CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-272/S046/S047
20-588/S036/S037
21-444/S020/S021

Trade Name: Risperdal

Generic Name: Risperidone

Sponsor: Johnson & Johnson

Approval Date: August 22, 2007

Indications: Treatment of schizophrenia in adults and adolescents aged 13-17 years. Alone, or in combination with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults, and alone in children and adolescents aged 10-17 years. Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-272/S046/S047
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-046/S-047
NDA 20-588/S-036/S-037
NDA 21-444/S-020/S-021

Johnson & Johnson PR&D
Attention: Heddie Martynowicz, M.S.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-2022

Dear Ms. Martynowicz:

Please refer to your supplemental new drug applications dated and received December 21, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets (NDA 20-272), Risperdal (risperidone) Oral Solution (NDA 20-588), and Risperdal M-Tab (risperidone) Orally Disintegrating Tablets (NDA 21-444).

We acknowledge receipt of your submission dated June 25, 2007.

Your submission of June 25, 2007 constituted a complete response to our June 20, 2007 action letter.

Supplemental new drug applications 20-272/S-046, 20-588/S-036, & 21-444/S-020 provide for the use of oral risperidone HCL for the treatment of schizophrenia in adolescents (ages 13-17), and supplemental new drug applications 20-272/S-047, 20-588/S-037 & 21-444/S-021 provide for the use of oral risperidone HCL for the treatment of bipolar I disorder in children (ages 10-12) and adolescents (ages 13-17).

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

We are waiving the requirements of 21 CFR 201.l57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling. These revisions are terms of the NDA approval. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission

"SPL for approved supplemental NDAs 20-272/S-046/S-047, 20-588/S-036/S-037, and 21-444/S-020/S-021."

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that, with regard to both bipolar disorder and schizophrenia, you have fulfilled the requirements for adolescents aged 13–17. In addition, you have fulfilled the bipolar disorder requirement for children aged 10–13 years. We are waiving the requirement for assessment of safety and effectiveness of the product in pediatric patients below the age of 10 with regard to bipolar disorder. Your current studies have met the terms of the initial Pediatric Written Request.

Promotional Materials

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac

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

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Thomas Laughren
8/22/2007 08:02:23 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-272/S046/S047
20-588/S036/S037
21-444/S020/S021

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-046/S-047
NDA 20-588/S-036/S-037
NDA 21-444/S-020/S-021

Johnson & Johnson PR&D
Attention: Heddie Martynowicz, M.S.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-2022

Dear Ms. Martynowicz:

Please refer to your supplemental new drug applications dated and received December 21, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets (NDA 20-272), Risperdal (risperidone) Oral Solution (NDA 20-588), and Risperdal M-Tab (risperidone) Orally Disintegrating Tablets (NDA 21-444).

We acknowledge receipt of your submissions dated:

December 21, 2006	February 14, 2007	April 4, 2007	April 6, 2007
April 18, 2007	April 19, 2007	May 1, 2007	May 14, 2007

Supplemental new drug applications 20-272/S-046, 20-588/S-036, & 21-444/S-020 provide for the use of oral risperidone HCl for the treatment of schizophrenia in adolescents (ages 13-17) and supplemental new drug applications 20-272/S-047, 20-588/S-037, & 21-444/S-021 provide for the use of oral risperidone HCl for the treatment of bipolar I disorder in children (ages 10-12) and adolescents (ages 13-17).

We have completed our review of these applications, as amended, and they are approvable. Before the applications may be approved, however, you must submit final printed labeling identical in content to the enclosed labeling text.

Labeling

For all the supplements, you must submit draft/final printed labeling revised as indicated in the attached marked-up labeling. The marked-up version is based on your submitted proposed labeling; we have used track changes to indicate our additions and deletions, and have added bracketed comments to explain our actions or requests. You may submit identical consolidated labeling in your Complete Response to all the supplemental applications.

In addition, submit revised content labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

All previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Pediatric Research Equity Act (PREA)
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that, with regard to both bipolar disorder and schizophrenia, you have fulfilled the requirements for adolescents aged 13-17. In addition, you have fulfilled the bipolar disorder requirement for children aged 10-13 years. We are waiving the requirement for assessment of safety and effectiveness of the product in pediatric patients below the age of 10 with regard to bipolar disorder. Your current studies have met the terms of the initial Pediatric Written Request.

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. 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.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with the changes before approval of these supplemental applications.

If you have any questions, call Kimberly Updegraff, M.S., R.Ph., Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

48 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Thomas Laughren
6/20/2007 11:36:29 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RISPERDAL® safely and effectively. See full prescribing information for RISPERDAL®.

RISPERDAL® (risperidone) tablets, RISPERDAL® (risperidone) oral solution, RISPERDAL® M-TAB® (risperidone) orally disintegrating tablets

Initial U.S. Approval: 1993

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® is not approved for use in patients with dementia-related psychosis. (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Schizophrenia/Adolescents (1.1)	06/2007
Indications and Usage, Bipolar Mania/Pediatrics (1.2)	06/2007
Indications and Usage, Autistic Disorder (1.3)	10/2006
Dosage and Administration, Schizophrenia/Adolescents (2.1)	06/2007
Dosage and Administration, Bipolar Mania/Pediatrics (2.2)	06/2007
Dosage and Administration, Autistic Disorder (2.3)	10/2006
Warnings and Precautions, Hyperprolactinemia (5.6)	10/2006

INDICATIONS AND USAGE

RISPERDAL® is an atypical antipsychotic agent indicated for:

- Treatment of schizophrenia in adults and adolescents aged 13-17 years (1.1)
- Alone, or in combination with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults, and alone in children and adolescents aged 10-17 years (1.2)
- Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years (1.3)

DOSAGE AND ADMINISTRATION

	Initial Dose	Titration	Target Dose	Effective Dose Range
Schizophrenia – adults (2.1)	2 mg /day	1-2 mg daily	4-8 mg daily	4-16 mg /day
Schizophrenia – adolescents (2.1)	0.5mg /day	0.5- 1 mg daily	3mg /day	1-6 mg /day
Bipolar mania – adults (2.2)	2-3 mg /day	1mg daily	1-6mg /day	1-6 mg /day
Bipolar mania in children/ adolescents (2.2)	0.5 mg /day	0.5-1mg daily	2.5mg /day	0.5-6 mg /day
Irritability associated with autistic disorder (2.3)	0.25 mg /day (<20 kg) 0.5 mg /day (≥20 kg)	0.25-0.5 mg at ≥ 2 weeks	0.5 mg /day (<20 kg) 1 mg /day (≥20 kg)	0.5-3 mg /day

DOSAGE FORMS AND STRENGTHS

- Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)
- Oral solution: 1 mg/mL (3)
- Orally disintegrating tablets: 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to the product (4)

WARNINGS AND PRECAUTIONS

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL® is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome (5.3)
- Tardive dyskinesia (5.4)
- Hyperglycemia and diabetes mellitus (5.5)
- Hyperprolactinemia (5.6)
- Orthostatic hypotension (5.7)
- Potential for cognitive and motor impairment (5.8)
- Seizures (5.9)
- Dysphagia (5.10)
- Priapism (5.11)
- Disruption of body temperature regulation (5.12)
- Antiemetic Effect (5.13)
- Suicide (5.14)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies (5.15)
- Diseases or conditions that could affect metabolism or hemodynamic responses (5.15)

ADVERSE REACTIONS

The most common adverse reactions in clinical trials (≥10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia. (6)

The most common adverse reactions that were associated with discontinuation from clinical trials were somnolence, nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen, L.P. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Due to CNS effects, use caution when administering with other centrally-acting drugs. Avoid alcohol. (7.1)
- Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced. (7.2)
- Effects of levodopa and dopamine agonists may be antagonized. (7.3)
- Cimetidine and ranitidine increase the bioavailability of risperidone. (7.5)
- Clozapine may decrease clearance of risperidone. (7.6)
- Fluoxetine and paroxetine increase plasma concentrations of risperidone. (7.10)
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. (7.11)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: should not breast feed. (8.3)
- Pediatric Use: safety and effectiveness not established for schizophrenia less than 13 years of age, for bipolar mania less than 10 years of age, and for autistic disorder less than 5 years of age. (8.4)
- Elderly or debilitated; severe renal or hepatic impairment; predisposition to hypotension or for whom hypotension poses a risk: Lower intial dose (0.5 mg twice daily), followed by increases in dose in increments of no more than 0.5 mg twice daily. Increases to dosages above 1.5 mg twice daily should occur at intervals of at least 1 week. (8.5, 2.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis. *[See Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Adults

RISPERDAL® (risperidone) is indicated for the acute and maintenance treatment of schizophrenia *[see Clinical Studies (14.1)]*.

Adolescents

RISPERDAL® is indicated for the treatment of schizophrenia in adolescents aged 13–17 years *[see Clinical Studies (14.1)]*.

1.2 Bipolar Mania

Monotherapy - Adults and Pediatrics

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults and in children and adolescents aged 10-17 years *[see Clinical Studies (14.2)]*.

Combination Therapy – Adults

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder *[see Clinical Studies (14.3)]*.

1.3 Irritability Associated with Autistic Disorder

Pediatrics

RISPERDAL® is indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5–16 years, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

Usual Initial Dose

RISPERDAL® can be administered once or twice daily. Initial dosing is generally 2 mg/day. Dose increases should then occur at intervals not less than 24 hours, in increments of 1-2 mg/day, as tolerated, to a recommended dose of 4-8 mg/day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4-16 mg/day *[see Clinical Studies (14.1)]*. However, doses above 6 mg/day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. In a single study supporting once-daily 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 it is unknown how long a patient with schizophrenia should remain on RISPERDAL®, 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*[see Clinical Studies (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Adolescents

The dosage of RISPERDAL® should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg/day, no additional benefit was seen above 3 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

There are no controlled data to support the longer term use of RISPERDAL® beyond 8 weeks in adolescents with schizophrenia. The physician who elects to use RISPERDAL® for extended periods in adolescents with schizophrenia should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that after 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 treating patients with concomitant 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. The period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

2.2 Bipolar Mania

Usual Dose

Adults

RISPERDAL® should be administered on a once-daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day *[see Clinical Studies (14.2, 14.3)]*. RISPERDAL® doses higher than 6 mg per day were not studied.

