or 'very good' scores on the compliance rating scale at endpoint. There was no significant between-group difference at any time point during the study.

4.2.6 Sponsor's Efficacy Conclusions

Because of the choice of comparator, as well as other design considerations, the conclusions that can be drawn from the results of RIS-INT-6 are somewhat limited. Nonetheless, the findings are not inconsistent with those of RIS-USA-79, and support the conclusion that risperidone is an effective antipsychotic for the long-term treatment of schizophrenia.

5. Statistical Reviewer's Findings and Comments

1. When the sponsor's study RIS-USA-79 was evaluated, this reviewer did not find any inconsistent test results with the sponsor's. For the primary endpoint and the secondary endpoints, this reviewer was able to exactly duplicate the sponsor's results.

2. [ ] the sponsor had statistically significant test results shown on the primary and some secondary efficacy endpoints in the whole study population (i.e, patients with either schizophrenia or schizoaffective disorder) for Study RIS-USA-79 [ ]

[ ]

[ ] Table 12 shows the summary of p-values for all study patients, only schizophrenia patients [ ] [ ]

Table 12. Summary of p-values for the Whole Study Population and Sub-populations

Efficacy variables	All Diagnoses (N=365)	Schizophrenia (N=300)	[ ]
Primary Variable			
• Time to Relapse (days)	0.001	0.007	
Secondary Variables			
• Number of patients with Psychotic Relapse			
---- at 1 year	0.009	0.016	
---- at Endpoint	0.002	0.011	
• PANSS, change from Baseline to Endpoint			
---- Total PANSS score	<0.001	0.004	
---- Positive symptoms	0.005	0.008	
---- Negative symptoms	0.004	0.026	
---- Disorganized thoughts	0.014	0.146	
---- Uncontrolled hostility/excitement	0.076	0.251	
---- Anxiety/depression factor	0.005	<0.001	

3. Except for two diagnosis groups, the sponsor did not perform any other subgroup analysis. They did mention in the protocol that " If the size of the study permits, relevant demographic or baseline value-defined subgroups will be examined for unusually large or small responses, e.g., comparison of effects by age, sex, and race." However, it is not clear what they mean' permits'.

   Since there are reasonable number of patients in both female and male groups as well as white and black race groups, it would be interested to know the analysis results among these subgroups. This reviewer performed subgroup analyses similar to what were shown in Table 4 and summarized results in Tables 13 and 14.

   As we can observe in Table 13, the risperidone was shown statistically significantly more effective than haloperidol for male patients but not for female patients. Since the risperidone treatment group did have smaller relapse rates than the haloperidol treatment group for female patients, the lack of ability to detect differences between these two groups may be due to the insufficient sample size.

   According to Table 14, there existed statistically significant difference between the risperidone and haloperidol treatment groups on both white and black patient groups.

Table 13. Subgroup Analyses for Gender

	Risperidone	Haloperidol	P-value*
Female Patients	N=50	N=60	0.1280
Number relapsed	12 (24%)	22 (36.7%)	
Relapse rate at 6 month[a]	11%	24%	
Relapse rate at 1 year[a]	32%	38%	
Relapse rate at end of trial[a]	32%	58%	
25% Quartile (days)	292	200	
50% Quartile (days)	----	590	
Male Patients	N=127	N=128	0.0012
Number relapsed	33 (26%)	53 (41.4%)	
Relapse rate at 6 month[a]	22%	33%	
Relapse rate at 1 year[a]	28%	49%	
Relapse rate at end of trial[a]	34%	61%	
25% Quartile (days)	282	107	
50% Quartile (days)	----	375	

* p-values were obtained from the log-rank test without any stratification.