Pediatrics

The dosage of RISPERDAL® should be initiated at 0.5mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg/day, no additional benefit was seen above 2.5 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with RISPERDAL®. While it is generally agreed that pharmacological treatment beyond an acute

response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of RISPERDAL® in such longer-term treatment (i.e., beyond 3 weeks). The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.3 Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)

The safety and effectiveness of RISPERDAL® in pediatric patients with autistic disorder less than 5 years of age have not been established.

The dosage of RISPERDAL® should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL® can be administered once daily, or half the total daily dose can be administered twice daily.

Dosing should be initiated at 0.25 mg per day for patients ≤ 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weigh less than 15 kg.

In clinical trials, 90% of patients who showed a response (based on at least 25% improvement on ABC-I, *[see Clinical Studies (14.4)]* received doses of RISPERDAL® between 0.5 mg and 2.5 mg per day. The maximum daily dose of RISPERDAL® in one of the pivotal trials, when the therapeutic effect reached plateau, was 1 mg in patients < 20 kg, 2.5 mg in patients ≥ 20 kg, or 3 mg in patients > 45 kg. No dosing data is available for children who weighed less than 15 kg.

Once sufficient clinical response has been achieved and maintained, consideration should be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Patients experiencing persistent somnolence may benefit from a once-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

2.4 Dosage in Special Populations

The recommended initial dose is 0.5 mg twice daily 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 twice daily. Increases to dosages above 1.5 mg twice daily 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 risperidone, possibly resulting in an enhanced effect *[see Clinical Pharmacology (12.3)]*. 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 Warnings and Precautions (5.2, 5.7, 5.15)]*. If a once-daily dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-daily regimen for 2-3 days at the target dose. Subsequent switches to a once-daily dosing regimen can be done thereafter.

2.5 Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with RISPERDAL® would be expected to cause decreases in the plasma concentrations of the sum of risperidone and 9-hydroxyrisperidone combined, which could lead to decreased efficacy of RISPERDAL® treatment. The dose of RISPERDAL® needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers *[see Drug Interactions (7.7)]*.

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of RISPERDAL® needs to be titrated accordingly when fluoxetine or paroxetine is co-administered *[see Drug Interactions (7.8)]*.

2.6 Administration of RISPERDAL® Oral Solution

RISPERDAL® Oral Solution can be administered directly from the calibrated pipette, or can be mixed with a beverage prior to administration. RISPERDAL® 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.

2.7 Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

3 DOSAGE FORMS AND STRENGTHS

RIPSERDAL® Tablets are available in the following strengths and colors: 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green). All are capsule shaped, and imprinted with "JANSSEN" on one side and either "Ris 0.25", "Ris 0.5", "R1", "R2", "R3", or "R4" on the other side according to their respective strengths.

RISPERDAL® Oral Solution is available in a 1 mg/mL strength.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in the following strengths, colors, and shapes: 0.5 mg (light coral, round), 1 mg (light coral, square), 2 mg (light coral, round), 3 mg (coral, round), and 4 mg (coral, round). All are biconvex and etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

4 CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone. Therefore, RISPERDAL® is contraindicated in patients with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL®(risperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[See also Boxed Warnings and Warnings and Precautions (5.1)]*

5.3 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 creatinine 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 in which 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.

5.4 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® 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 treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, RISPERDAL® elevates prolactin levels and the elevation persists during chronic administration. RISPERDAL® is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

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. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and

pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Non-Clinical Toxicology (13.1)]*. 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.

5.7 Orthostatic Hypotension

RISPERDAL® 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 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment *[see Dosage and Administration (2.1, 2.4)]*. 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.

5.8 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.

5.9 Seizures

During premarketing testing in adult patients with schizophrenia, 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.

5.10 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. *[See also Boxed Warning and Warnings and Precautions (5.1)]*

5.11 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.

5.12 Body Temperature Regulation

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

5.13 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.

5.14 Suicide

The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, 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.

5.15 Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, are reported to have an increased sensitivity to

antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

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.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients *[see Dosage and Administration (2.4)]*.

5.16 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension *[see Warnings and Precautions (5.7)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Dysphagia *[see Warnings and Precautions (5.10)]*

- Priapism *[see Warnings and Precautions (5.11)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.12)]*
- Antiemetic effect *[see Warnings and Precautions (5.13)]*
- Suicide *[see Warnings and Precautions (5.14)]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions (5.15)]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions (5.15)]*

The most common adverse reactions in clinical trials (≥ 10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia.

The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were somnolence, nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia *[see Adverse Reactions (6.5)]*.

The data described in this section are derived from a clinical trial database consisting of 9712 adult and pediatric patients exposed to one or more doses of RISPERDAL® for the treatment of schizophrenia, bipolar mania, autistic disorder, and other psychiatric disorders in pediatrics and elderly patients with dementia. Of these 9712 patients, 2626 were patients who received RISPERDAL® while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with RISPERDAL® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using WHOART terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of RISPERDAL® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for RISPERDAL® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The majority of all adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia

Adult Patients with Schizophrenia

Table 1 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with schizophrenia in three 4- to 8-week, double-blind, placebo-controlled trials.

Table 1. Adverse Reactions in ≥1% of RISPERDAL®-Treated Adult Patients with Schizophrenia in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Event		
	RISPERDAL®		
Body System Adverse Reaction	**2-8 mg per day (N=366)**	**>8-16 mg per day (N=198)**	**Placebo (N=225)**
Body as a whole - general disorders			
Back pain	3	2	<1
Fatigue	3	1	0
Chest pain	3	1	2
Fever	2	1	1
Asthenia	1	1	<1
Syncope	<1	1	<1
Edema	<1	1	0
Cardiovascular disorders, general			
Hypotension postural	2	<1	0
Hypotension	<1	1	0
Central and peripheral nervous system disorders			
Parkinsonism*	12	17	6
Dizziness	10	4	2
Dystonia*	5	5	2
Akathisia*	5	5	2
Dyskinesia	1	1	<1
Gastrointestinal system disorders			
Dyspepsia	10	7	6
Nausea	9	4	4
Constipation	8	9	7
Abdominal pain	4	3	0
Mouth dry	4	<1	<1
Saliva increased	3	1	<1
Diarrhea	2	<1	1

Hearing and vestibular disorders			
Earache	1	1	0
Heart rate and rhythm disorders			
Tachycardia	2	5	0
Arrhythmia	0	1	0
Metabolic and nutritional disorders			
Weight increase	1	<1	0
Creatine phosphokinase increased	<1	2	<1
Musculoskeletal system disorders			
Arthralgia	2	3	<1
Myalgia	1	0	0
Platelet, bleeding and clotting disorders			
Epistaxis	<1	2	0
Psychiatric disorders			
Anxiety	16	12	11
Somnolence	14	5	4
Anorexia	2	0	<1
Red blood cell disorders			
Anemia	<1	1	0
Reproductive disorders, male			
Ejaculation failure	<1	1	0
Respiratory system disorders			
Rhinitis	7	11	6
Coughing	3	3	3
Upper respiratory tract infection	2	3	<1
Dyspnea	2	2	0
Skin and appendages disorders			
Rash	2	4	2
Seborrhea	<1	2	0
Urinary system disorders			
Urinary tract infection	<1	3	0
Vision disorders			
Vision abnormal	3	1	<1

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Schizophrenia

Table 2 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with schizophrenia in a 6-week double-blind, placebo-controlled trial.

Table 2. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients with Schizophrenia in a Double-Blind Trial

	Percentage of Patients Reporting Event		
	RISPERDAL®		
Body System Adverse Reaction	**1-3 mg per day** **(N=55)**	**4-6 mg per day** **(N=51)**	**Placebo** **(N=54)**
Central and peripheral nervous system disorders			
Parkinsonism*	13	16	6
Tremor	11	10	6
Dystonia*	9	18	7
Dizziness	7	14	2
Akathisia*	7	10	6
Gastrointestinal system disorders			
Saliva increased	0	10	2
Psychiatric disorders			
Somnolence	24	12	4
Anxiety	7	6	0

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradykinesia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Mania

Adult Patients with Bipolar Mania

Table 3 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with bipolar mania in four 3-week, double-blind, placebo-controlled monotherapy trials.

Table 3. Adverse Reactions in ≥1% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Monotherapy Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 1-6 mg per day (N=448)	Placebo (N=424)
Body as a whole - general disorders		
Fatigue	2	<1
Fever	1	<1
Asthenia	1	<1
Edema	1	<1
Central and peripheral nervous system disorders		
Parkinsonism*	20	6
Dystonia*	11	3
Akathisia*	9	3
Tremor	6	4
Dizziness	5	5
Gastrointestinal system disorders		
Nausea	5	2
Dyspepsia	4	2
Saliva increased	3	<1
Diarrhea	3	2
Mouth dry	1	1
Heart rate and rhythm disorders		
Tachycardia	1	<1
Liver and biliary system disorders		
SGOT increased	1	<1
Musculoskeletal disorders		
Myalgia	2	2
Psychiatric disorders		
Somnolence	12	4
Anxiety	2	2
Reproductive disorders, female		
Lactation nonpuerperal	1	0
Respiratory disorders		
Rhinitis	2	2
Skin and appendages disorders		
Acne	1	0
Vision disorders		
Vision abnormal	2	<1

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Table 4 lists the adverse reactions reported in 2% or more of RISPERDAL®-treated adult patients with bipolar mania in two 3-week, double-blind, placebo-controlled adjuvant therapy trials.

Table 4. Adverse Reactions in ≥2% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Adjuvant Therapy Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® + Mood Stabilizer (N=127)	Placebo + Mood Stabilizer (n=126)
Body as a whole – general disorders		
Chest pain	2	2
Fatigue	2	2
Central and peripheral nervous system disorders		
Parkinsonism*	9	4
Dizziness	8	2
Dystonia*	6	3
Akathisia*	6	0
Tremor	5	2
Gastrointestinal system disorders		
Nausea	6	5
Diarrhea	6	4
Saliva increased	4	0
Abdominal pain	2	0
Heart rate and rhythm disorders		
Palpitation	2	0
Metabolic and nutritional disorders		
Weight increase	2	2
Psychiatric disorders		
Somnolence	12	5
Anxiety	4	2
Respiratory disorders		
Pharyngitis	5	2
Coughing	3	1
Skin and appendages disorders		
Rash	2	2
Urinary system disorders		
Urinary incontinence	2	1
Urinary tract infection	2	1

* Parkinsonism includes extrapyramidal disorder, hypokinesia and bradykinesia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Bipolar Mania

Table 5 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with bipolar mania in a 3-week double-blind, placebo-controlled trial.

Table 5. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Event		
	RISPERDAL®		
Body System Adverse Reaction	**0.5-2.5 mg per day** **(N=50)**	**3-6 mg per day** **(N=61)**	**Placebo** **(N=58)**
Body as a whole - general disorders			
Fatigue	18	30	3
Central and peripheral nervous system disorders			
Dizziness	16	13	5
Dystonia*	8	13	2
Parkinsonism*	2	7	2
Akathisia*	0	7	2
Gastrointestinal system disorders			
Abdominal pain	18	15	5
Dyspepsia	16	5	3
Nausea	16	13	7
Vomiting	12	10	7
Diarrhea	8	7	2
Heart rate and rhythm disorders			
Tachycardia	0	5	2
Psychiatric disorders			
Somnolence	42	56	19
Appetite increased	4	7	2
Anxiety	0	8	3
Reproductive disorders, female			
Lactation nonpuerperal	2	5	0
Respiratory system disorders			
Rhinitis	14	13	10
Dyspnea	2	5	0
Skin and appendages disorders			
Rash	0	7	2
Urinary system disorders			
Urinary incontinence	0	5	0
Vision disorders			
Vision abnormal	4	7	0

* Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradykinesia. Akathisia includes hyperkinesia and akathisia.

6.3 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Autistic Disorder

Table 6 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients treated for irritability associated with autistic disorder in two 8-week, double-blind, placebo-controlled trials.

Table 6. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients Treated for Irritability Associated with Autistic Disorder in Double-Blind, Placebo-Controlled Trials

Body System Adverse Reaction	Percentage of Patients Reporting Event RISPERDAL® 0.5-4.0 mg per day (N=76)	 Placebo (N=80)
Body as a whole - general disorders		
Fatigue	42	13
Fever	20	19
Central and peripheral nervous system disorders		
Dystonia*	12	6
Tremor	12	1
Dizziness	9	3
Parkinsonism*	8	0
Automatism	7	1
Dyskinesia	7	0
Gastrointestinal system disorders		
Vomiting	25	21
Saliva increased	22	6
Constipation	21	8
Mouth dry	13	6
Nausea	8	8
Heart rate and rhythm disorders		
Tachycardia	7	0
Metabolic and nutritional disorders		
Weight increase	5	0
Psychiatric disorders		
Somnolence	67	23
Appetite increased	49	19
Anxiety	16	15
Anorexia	8	8
Confusion	5	0
Respiratory system disorders		
Rhinitis	36	23
Upper respiratory tract infection	34	15
Coughing	24	18
Skin and appendages disorders		
Rash	11	8
Urinary system disorders		
Urinary incontinence	22	20

* Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia.

6.4 Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL®

The following adverse reactions occurred in < 1% of the adult patients and in < 5% of the pediatric patients treated with RISPERDAL® in the above double-blind, placebo-controlled clinical trial data sets. In addition, the following also includes adverse reactions reported in RISPERDAL®-treated patients who participated in other studies, including double-blind,

active-controlled and open-label studies in schizophrenia and bipolar mania studies in pediatric patients with psychiatric disorders other than schizophrenia, bipolar mania, or austistic disorder, and studies in elderly patients with dementia.

Body as a Whole, General Disorders: edema peripheral, pain, influenza-like symptoms, leg pain, malaise, allergy, crying abnormal, allergic reaction, rigors, allergy aggravated, anaphylactoid reaction, hypothermia

Central Nervous System Disorders: gait abnormal, speech disorder, coma, ataxia, dysphonia, stupor, cramps legs, vertigo, hypoesthesia, tardive dyskinesia, neuroleptic malignant syndrome

Endocrine Disorders: hyperprolactinemia, gynecomastia

Gastrointestinal System Disorders: dysphagia, flatulence

Heart Rate and Rhythm Disorders: AV block, bundle branch block

Liver and Biliary Disorders: SGPT increased, hepatic enzymes increased

Metabolic and Nutritional Disorders: thirst, hyperglycemia, xerophthalmia, generalized edema, diabetes mellitus aggravated, diabetic coma

Musculoskeletal Disorders: muscle weakness, rhabdomyolysis

Platelet, Bleeding, and Clotting Disorders: purpura

Psychiatric Disorders: insomnia, agitation, emotional lability, apathy, nervousness, concentration impaired, impotence, decreased libido

Reproductive Disorders, Female: amenorrhea, menstrual disorder, leukorrhea

Reproductive Disorders, Male: ejaculation disorder, abnormal sexual function, priapism

Resistance Mechanism Disorders: otitis media, viral infection

Respiratory Disorders: respiratory disorder

Skin and Appendages Disorders: skin ulceration, skin discoloration, rash erythematous, skin exfoliation, rash maculopapular, erythema multiforme

Urinary Disorders: micturition frequency

Vascular Disorders: cerebrovascular disorder

Vision Disorders: conjunctivitis

White Cell Disorders: leucopenia, granulocytopenia

6.5 Discontinuations Due to Adverse Reactions

Schizophrenia - Adults

Approximately 7% (39/564) of RISPERDAL®-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more RISPERDAL®-treated patients were:

Table 7. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Schizophrenia Trials

	RISPERDAL®		
Adverse Reaction	**2-8 mg/day (N=366)**	**>8-16 mg/day (N=198)**	**Placebo (N=225)**
Dizziness	1.4%	1.0%	0%
Nausea	1.4%	0%	0%
Agitation	1.1%	1.0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0.5%	0%
Dystonia	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Hypotension postural	0.3%	0.5%	0%
Tachycardia	0.3%	0.5%	0%
Akathisia	0%	1.0%	0%

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Schizophrenia - Pediatrics

Approximately 7% (7/106), of RISPERDAL®-treated patients discontinued treatment due to an adverse event in a double-blind, placebo-controlled trial, compared with 4% (2/54) placebo-treated patients. The adverse reactions associated with discontinuation for at least one RISPERDAL®-treated patient were somnolence (2%), dizziness (2%), anorexia (1%), anxiety (1%), ataxia (1%), hypotension (1%), and palpitation (1%).

Bipolar Mania - Adults

In double-blind, placebo-controlled trials with RISPERDAL® as monotherapy, approximately 6% (25/448) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 5% (19/424) of placebo-treated patients. The adverse reactions associated with discontinuation in RISPERDAL®-treated patients were:

Table 8. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Bipolar Mania Clinical Trials

Adverse Reaction	RISPERDAL® 1-6 mg/day (N=448)	Placebo (N=424)
Parkinsonism	0.4%	0%
Somnolence	0.2%	0%
Dizziness	0.2%	0%
Dystonia	0.2%	0%
SGOT increased	0.2%	0.2%
SGPT increased	0.2%	0.2%

Bipolar Mania - Pediatrics

In a double-blind, placebo-controlled trial 12% (13/111) of RISPERDAL®-treated patients discontinued due to an adverse event, compared with 7% (4/58) of placebo-treated patients. The adverse reactions associated with discontinuation in more than one RISPERDAL®-treated pediatric patient were somnolence (5%), nausea (3%), abdominal pain (2%), and vomiting (2%).

Autistic Disorder - Pediatrics

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n = 156), one RISPERDAL®-treated patient discontinued due to an adverse reaction (Parkinsonism), and one placebo-treated patient discontinued due to an adverse event.

6.6 Dose Dependency of Adverse Reactions in Clinical Trials

Extrapyramidal Symptoms

Data from two fixed-dose trials in adults with schizophrenia provided evidence of dose-relatedness for extrapyramidal symptoms associated with RISPERDAL® treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of RISPERDAL® (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	RISPERDAL® 2 mg	RISPERDAL® 6 mg	RISPERDAL® 10 mg	RISPERDAL® 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	11%	15%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day):

Dose Groups	RISPERDAL® 1 mg	RISPERDAL® 4 mg	RISPERDAL® 8 mg	RISPERDAL® 12 mg	RISPERDAL® 16 mg
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	11%	17%	18%	20%

Other Adverse Reactions

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 reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectile dysfunction, ejaculation disorder, sexual function abnormal, fatigue, and skin discoloration.

6.7 Changes in Body Weight

The proportions of RISPERDAL® and placebo-treated adult patients with schizophrenia 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%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the RISPERDAL® (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

Changes in body weight were also evaluated in pediatric patients *[see Use in Specific Populations (8.4)]*

6.8 Changes in ECG

Between-group comparisons for pooled placebo-controlled trials in adults revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In pooled placebo-controlled acute mania trials in adults, there were small decreases in mean heart rate, similar among all treatment groups.

In the two placebo-controlled trials in children and adolescents with autistic disorder (aged 5 – 16 years) mean changes in heart rate were an increase of 8.4 beats per minute in the

RISPERDAL® groups and 6.5 beats per minute in the placebo group. There were no other notable ECG changes.

In a placebo-controlled acute mania trial in children and adolescents (aged 10 – 17 years), there were no significant changes in ECG parameters, other than the effect of RISPERDAL® to transiently increase pulse rate (< 6 beats per minute). In two controlled schizophrenia trials in adolescents (aged 13 – 17 years), there were no clinically meaningful changes in ECG parameters including corrected QT intervals between treatment groups or within treatment groups over time.

6.9 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RISPERDAL®; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: anaphylactic reaction, angioedema, atrial fibrillation, diabetic ketoacidosis in patients with impaired glucose metabolism, intestinal obstruction, jaundice, mania, QT prolongation, and sleep apnea.

Other adverse events reported since market introduction, which were temporally related to RISPERDAL® but not necessarily causally related, include the following: pancreatitis, pituitary adenoma, pulmonary embolism, precocious puberty, cardiopulmonary arrest, and sudden death.

7 DRUG INTERACTIONS

7.1 Centrally-Acting Drugs and Alcohol

Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally-acting drugs and alcohol.

7.2 Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

7.3 Levodopa and Dopamine Agonists

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

7.4 Amitriptyline

Amitriptyline did not affect the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined.

7.5 Cimetidine and Ranitidine

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and

9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%.

7.6 Clozapine

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

7.7 Lithium

Repeated oral doses of RISPERDAL® (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

7.8 Valproate

Repeated oral doses of RISPERDAL® (4 mg once daily) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of RISPERDAL®.

7.9 Digoxin

RISPERDAL® (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

7.10 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs *[see Clinical Pharmacology (12.3)]*. 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 CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

Fluoxetine and Paroxetine

Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of

RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Erythromycin

There were no significant interactions between RISPERDAL® and erythromycin .