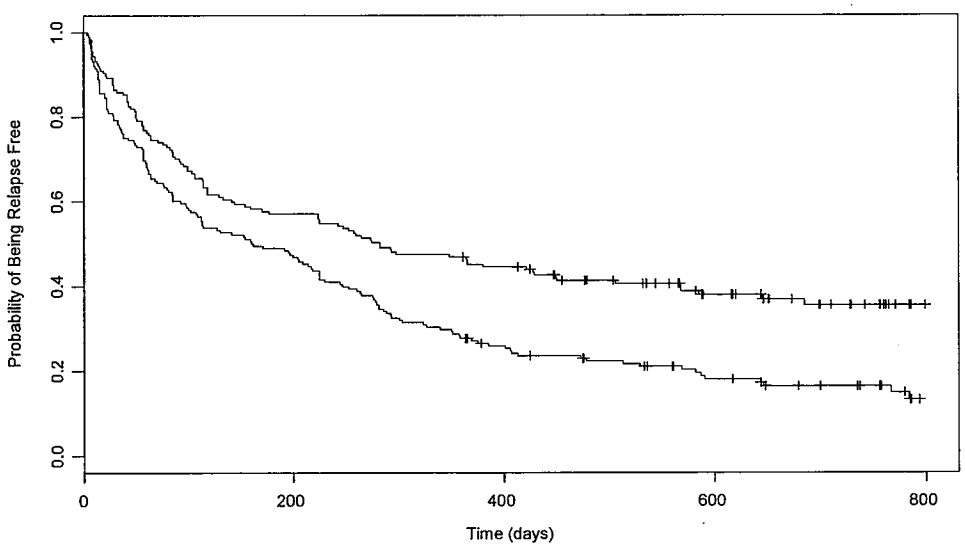
Table 14. Subgroup Analyses for Race of White and Black

	Risperidone	Haloperidol	P-value*
White Patients	N=81	N=93	0.0133
Number relapsed	25 (30.9%)	39 (41.9%)	
Relapse rate at 6 month[a]	27%	39%	
Relapse rate at 1 year[a]	35%	59%	
Relapse rate at end of trial[a]	41%	70%	
25% Quartile (days)	154	79	
50% Quartile (days)	----	278	
Black Patients	N=67	N=63	0.0333
Number relapsed	13 (19.4%)	23 (36.5%)	
Relapse rate at 6 month[a]	12%	17%	
Relapse rate at 1 year[a]	26%	35%	
Relapse rate at end of trial[a]	26%	55%	
25% Quartile (days)	348	225	
50% Quartile (days)	----	582	

*p-values were obtained from the log-rank test without any stratification.

4. To check if the early discontinued patients influence the test results for the primary endpoint, time to relapse, this reviewer treated them as failures by reversing their censoring variables and reran the analyses. The p-value shows .0008. So, it assures us the robustness of the test result for the primary endpoint. The Kaplan-Meier Survival curves for this case is shown in the following figure.

Figure 2. Kaplan-Meier Survival Probability plot of time to relapse after reversing censoring variables for the early discontinued patients. (Note: The upper curve is for Risperidone group and the lower curve is for Haloperidol group)



Yeh-Fong Chen, Ph.D.
Mathematical Statistician

Concurrence:

Dr. Jin

Dr. Chi

cc: NDA 20-272 (S-008)
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Andreason
HFD-120/Mr. Hardeman
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Chen
This review consists of 21 pages. MS Word: C:/yfchen/nda20272_s008/review.doc

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/s/

Yeh-Fong Chen
12/20/01 10:03:07 AM
BIOMETRICS

Kun Jin
12/20/01 11:21:05 AM
BIOMETRICS

George Chi
12/21/01 11:44:39 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-008 & 20-588/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-272 SE8-008 & 20-588 SE8-004
Trade Name Risperdal Generic Name risperidone
Applicant Name: Johnson & Johnson Pharmaceutical Research & Development
HFD- 120
Approval Date 3/3/02

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_**X**_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-272 Risperdal tablets

NDA # 20-588 Risperdal oral soln

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # RIS-USA-79

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _____RIS-USA-79

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # 31-931 YES /_X_/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Steven D. Hardeman, R.Ph. 3-21-02

Signature of Preparer Date

Title: Senior Regulatory Project Manager

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/s/

Steve Hardeman
3/21/02 11:45:06 AM
Signed for Dr. Katz

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272\S-008
NDA 20-588\S-004

Johnson & Johnson Pharmaceutical Research & Development L.L.C
Attention: Susan J. Merchant
Manager, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Ms. Merchant:

We acknowledge receipt of your April 22, 2002 submission containing final printed labeling in response to our March 3, 2002 letter approving your supplemental new drug applications for Risperdal® (risperidone) Tablets and Oral Solution.