7.11 Carbamazepine and Other Enzyme Inducers

Carbamazepine co-administration decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of RISPERDAL® may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with RISPERDAL® may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of RISPERDAL® treatment.

7.12 Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, RISPERDAL® did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 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 of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 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 of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0),

and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 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. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of RISPERDAL® during the last trimester of pregnancy.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast-feed.

8.4 Pediatric Use

The efficacy and safety of RISPERDAL® in the treatment of schizophrenia were demonstrated in 417 adolescents, aged 13 – 17 years, in two short-term (6 and 8 weeks, respectively) double-blind controlled trials (*see Indications and Usage (1.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]*. Additional safety and efficacy information was also assessed in one long-term (6-month) open-label extension study in 284 of these adolescent patients with schizophrenia.

Safety and effectiveness of RISPERDAL® in children less than 13 years of age with schizophrenia have not been established.

The efficacy and safety of RISPERDAL® in the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in 169 children and adolescent patients, aged 10 – 17 years, were demonstrated in one double-blind, placebo-controlled, 3-week trial (*see Indications and Usage (1.2), Adverse Reactions (6.2), and Clinical Studies (14.2)]*.

Safety and effectiveness of RISPERDAL® in children less than 10 years of age with bipolar disorder have not been established.

The efficacy and safety of RISPERDAL® in the treatment of irritability associated with autistic disorder were established in two 8-week, double-blind, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years *[see Indications and Usage (1.3), Adverse Reactions (6.3) and Clinical Studies (14.4)]*. Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania who were of similar age and weight, and who received similar dosages of RISPERDAL® as patients treated for irritability associated with autistic disorder.

The safety and effectiveness of RISPERDAL® in pediatric patients less than 5 years of age with autistic disorder have not been established.

Tardive Dyskinesia

In clinical trials in 1885 children and adolescents treated with RISPERDAL®, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of RISPERDAL® treatment *[see also Warnings and Precautions (5.4)]*.

Weight Gain

In a long-term, open-label extension study in adolescent patients with schizophrenia, weight increase was reported as a treatment-emergent adverse event in 14% of patients. In 103 adolescent patients with schizophrenia, a mean increase of 9.0 kg was observed after 8 months of RISPERDAL® treatment. The majority of that increase was observed within the first 6 months. The average percentiles at baseline and 8 months, respectively, were 56 and 72 for weight, 55 and 58 for height, and 51 and 71 for body mass index.

In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed, which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index.

In one 3-week, placebo-controlled trial in children and adolescent patients with acute manic or mixed episodes of bipolar I disorder, increases in body weight were higher in the RISPERDAL® groups than the placebo group, but not dose related (1.90 kg in the RISPERDAL® 0.5-2.5 mg

group, 1.44 kg in the RISPERDAL® 3-6 mg group, and 0.65 kg in the placebo group). A similar trend was observed in the mean change from baseline in body mass index.

When treating pediatric patients with RISPERDAL® for any indication, weight gain should be assessed against that expected with normal growth. *[See also Adverse Reactions (6.7)]*

Somnolence

Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. Somnolence was the most commonly observed adverse event in the clinical trial of bipolar disorder in children and adolescents, as well as in the schizophrenia trials in adolescents. As was seen in the autistic disorder trials, these events were most often of early onset and transient in duration. *[See also Adverse Reactions (6.1, 6.2, 6.3)]* Patients experiencing persistent somnolence may benefit from a change in dosing regimen *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

Hyperprolactinemia, Growth, and Sexual Maturation

RISPERDAL® has been shown to elevate prolactin levels in children and adolescents as well as in adults *[see Warnings and Precautions (5.6)]*. In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania, 49% of patients who received RISPERDAL® had elevated prolactin levels compared to 2% of patients who received placebo. Similarly, in placebo-controlled trials in children and adolescents (aged 10 to 17 years) with bipolar disorder, or adolescents (aged 13 to 17 years) with schizophrenia, 82–87% of patients who received RISPERDAL® had elevated levels of prolactin compared to 3-7% of patients on placebo. Increases were dose-dependent and generally greater in females than in males across indications.

In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.

The long-term effects of RISPERDAL® on growth and sexual maturation have not been fully evaluated.

8.5 Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than 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 (12.3) and Dosage and Administration (2.4, 2.5)]*. 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 twice daily followed by careful titration *[see Warnings and Precautions (5.7)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, 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 (2.4)]*.

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus RISPERDAL® when compared to patients treated with RISPERDAL® alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[See Boxed Warning and Warnings and Precautions (5.1)]*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

RISPERDAL® (risperidone) is not a controlled substance.

9.2 Abuse

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of 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).

9.3 Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

Premarketing experience included eight reports of acute RISPERDAL® overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to RISPERDAL® overdose include prolonged QT intervaland convulsions. Torsade de pointes has been reported in association with combined overdose of RISPERDAL® and paroxetine.

10.2 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. Because of the rapid disintegration of RISPERDAL® M-TAB®Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

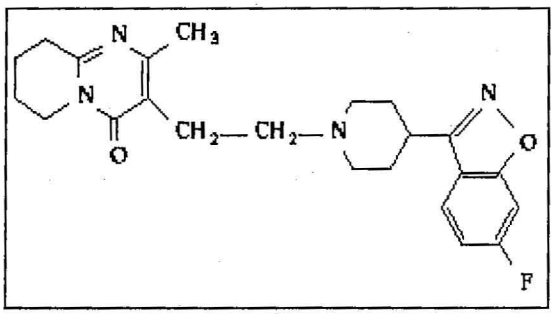
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. 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.

11 DESCRIPTION

RISPERDAL® contains risperidone, a psychotropic agent belonging to the chemical class of 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-4H-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. RISPERDAL® tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). The 0.25 mg, 0.5 mg, 2 mg, 3 mg, and 4 mg tablets 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. RISPERDAL® Oral Solution contains the following inactive ingredients: tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (light coral), 3 mg (coral), and 4 mg (coral) strengths. RISPERDAL®

M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 3 mg and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of RISPERDAL®, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism.

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_1 histaminergic receptors. RISPERDAL® acts as an antagonist at 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.

12.2 Pharmacodynamics

The clinical effect from RISPERDAL® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$ *[see Clinical Pharmacology (12.1)]* may explain some of the other effects of RISPERDAL®.

12.3 Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 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 twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of

9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours 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).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, RISPERDAL® can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/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.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage 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 CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions . First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone *[see Drug Interactions*

(7.12)]. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits 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 RISPERDAL® do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with RISPERDAL® may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone *[see Drug Interactions (7.7)]*. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely *[see Drug Interactions 7.12)]*.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 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. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

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 Dosage and Administration (2.4) and Warnings and Precautions (5.15)]*.

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 Dosage and Administration (2.4)* and *Warnings and Precautions (5.15)]*.

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 (2.4)]*.

Pediatric

The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 mg/kg, 2.5 mg/kg, 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 recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 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/m^2 (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (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	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, 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 5-6 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 Warnings and Precautions (5.6)]*.

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 (MRHD) on a mg/m^2 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 MRHD on a mg/m^2 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.

14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

Short-Term Efficacy

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, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

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 (twice-daily 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 mg/day, 6 mg/day, 10 mg/day, and 16 mg/day, on a twice-daily 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 mg/day, 4 mg/day, 8 mg/day, 12 mg/day, and 16 mg/day, on a twice-daily 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 once-daily 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.

Pediatrics

The efficacy of RISPERDAL® in the treatment of schizophrenia in adolescents aged 13–17 years was demonstrated in two short-term (6 and 8 weeks), double-blind controlled trials. All patients met DSM-IV diagnostic criteria for schizophrenia and were experiencing an acute episode at time of enrollment. In the first trial (study #1), patients were randomized into one of three treatment groups: RISPERDAL® 1-3 mg/day (n = 55, mean modal dose = 2.6 mg), RISPERDAL® 4-6 mg/day (n = 51, mean modal dose = 5.3 mg), or placebo (n = 54). In the second trial (study #2), patients were randomized to either RISPERDAL® 0.15-0.6 mg/day (n = 132, mean modal dose = 0.5 mg) or RISPERDAL® 1.5–6 mg/day (n = 125, mean modal dose = 4 mg). In all cases, study medication was initiated at 0.5 mg/day (with the exception of the 0.15-0.6 mg/day group in study #2, where the initial dose was 0.05 mg/day) and titrated to the target dosage range by approximately Day 7. Subsequently, dosage was increased to the maximum tolerated dose within the target dose range by Day 14. The primary efficacy variable in all studies was the mean change from baseline in total PANSS score.

Results of the studies demonstrated efficacy of RISPERDAL® in all dose groups from 1-6 mg/day compared to placebo, as measured by significant reduction of total PANSS score. The efficacy on the primary parameter in the 1-3 mg/day group was comparable to the 4-6 mg/day group in study #1, and similar to the efficacy demonstrated in the 1.5–6 mg/day group in study #2. In study #2, the efficacy in the 1.5-6 mg/day group was statistically significantly greater than that in the 0.15-0.6 mg/day group. Doses higher than 3 mg/day did not reveal any trend towards greater efficacy.

14.2 Bipolar Mania - Monotherapy

Adults

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in two short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The

primary outcome in these trials was change from baseline in the YMRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

Pediatrics

The efficacy of RISPERDAL® in the treatment of mania in children or adolescents with Bipolar I disorder was demonstrated in a 3-week, randomized, double-blind, placebo controlled, multicenter trial including patients ranging in ages from 10 to 17 years who were experiencing a manic or mixed episode of bipolar I disorder. Patients were randomized into one of three treatment groups: RISPERDAL® 0.5-2.5 mg/day (n = 50, mean modal dose = 1.9 mg), RISPERDAL® 3-6 mg/day (n = 61, mean modal dose = 4.7 mg), or placebo (n = 58). In all cases, study medication was initiated at 0.5 mg/day and titrated to the target dosage range by Day 7, with further increases in dosage to the maximum tolerated dose within the targeted dose range by Day 10. The primary rating instrument used for assessing efficacy in this study was the mean change from baseline in the total YMRS score.

Results of this study demonstrated efficacy of RISPERDAL® in both dose groups compared with placebo, as measured by significant reduction of total YMRS score. The efficacy on the primary parameter in the 3-6 mg/day dose group was comparable to the 0.5-2.5 mg/day dose group. Doses higher than 2.5 mg/day did not reveal any trend towards greater efficacy.

14.3 Bipolar Mania – Combination Therapy

The efficacy of RISPERDAL® with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in adult patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at

2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of YMRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

14.4 Irritability Associated with Autistic Disorder

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of these subjects were under 12 years of age and most weighed over 20 kg (16-104.3 kg).

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

The results of these trials are as follows:

(1) In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=101), aged 5 to 16 years, received twice daily doses of placebo or RISPERDAL® 0.5-3.5 mg/day on a weight-adjusted basis. RISPERDAL®, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day), significantly improved scores on the ABC-I subscale and on the CGI-C scale compared with placebo.

(2) In the other 8-week, placebo-controlled trial in children with autistic disorder (n=55), aged 5 to 12 years, RISPERDAL® 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day), significantly improved scores on the ABC-I subscale compared with placebo.

Long-Term Efficacy

Following completion of the first 8-week double-blind study, 63 patients entered an open-label study extension where they were treated with RISPERDAL® for 4 or 6 months (depending on whether they received RISPERDAL® or placebo in the double-blind study). During this open-label treatment period, patients were maintained on a mean modal dose of RISPERDAL® of 1.8-2.1 mg/day (equivalent to 0.05 - 0.07 mg/kg/day).

Patients who maintained their positive response to RISPERDAL® (response was defined as ≥ 25% improvement on the ABC-I subscale and a CGI-C rating of 'much improved' or 'very much improved') during the 4-6 month open-label treatment phase for about 140 days, on average, were randomized to receive RISPERDAL® or placebo during an 8-week, double-blind withdrawal study (n=39 of the 63 patients). A pre-planned interim analysis of data from patients who completed the withdrawal study (n=32), undertaken by an independent Data Safety Monitoring Board, demonstrated a significantly lower relapse rate in the RISPERDAL® group compared with the placebo group. Based on the interim analysis results, the study was terminated due to demonstration of a statistically significant effect on relapse prevention. Relapse was defined as ≥ 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline of the randomized withdrawal phase).

16 HOW SUPPLIED/STORAGE AND HANDLING

RISPERDAL® (risperidone) Tablets

RISPERDAL® (risperidone) Tablets are imprinted "JANSSEN" on one side and either "Ris 0.25", "Ris 0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

0.25 mg dark yellow, capsule-shaped tablets: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose blister packs of 100 NDC 50458-301-01.

0.5 mg red-brown, capsule-shaped tablets: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose blister packs of 100 NDC 50458-302-01.

1 mg white, capsule-shaped tablets: bottles of 60 NDC 50458-300-06, hospital unit dose blister packs of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange, capsule-shaped tablets: bottles of 60 NDC 50458-320-06, hospital unit dose blister packs of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow, capsule-shaped tablets: bottles of 60 NDC 50458-330-06, hospital unit dose blister packs of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green, capsule-shaped tablets: bottles of 60 NDC 50458-350-06, hospital unit dose blister packs of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) Oral Solution

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.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of 4 (2 X 2) tablets. Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-395-28, long-term care blister packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-315-28, long-term care blister packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Protect from light and moisture.

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

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

17.1 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration *[see Warnings and Precautions (5.7)]*.

17.2 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 *[see Warnings and Precautions (5.8)]*.

17.3 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

17.4 Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL® *[see Use in Specific Populations (8.2)]*.

17.5 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 *[see Drug Interactions (7)]*.

17.6 Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL® *[see Drug Interactions (7.1)]*.

17.7 Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL®

M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Revised DRAFT 06/2007

RISPERDAL® Tablets are manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico
RISPERDAL® Oral Solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium
RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico

RISPERDAL® Tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and Oral Solution are distributed by:
Janssen, L.P.
Titusville, NJ 08560

TER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

MEDICAL REVIEW(S)

MEMORANDUM

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

DATE: 17 August 2007

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 20-272 SE5 046/047, NDA 20-588 SE5 036/037, NDA 21-444 SE5 020/021

SUBJECT: Recommendation of Approval Action for risperidone (Risperdal®) for the Treatment of Schizophrenia and Bipolar I Disorder in Pediatric Patients (response to PWR)

1 BACKGROUND AND REGULATORY HISTORY

Risperidone is a second-generation (atypical) antipsychotic approved for the acute and maintenance treatment of schizophrenia in adults, the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, and for the irritability associated with autistic disorder in children and adolescents. In this application, Johnson and Johnson Pharmaceutical Research and Development has responded to a DPP-issued Pediatric Written Request (PWR) with studies of risperidone for the short-term treatment of schizophrenia and the acute manic and mixed episodes of bipolar I disorder in the pediatric population.

The PWR for studying both indications (schizophrenia in adolescents and bipolar I disorder in children and adolescents) was issued on November 25, 2002. The main requirements were to conduct a pediatric PK study, efficacy studies in pediatric schizophrenia and bipolar I disorder, and a long-term pediatric safety study. The PWR required that a sufficient number of pediatric patients be included in the trial to allow for the statistical power required to discern a difference between drug and placebo groups in both disorders, and that at least 6 months of safety data be collected from the long-term safety study. The age groups for study were defined as adolescents (13-17 years old) for schizophrenia, and children and adolescents (10-17 years old) for bipolar I disorder.

The Division met with the sponsor in May and August 2003 to clarify the requirements of the PWR. These discussions centered on study design and proposed dose ranges to be explored. On September 19, 2006, the Division held a Type B Meeting with the sponsor to discuss plans for supplemental new drug applications for pediatric schizophrenia and bipolar I disorder as outlined in the PWR.

The Agency Pediatric Exclusivity Board met on 28 February 2007, determined that the sponsor had met the requirements of the PWR, and granted exclusivity.

On 20 June 2007 the Division issued an Approvable Letter for these supplements. The single issue that prevented an approval action was agreement on labeling, which was presented in PLR format

for the first time for these products. We provided the sponsor with a marked up version of labeling as part of the Approvable Letter, and they responded by incorporating our changes and so we have now agreed on labeling and these supplements can be approved.

This NDA has been reviewed by June Cai, M.D., Medical Officer, DPP, John Lawrence, Ph.D., Office of Biostatistics, Andre Jackson, Ph.D., Office of Clinical Pharmacology, Barry Rosloff, Ph.D., Pharmacology/Toxicology, and N. Chidambaram, Ph.D., Chemistry.

2 PHASE 4 COMMITMENTS

No Phase 4 requirements have been identified.

3 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that risperidone is effective and reasonably safe in the treatment of pediatric schizophrenia and bipolar I disorder, and we should proceed with an APPROVAL action. Annotated Draft Labeling incorporating the changes made by the Division and accepted by the sponsor should be attached to the Action Letter.

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

/s/

Mitchell Mathis
8/20/2007 08:21:10 AM
MEDICAL OFFICER
Approval Rec

APPEARS THIS WAY ON ORIGINAL

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

DATE: June 20, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable actions for Risperdal Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia

TO: File NDAs 20-272/S-046 & 047, NDAs 20-588/S-036 & 037, and NDAs 21-444/S-020 & 021
[Note: This overview should be filed with the 12-21-06 original submission of these supplements.]

1.0 BACKGROUND

Risperdal (risperidone) is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including a maintenance claim for schizophrenia, and for irritability associated with autism. We issued a written request (WR) for both schizophrenia and mania, and these supplements are a response to that WR. The 12-21-06 response includes the results from acute studies in mania (RIS-BIM-301) and schizophrenia (RIS-SCH-302 and RIS-USA-231), longer-term safety data from open-label study RIS-USA-234, and also pediatric PK data from study RIS-USA-160.

2.0 CHEMISTRY

The only CMC issues requiring review were the labeling and environmental assessment. The minor labeling issues have been addressed, and the sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

The juvenile rat study done in support of the autism application was considered nonoptimal due to inadequate dosing. Thus, the sponsor is performing a second juvenile rat study and a juvenile

dog study, and these ongoing studies, along with the previous rat study, are considered sufficient to support these supplements.

4.0 BIOPHARMACEUTICS

OCP has considered the pk data derived from this program sufficient to support these supplements, including the proposed labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on 3 short-term, multicenter, double-blind, parallel group, randomized, efficacy and safety studies in pediatric patients. One of these studies was in patients with acute mania in bipolar I disorder (RIS-BIM-301) and the other 2 were in schizophrenia (RIS-SCH-302 and RIS-USA-231).

5.1.1 Study RIS-BIM-301 (Acute Mania in Bipolar I Disorder)

This was a 3-week study in bipolar I disorder pediatric patients (ages 10-17) with acute manic or mixed episodes. It was conducted at 21 US sites. N=161 patients (in the ITT group) were randomized 1:1:1 to 3 treatment groups: risperidone 0.5-2.5 mg/day; risperidone 3-6 mg/day; placebo. Roughly 50-60% of patients completed the study (50% and 61% of risperidone patients and 58% of placebo patients). The primary endpoint was change from baseline to endpoint on the YMRS total score, and the primary analysis was ANCOVA (LOCF). A step-down sequential testing strategy was used to control for multiple comparisons. Both dose groups were superior to placebo ($p<0.001$ for both, with essentially no numerical superiority for one dose over the other). No endpoints were designated as key secondary endpoints and no multiple comparison procedure was planned for secondary endpoints. Therefore, I will not comment further on secondary endpoints. Drs. Cai, Lawrence, and Mathis all considered this a positive study, and I agree.

5.1.2 Study RIS-SCH-302 (Acute Schizophrenia)

This was a 6-week placebo-controlled study in adolescent patients (ages 13-17) with schizophrenia. It was conducted at 23 sites in 4 countries. N=160 patients (in the ITT dataset) were randomized 1:1:1 to 3 treatment groups: risperidone 1-3 mg/day; risperidone 4-6 mg/day; placebo. Roughly ¾ of patients completed the study (82% and 86% of risperidone patients and 67% of placebo patients). The primary endpoint was change from baseline to endpoint on the PANSS total score, and the primary analysis was ANCOVA (LOCF). A step-down sequential testing strategy was used to control for multiple comparisons. Both dose groups were superior to placebo ($p<0.001$ for both, with essentially no numerical superiority for one dose over the other).

No endpoints were designated as key secondary endpoints and no multiple comparison procedure was planned for secondary endpoints. Therefore, I will not comment further on secondary endpoints. Drs. Cai, Lawrence, and Mathis all considered this a positive study, and I agree.