We have reviewed the labeling that you submitted in accordance with our March 3, 2002 letter and we find it acceptable.

However, we note that under CLINICAL TRIALS section, "short-term efficacy" subheading is missing and it needs to be added at the next printing.

If you have any questions, call Ms. Melaine Shin R.Ph., Regulatory Management Officer, at 301-594-5793.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
1/14/03 08:50:41 AM

Division of Neuropharmacological Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: **NDA 20-272/SE8-008**
NDA 20-588/SE8-004

Name of Drug: Risperdal® (risperidone) Tablets and Oral Solution

Applicant: Johnson & Johnson Pharmaceutical Research & Development L.L.C.

Material Reviewed:

- **NDA 20-272/SE8-008 (FA) : April 22, 2002**
- **NDA 20-588/SE8-004 (FA) : April 22, 2002**
- **AP letter based on submitted labeling text: March 3, 2002**

Background and Summary:

NDA 20-272/S-008 and NDA 20-588/S-004 were approved on March 3, 2002 which incorporated the addition of safety and efficacy information in the long-term treatment of schizophrenia. The sponsor submitted the FPL on April 22, 2002.

Review:

1. Under CLINICAL TRIALS section, subsection heading "short-term efficacy" is missing.

2. Under STORAGE AND HANDLING section, the following were added:

   7503220
   US Patent 4,804,663
   February 2002
   ©Janssen 2000

   RISPERDAL® tablets are manufactured by:
   JOLLC, Gurabo, Puerto Rico or
   Janssen-Cilag, SpA, Latina, Italy

   RISPERDAL® oral solution is manufactured by:
   Janssen Pharmaceutica N.V.
   Beerse, Belgium

RISPERDAL® tablets and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

Conclusions:

Upon discussion with the Clinical Team Leader, Dr. Thomas Laughren, I recommend that we issue an Acknowledge & Retain letter and ask the sponsor to provide the corrected version (addition of "short-term efficacy" subheading) of FPL at the next printing.

_____
Melaine Shin, R.Ph.
Regulatory Management Officer

_____
Robbin Nighswander, R.Ph.
Supervisory Regulatory Health Project Manager

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/s/

Melaine Shin
12/19/02 11:26:52 AM
CSO

Robbin Nighswander
1/2/03 10:22:56 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272

Janssen Research Foundation
Attention: EDWARD G. BRANN
1125 TRENTON-HARBOURTON ROAD
P.O.BOX 200
TITUSVILLE, NJ 08560

Dear MR. BRANN:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RISPERDAL (RISPERIDONE) TABLETS.

We have received your submission of May 11, 2000, reporting on your postmarketing study commitment to assess the long-term safety and efficacy of risperidone.

We conclude that study RIS-USA-79, entitled "A Comparison of Risperidone and Haloperidol for Prevention of Relapse in Subjects with Schizophrenia and Schizoaffective Disorders" fulfills the above postmarketing study commitment.

This completes all of your postmarketing study commitments acknowledged in our letter of December 29, 1993.

We encourage you to propose labeling changes based on the results of study RIS-USA-79 in a prior approval NDA supplement.

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

Sincerely,

RUSSELL KATZ, M.D.
DIRECTOR
DIVISON OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS
OFFICE OF DRUG EVALUATION I
CENTER FOR DRUG EVALUATION AND RESEARCH

/s/

Russell Katz
3/28/01 03:25:34 PM