5.1.3 Study RIS-USA-231 (Acute Schizophrenia)

This was an 8-week placebo-controlled study in adolescent patients (ages 13-17) with schizophrenia. It was conducted at 41 sites in 8 countries. N=257 patients (in the modified ITT dataset) were randomized 1:1 to 2 treatment groups: low dose risperidone (0.15-0.6 mg/day for subjects weighing ≥ 50 kg or 0.003-0.12 mg/kg/day for subjects weighing < 50 kg); high dose risperidone (1.5-6 mg/day for subjects weighing ≥ 50 kg or 0.003-0.12 mg/kg/day for subjects weighing < 50 kg). Roughly 2/3 of patients completed the study. The primary endpoint was change from baseline to endpoint on the PANSS total score, and the primary analysis was ANCOVA (LOCF). The high dose group was superior to the low dose group ($p<0.001$). No endpoints were designated as key secondary endpoints and no multiple comparison procedure was planned for secondary endpoints. Therefore, I will not comment further on secondary endpoints. Drs. Cai, Lawrence, and Mathis all considered this a positive study, and I agree.

5.1.4 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for all 3 studies. As noted, there was no indication of greater efficacy for the higher doses compared to the lower doses for studies 301 and 302. Based on these findings, Dr. Cai has recommended limiting the dose to 2.5 mg/day for mania and 3 mg for schizophrenia. Dr. Mathis disagrees with such a restrictive approach, and I agree. These findings, of course, must be noted in labeling, however, I agree with Dr. Mathis that clinicians can use their judgment in deciding how to dose individual patients. Subgroup analyses based on gender and race for each study suggested that the positive results were seen in all subgroups.

5.2 Safety Data

Safety data for these supplements were derived from the 3 short-term trials noted above (302 and 231 for schizophrenia and 301 for bipolar), plus from an open-label study (RIS-USA-234). There were no deaths among the risperidone-exposed patients. There were several serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for risperidone in adults, i.e., EPS, hypotension and tachycardia, increased appetite and weight gain, somnolence, sedation, fatigue, dizziness, dry mouth, and increased prolactin. I agree with Drs. Mathis and Cai that these adverse events can be adequately addressed in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided an extensive literature review and this did not reveal any important new safety information regarding the pediatric population.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, risperidone is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in pediatric patients.

8.0 DSI INSPECTIONS

Inspections were conducted at 3 sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

9.1 Labeling

We have included a modified version of labeling with the approvable letter.

9.2 Foreign Labeling

Risperidone is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in pediatric patients.

9.3 Approvable Letter

The approvable letter includes our proposed labeling.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that J&J has submitted sufficient data to support the conclusion that risperidone is effective and acceptably safe in the treatment of pediatric patients with schizophrenia and acute mania/mixed episodes in bipolar disorder. However, before we can take an approval action, we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

APPEARS THIS WAY ON ORIGINAL

cc:
Orig NDAs 20-272/S-046 & 047, NDAs 20-588/S-036 & 037, and NDAs 21-444/S-020 & 021
HFD-130/TLaughren/MMathis/NKhin/JCai/KUpdegraff

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/s/

Thomas Laughren
6/20/2007 08:02:29 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: 18 June 2007

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 20-272 SE5 046/047, NDA 20-588 SE5 036/037, NDA 21-444 SE5 020/021

SUBJECT: Recommendation of Approvable Action for risperidone (Risperdal®) for the Treatment of Schizophrenia and Bipolar I Disorder in Pediatric Patients (response to PWR)

1 BACKGROUND AND REGULATORY HISTORY

Risperidone is a second-generation (atypical) antipsychotic approved for the acute and maintenance treatment of schizophrenia in adults, the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, and for the irritability associated with autistic disorder in children and adolescents. In this application, Johnson and Johnson Pharmaceutical Research and Development has responded to a DPP-issued Pediatric Written Request (PWR) with studies of risperidone for the short-term treatment of schizophrenia and the acute manic and mixed episodes of bipolar I disorder in the pediatric population.

The PWR for studying both indications (schizophrenia in adolescents and bipolar I disorder in children and adolescents) was issued on November 25, 2002. The main requirements were to conduct a pediatric PK study, efficacy studies in pediatric schizophrenia and bipolar I disorder, and a long-term pediatric safety study. The PWR required that a sufficient number of pediatric patients be included in the trial to allow for the statistical power required to discern a difference between drug and placebo groups in both disorders, and that at least 6 months of safety data be collected from the long-term safety study. The age groups for study were defined as adolescents (13-17 years old) for schizophrenia, and children and adolescents (10-17 years old) for bipolar I disorder.

The Division met with the sponsor in May and August 2003 to clarify the requirements of the PWR. These discussions centered on study design and proposed dose ranges to be explored. On September 19, 2006, the Division held a Type B Meeting with the sponsor to discuss plans for supplemental new drug applications for pediatric schizophrenia and bipolar I disorder as outlined in the PWR.

The Agency Pediatric Exclusivity Board met on 28 February 2007, determined that the sponsor had met the requirements of the PWR, and granted exclusivity.

This NDA has been reviewed by June Cai, M.D., Medical Officer, DPP, John Lawrence, Ph.D., Office of Biostatistics, Andre Jackson, Ph.D., Office of Clinical Pharmacology, Barry Rosloff, Ph.D., Pharmacology/Toxicology, and N. Chidambaram, Ph.D., Chemistry.

2 CHEMISTRY

The chemists recommend an APPROVAL action pending the sponsor accepting minor editorial changes to labeling.

3 PHARMACOLOGY/TOXICOLOGY

Dr. Rosloff has noted that the sponsor is currently performing juvenile rat and dog studies as part of a Phase 4 commitment to the irritability associated with autistic disorder clam. These same studies will be used to support the current applications.

4 CLINICAL PHARMACOLOGY

The Clinical Pharmacologists have recommended an APPROVABLE action for these applications. They have concluded that weight normalized mean exposures based upon trough levels prior to next dose in children, adolescents, and adults are comparable and that dose adjustments based on body weight are not warranted for risperidone in children and adolescents. They agree with the sponsor's recommended pediatric target dose of 3 mg/day for schizophrenia and 2.5 mg/day for bipolar I disorder. They have reviewed and are in agreement with the clinical pharmacology sections of the sponsor's proposed labeling.

5 CLINICAL DATA

5.1 Overview of Studies

The response to the Agency-issued PWR consists of two studies in schizophrenia and one in bipolar I disorder. Studies RIS-SCH302 and RIS-USA-231 evaluated the safety and efficacy of risperidone in adolescents with schizophrenia. RIS-BIM-301 evaluated the safety and efficacy of risperidone in children and adolescents with bipolar I disorder.

5.2 Efficacy Findings

Schizophrenia

RIS-SCH-302 was a randomized, double-blind, placebo-controlled, multi-center study conducted at 23 sites in 4 countries. It included 3 treatment groups: placebo, risperidone 1-3 mg/day, and risperidone 4-6 mg/day. After a screening/washout phase, pediatric patients with schizophrenia were entered into a six week double-blind treatment phase. Risperidone was titrated within the assigned dose range to the maximum tolerated dose by Day 14.

The primary efficacy measure was change from baseline in the Positive and Negative Symptom Scale for Schizophrenia (PANSS) at 6 weeks. Last observations were carried forward to week 6. The results are shown in the table below.

Study RIS-USA-302: PANSS Total Score Changes Baseline to Day 43 End Point Efficacy Analysis Set

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Baseline			
N	54	54	50
Mean (SD)	93.2 (10.27)	95.4 (11.01)	93.0 (11.87)
Median (Range)	94.0 (62;120)	96.0 (67;120)	90.0 (71;117)
Day 43 End Point			
N	54	54	50
Mean (SD)	84.4 (16.59)	74.1 (17.79)	71.8 (18.35)
Median (Range)	86.0 (42;126)	74.5 (34;124)	71.0 (34;117)
Change from Baseline			
N	54	54	50
Mean (SD)	-8.9 (16.11)	-21.3 (19.61)	-21.2 (18.29)
Median (Range)	-7.0 (-53;21)	-19.0 (-69;38)	-20.0 (-60;22)
P-value(minus PLACEBO)[a,b]		<0.001	<0.001
Diff. of LS Means (SE)		-12.0 (3.02)	-12.8 (3.07)
95% CI		(-17.95;-5.99)	(-18.83;-6.71)

Source: Dr. Lawrence's Review

Team Leader Comment: Both dose ranges of risperidone demonstrated statistically significant and clinically important decreases in the mean PANSS scores at endpoint (primary measure of efficacy) compared to placebo.

RIS-USA-231 was a randomized, double-blind, low-dose-controlled, multi-center study conducted at 41 sites in 8 countries. It included 2 treatment groups—high dose and low dose as shown in the sponsor's table below.

	Risperidone low-dose group		Risperidone high-dose group	
	<50 kg (mg/kg/day)	≥50 kg (mg/day)	<50 kg (mg/kg/day)	≥50 kg (mg/day)
Pre-Amendment 3[a]	0.003 to 0.008	0.15 to 0.4	0.03 to 0.08	1.5 to 4
Post-Amendment 3[b]	0.007 to 0.012	0.35 to 0.6	0.07 to 0.12	3.5 to 6

[a] The maximum dose was 4 mL/day (0.4 mg/day [low-dose group] or 4 mg/day [high-dose group]), irrespective of body weight.

[b] The maximum dose was 6 mL/day (0.6 mg/day [low-dose group] or 6 mg/day [high-dose group]), irrespective of body weight.

After a screening/washout phase, pediatric patients with schizophrenia were entered into an eight week double-blind treatment phase. Risperidone was titrated to the assigned target dose by Day 12.

The primary efficacy measure was change from baseline in the Positive and Negative Symptom Scale for Schizophrenia (PANSS) at 8 weeks. Last observations were carried forward to week 8. The results are shown in the table below.

Study RIS-USA-231: PANSS Total Score Change from Baseline To Day 56—Efficacy Analysis Set

	RIS LOW DOSE	RIS HIGH DOSE
Baseline		
N	131	124
Mean (SD)	93.3 (14.14)	96.4 (15.39)
Median (Range)	94.0 (61;119)	97.0 (63;126)
Day 56 End Point		
N	131	124
Mean (SD)	80.8 (24.33)	72.8 (22.52)
Median (Range)	80.0 (33;132)	71.0 (32;146)
Change from Baseline		
N	131	124
Mean (SD)	-12.5 (20.32)	-23.6 (22.83)
Median (Range)	-11.0 (-68;29)	-23.0 (-94;51)
P-value (minus RIS LOW DOSE)*		<0.001
Diff. of LS Means (SE)		-10.3 (2.65)
95% CI		(-15.53;-5.09)

Source: Study Report, p 103 and FDA analysis.

Team Leader Comment: The high dose risperidone group demonstrated a statistically significant and clinically important decrease in the mean PANSS scores at endpoint (primary measure of efficacy) compared to low dose risperidone.

Bipolar I Disorder

RIS-BIM-301 evaluated the safety and efficacy of 2 dose ranges of risperidone monotherapy compared to placebo in pediatric patients with a diagnosis of bipolar I disorder. The dose ranges were 0.5-2.5 mg/day and 3-6 mg/day. This study was a randomized, double-blind, placebo-controlled, multi-center study of patients with bipolar I disorder between 10 and 17 years of age who were experiencing a manic or mixed mood episode at enrollment. After a screening/washout phase, patients were entered into a three week double-blind treatment phase. Risperidone was titrated to a target dose range by Day 7 and to maximum tolerated dose within the range by Day 10.

The primary efficacy measure was change from baseline in the Young Mania Rating Scale (YMRS) at 3 weeks. Last observations were carried forward to week 3. The results are shown in the table below.

Study RIS-BIM-301: YMRS Change from Baseline to Day 21

	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Baseline			
N	57	49	60
Mean (SD)	31.0 (7.46)	31.1 (5.97)	30.5 (5.92)
Median (Range)	31.0 (19;45)	31.0 (16;44)	31.0 (20;44)
Day 21 endpoint			
N	57	49	60
Mean (SD)	21.9 (9.51)	12.6 (7.22)	13.9 (9.70)
Median (Range)	22.0 (3;44)	12.0 (0;30)	11.5 (0;40)
Change from Baseline			
N	57	49	60
Mean (SD)	-9.1 (10.95)	-18.5 (9.70)	-16.5 (10.29)
Median (Range)	-8.0 (-36;22)	-17.0 (-39;-3)	-18.0 (-35;6)
P-value(minus PLACEBO)(a,b)		<0.001	<0.001
Diff. of LS Means (SE)		-9.2 (1.76)	-8.0 (1.70)
95% CI		(-12.69;-5.74)	(-11.33;-4.62)

Source: Study Report, p 120 and FDA analysis.

Team Leader Comment: Both dose ranges demonstrate efficacy, i.e., statistically significant and clinically meaningful lower mean YMRS scores compared to placebo at 21 days.

5.3 Efficacy Conclusions

It is clear from the data presented above that risperidone is effective in treating pediatric schizophrenia and bipolar I disorder. Dr. Cai has noted in her reviews that doses above 3 mg/day for schizophrenia and 2.5 mg/day for bipolar I disorder do not show additional benefit and are associated with greater side effects (see safety review below) in the populations studied. She has therefore recommended that pediatric doses be limited in labeling to 3 mg/day for schizophrenia and 2.5 mg/day for bipolar I disorder. While I believe we should certainly label the drug with the information learned from the clinical trials, and even identify target doses of 3 mg/day for pediatric schizophrenia and 2.5 mg/day for pediatric bipolar I disorder, I think it would be too restrictive to the prescriber to limit the dose to a maximum when we know that doses up to 6 mg/day were also shown to be efficacious in the same studies that demonstrated efficacy for the lower dose ranges.

In addition, as pointed out above in the description of the controlled studies in pediatric schizophrenia and bipolar I disorder, the dose was titrated to the maximum tolerated dose within the assigned dose group, which put most patients at the higher end of their assigned dose range for the fixed dose phase of the study. In fact, the median modal dose during the fixed-dose phase (Days 15-42) of RIS-SCH-302 was 3 mg/day in the 1-3 mg/day dose group and 6 mg/day in the 4-6 mg/day dose group. Likewise, the median modal dose during the fixed dose phase (Days 11-21) of RIS-BIM-301 was 2.5 mg in the 0.5-2.5 mg/day dose group and 5 mg/day in the 3-6 mg/day dose group. Therefore, the median modal doses in both trials were at or near the top of their respective dose ranges, and the efficacy results (and adverse events) noted from the trials come from the higher doses in both groups for both study populations. As a result, we don't know the exact range of effectiveness with certainty, but we do know that doses up to 6 mg/day are effective for

schizophrenia in adolescent patients, and for mania/mixed mood episodes of bipolar I disorder in children and adolescents. I would not, therefore, restrict labeling to the lower dose range, but would recommend that we define 6 mg/day as the upper boundary for the effective dose range for both disorders in pediatric patients.

6.0 Safety Data

Treatment of pediatric patients with risperidone has been reasonably safe and well tolerated. The safety profile for use in pediatric patients appears similar to that in adults.

6.1 Studies Used to Assess Safety

Schizophrenia

The safety evaluation for schizophrenia is based upon three studies conducted in adolescents with schizophrenia. Two of these studies were the same trials used to demonstrate efficacy. One was placebo-controlled (RIS-SCH-302[6 weeks]), one low-dose controlled (RIS-USA-231 [8 weeks]), and one was open-label (RIS-USA-234 [6 months]).

Bipolar I Disorder

The safety evaluation for bipolar I disorder is based on three studies of adolescents and children. One of these studies was placebo-controlled (the same trial used to demonstrate efficacy) and conducted in pediatric patients with bipolar I disorder (RIS-BIM-301[3 weeks]), one was the same long-term open-label study in adolescents with schizophrenia (RIS-USA-234 [6 months]) mentioned above, and one was a pharmacokinetic study in which subjects (5-17 years old) took risperidone at a daily dose of 0.01-0.08 mg/kg/day with a maximum daily dose of 4 mg.

6.2 Deaths

There were no deaths in any of the controlled trials.

6.3 Adverse Events Leading to Dropout

Schizophrenia

The events leading to discontinuation of the study medication in the two controlled trials of pediatric patients with schizophrenia are similar to those seen in adults and are summarized in the tables below.

RIS-SCH-302: Treatment-emergent Adverse Events Resulting in Discontinuation

AE System Organ Class Adverse Event Preferred Term	Placebo (N=54) n (%)	RIS 1-3 mg (N=55) n (%)	RIS 4-6 mg (N=51) n (%)	ALL RIS (N=106) n (%)
Total no. subjects with perm stop med	2 (4)	3 (5)	4 (8)	7 (7)
Psychiatric disorders	2 (4)	2 (4)	4 (8)	6 (6)
Somnolence	0	0	2 (4)	2 (2)
Anorexia	0	0	1 (2)	1 (1)
Anxiety	0	0	1 (2)	1 (1)
Psychosis	2 (4)	2 (4)	1 (2)	3 (3)
Centr & periph nervous system disorders	0	1 (2)	2 (4)	3 (3)
Ataxia	0	0	1 (2)	1 (1)
Dizziness	0	1 (2)	1 (2)	2 (2)
Cardiovascular disorders, general	0	0	1 (2)	1 (1)
Hypotension	0	0	1 (2)	1 (1)
Heart rate and rhythm disorders	0	0	1 (2)	1 (1)
Palpitation	0	0	1 (2)	1 (1)
Body as a whole - general disorders	1 (2)	0	0	0
Fever	1 (2)	0	0	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Source: Dr. Cai's review

RIS-SCH-231: Treatment-emergent Adverse Events Resulting in Discontinuation

AE System Organ Class Adverse Event Preferred Term	RIS 0.15-0.6 mg (N=132) n (%)	RIS 1.5-6 mg (N=125) n (%)
Total no. subjects with perm stop med	6 (4.5)	5 (4.0)
Psychiatric disorders	4 (3.0)	3 (2.4)
Psychosis	3 (2.3)	2 (1.6)
Agitation	1 (0.8)	1 (0.8)
Insomnia	0	1 (0.8)
Suicide attempt[a]	1 (0.8)	0
Cardiovascular disorders, general	1 (0.8)	1 (0.8)
ECG abnormal	0	1 (0.8)
Hypertension	1 (0.8)	0
Centr & periph nervous system disorders	1 (0.8)	1 (0.8)
EEG abnormal	0	1 (0.8)
Oedema cerebral	1 (0.8)	0
Respiratory system disorders	0	1 (0.8)
Upper resp tract infection	0	1 (0.8)
Heart rate and rhythm disorders	1 (0.8)	0
Tachycardia	1 (0.8)	0
Liver and biliary system disorders	1 (0.8)	0
SGOT increased	1 (0.8)	0
SGPT increased	1 (0.8)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. [a] Verbatim term: suicidal ideation.
EEG= electroencephalogram.
Source: Dr. Cai's review.

Bipolar I Disorder

There were no adverse events leading to discontinuation in Study RIS-USA-160.

Adverse events leading to discontinuation of risperidone in the single controlled trial of bipolar I disorder in children and adolescents are listed in the table below.

RIS-BIM-301: Treatment-emergent Adverse Events Resulting in Discontinuation

Study Phase: Treatment

AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with perm stop med	4 (7)	3 (6)	10 (16)	13 (12)
Psychiatric disorders	3 (5)	1 (2)	7 (11)	8 (7)
Somnolence	0	1 (2)	4 (7)	5 (5)
Psychosis manic-depressive	3 (5)	0	3 (5)	3 (3)
Aggressive reaction	0	0	1 (2)	1 (1)
Nervousness	0	0	1 (2)	1 (1)
Suicide attempt	2 (3)	0	1 (2)	1 (1)
Centr & periph nervous system disorders	0	1 (2)	3 (5)	4 (4)
Bradykinesia	0	0	1 (2)	1 (1)
Hyperkinesia	0	0	1 (2)	1 (1)
Hypertonia	0	0	1 (2)	1 (1)
Speech disorder	0	0	1 (2)	1 (1)
Vertigo	0	1 (2)	0	1 (1)
Gastro-intestinal system disorders	0	2 (4)	3 (5)	5 (5)
Abdominal pain	0	1 (2)	1 (2)	2 (2)
Nausea	0	2 (4)	1 (2)	3 (3)
Saliva increased	0	0	1 (2)	1 (1)
Vomiting	0	1 (2)	1 (2)	2 (2)
Body as a whole - general disorders	1 (2)	0	1 (2)	1 (1)
Allergic reaction	0	0	1 (2)	1 (1)
Syncope	1 (2)	0	0	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AE = adverse event; med = medication; N = total sample size; n = number with adverse event; no. = number; perm = permanent; RIS = risperidone
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Source: Dr. Cai's review.

From the table above it is notable that 12% (13/111) of pediatric patients treated with risperidone discontinued treatment due to an adverse event compared to 7% (4/58) of patients taking placebo. Adverse events leading to discontinuation in more than one patient include somnolence, nausea, abdominal pain, and vomiting.

Team Leader Comment: Overall, events leading to dropout from the pediatric trials are similar to those seen in the adult trials of risperidone.

6.4 Serious Adverse Events (SAEs)

RIS-SCH-302

Two SAEs were reported for patients taking drug in this study, one in each of the risperidone treatment groups and both while each patient was taking 1 mg/day. Both events were related to

psychosis requiring hospitalization and treatment with other antipsychotics, and neither is considered related to study drug.

RIS-USA-231

Nine SAEs were reported as psychosis, one occurred in a patient who also had cerebral edema in the low-dose risperidone group. It is unclear if this SAE was related to risperidone.

US-BIM-301

The following table of SAEs includes events occurring during the treatment phase and for 30 days after the last dose of risperidone.

RIS-BIM-301: ITT Analysis Set, SAEs Occurring During Treatment or Within 30 Days of Last Medication Dose

AE System Organ Class Adverse Event Preferred Term	Placebo (N=58) n (%)	Risperidone 0.5–2.5 mg (N=50) n (%)	Risperidone 3–6 mg (N=61) n (%)	All Risperidone (N=111) n (%)
Total no. subjects with serious AEs	3 (5)	3 (6)	5 (8)	8 (7)
Psychiatric disorders	3 (5)	2 (4)	4 (7)	6 (5)
Psychosis manic-depressive	2 (3)	1 (2)	4 (7)	5 (5)
Suicide attempt	1 (2)	2 (4)	2 (3)	4 (4)
Manic reaction	1 (2)	0	0	0
Body as a whole - general disorders	0	0	1 (2)	1 (1)
Allergic reaction	0	0	1 (2)	1 (1)
Respiratory system disorders	0	1 (2)	0	1 (1)
Asthma	0	1 (2)	0	1 (1)
Bronchospasm	0	1 (2)	0	1 (1)

Team Leader Comment: Although the numbers are small, the majority of SAEs in Study 301 are psychiatric, and many of those (e.g. psychosis, manic-depressive) are related to bipolar I disorder. Dr. Cai has reviewed the cases of "suicide attempt" listed above, as well as the sponsor's subsequent analysis of the data related to this category. The sponsor's analysis includes all incidences of suicide attempts, suicidal ideation, self injurious behaviors, falls, injuries, and aggressive reaction. Dr. Cai points out, and I agree, that self-injurious behavior with no intent to produce harm is common in the pediatric population, and that indeed the only genuine suicide attempt in Study 301 occurred in a patient taking placebo. I also agree with Dr. Cai that due to the small number of subjects in the study, no meaningful conclusions can be drawn about drug effect on suicidal ideation (see Dr. Cai's review for a more detailed analysis).

RIS-USA-234

This six month, open-label safety study did not reveal any unexpected serious adverse events in the pediatric population.

6.5 Common and Drug-Related Adverse Events

Schizophrenia

The table below represents common and therefore likely drug-related adverse events that occurred in at least 5% in any treatment group with rates at least twice that of placebo from Study RIS-SCH-302.

Common Adverse Events in Study RIS-SCH-302

Subject N / Adverse Events (%)	Placebo	RIS 1-3 mg	RIS 4-6 mg	All RIS
	54	55	51	106
Extrapyramidal disorder	2 (4)	5 (9)	8 (16)	13 (12)
Dizziness	1 (2)	4 (7)	7 (14)	11 (10)
Hypertonia	4 (7)	3 (5)	7 (14)	10 (9)
Somnolence	2 (4)	13 (24)	6 (12)	19 (18)
Agitation	4 (7)	8 (15)	4 (8)	12 (11)
Anxiety	0	4 (7)	3 (6)	7 (7)
Saliva Increased	1 (2)	0	5 (10)	5 (5)

Source: Dr. Cai's review

Team Leader Comment: From the table above it is clear that the higher-dose risperidone group experienced more extrapyramidal symptoms, hypertonia, and dizziness. It is also clear that the lower dose group had more anxiety and agitation, which may represent partially-treated symptoms of schizophrenia. Somnolence was more common in the lower dose group.

Bipolar I Disorder

The table below represents common and therefore potentially drug-related adverse events that occurred in at least 5% in any treatment group with rates at least twice that of placebo (bold type).

Common Adverse Events in Study RIS-BIM-301

AE System Organ Class	**PLACEBO (N=58)**	**RIS 0.5-2.5 mg (N=50)**	**RIS 3-6 mg (N=61)**
Adverse Event Preferred Term	n (%)	n (%)	n (%)
Total no. subjects with AEs	44 (76)	45 (90)	58 (95)
Psychiatric disorders	20 (34)	24 (48)	**45 (74)**
Somnolence	11 (19)	**21 (42)**	**34 (56)**
Anxiety	2 (3)	0	**5 (8)**
Appetite increased	1 (2)	**2 (4)**	**4 (7)**
Suicide attempt	2 (3)	1 (2)	**4 (7)**
Centr & periph nervous system disorders	22 (38)	27 (54)	34 (56)
Dizziness	3 (5)	**8 (16)**	**8 (13)**
Hypertonia	1 (2)	**2 (4)**	**5 (8)**
Hyperkinesia	1 (2)	0	**4 (7)**
Extrapyramidal disorder	1 (2)	1 (2)	**3 (5)**
Dystonia	0	**3 (6)**	**2 (3)**
Gastro-intestinal system disorders	14 (24)	**25 (50)**	26 (43)
Abdominal pain	3 (5)	**9 (18)**	**9 (15)**
Nausea	4 (7)	**8 (16)**	8 (13)

Diarrhea	1 (2)	**4 (8)**	**4 (7)**
Dyspepsia	2 (3)	**8 (16)**	3 (5)
Body as a whole - general disorders	13 (22)	18 (36)	23 (38)
Fatigue	2 (3)	**9 (18)**	**18 (30)**
Injury	2 (3)	**3 (6)**	1 (2)
Respiratory system disorders	12 (21)	12 (24)	17 (28)
Dyspnea	0	**1 (2)**	**3 (5)**
Pharyngitis	3 (5)	**5 (10)**	2 (3)
Sinusitis	2 (3)	**3 (6)**	1 (2)
Skin and appendages disorders	3 (5)	**5 (10)**	**7 (11)**
Rash	1 (2)	0	**4 (7)**
Heart rate and rhythm disorders	1 (2)	0	**6 (10)**
Tachycardia	1 (2)	0	**3 (5)**
Reproductive disorders, female	4 (7)	1 (2)	**4 (7)**
Lactation nonpuerperal	0	1 (2)	**3 (5)**
Urinary system disorders	0	0	**4 (7)**
Urinary incontinence	0	0	**3 (5)**
Vision disorders	2 (3)	**3 (6)**	**4 (7)**
Vision abnormal	0	**2 (4)**	**4 (7)**

Source: Dr. Cai's review.

Extrapyramidal AEs

Dr. Cai has pointed out in her review that AEs which likely represent treatment-emergent extrapyramidal symptoms include the categories listed above as hypertonia, hyperkinesia, extrapyramidal disorder, and dystonia. She combined these categories and calculated the combined incidence rates for extrapyramidal disorder as 23% (14/61) for the risperidone 3-6 mg/day group, 12% (6/50) in the risperidone 0.5-2.5 mg/day group, and 5.1% (3/58) for the placebo group.

Team Leader Comment: I agree that we should include all extrapyramidal symptoms in one category. As with adults, the higher dose group has a predictably higher incidence of treatment-emergent extrapyramidal symptoms. There were no reports of tardive dyskinesia in the pediatric study populations.

Somnolence

Somnolence is a very commonly observed treatment-emergent adverse event with risperidone in controlled studies for both pediatric schizophrenia and bipolar I disorder.

Team Leader Comment: Somnolence is a known adverse event seen with use of risperidone and it will be included in Warnings and Precautions section of labeling.

Suicide-Related AEs

There were 7 reports of adverse events coded to "suicide attempt" during the treatment phase of Study RIS-BIM-301, but not all of these were also coded as serious adverse events. The suicide attempts considered serious by the sponsor include 1 in the placebo group and 2 in the risperidone 3-6 mg/day group. All of these events coded as serious in the risperdidone group were suicidal ideation. Three subjects in the risperidone groups had events coded at least 4 days after the last dose of risperidone and so these events were not considered treatment-emergent. The sponsor conducted a blinded (done by an external consultant) review of all potentially suicide-related

adverse events (including all potentially self-injurious behaviors) and concluded that there was no clinically meaningful imbalance between placebo and risperidone treatment groups.

Dr. Cai reviewed the potentially suicide-related cases and confirmed that all 4 cases of treatment-emergent adverse events coded to suicide attempt in the risperdone 3-6 mg/day group were actually suicidal ideation and not suicide attempts. She concluded that significant differences could not be discerned between placebo and risperidone treatment groups.

Team Leader Comment: I agree with Dr. Cai that no meaningful conclusions about potentially suicide-related AEs can be drawn from study RIS-BIM-301.

6.6 Vital Sign Changes

RIS-SCH-302

The only clinically relevant mean vital sign change was an increase in standing pulse rate of +5.75 bpm and supine pulse rate of +4.39 bpm on Day 15 in the risperidone 1-3 mg/day dose group.

RIS-BIM-301

There were no clinically relevant changes in mean vital signs parameters (including supine and standing pulse rate, systolic blood pressure, and diastolic blood pressure). There was an increase in the number of subjects with clinically important changes in standing pulse rate (increase greater than 15 bpm or increase to above 120 bpm from a normal pre-treatment pulse rate) during risperidone therapy (risperidone 0.5-2.5 mg group, 2 [4%] subjects; risperidone 3-6 mg group, 8 [14%] subjects); 1 subject (2%) in the placebo group had a change of clinical importance in standing pulse rate. No subject in the study met the criteria for orthostatic hypotension.

Team Leader Comment: Decreased blood pressure, orthostatic hypotension, and tachycardia are known adverse events associated with the use of risperidone and are prominently labeled.

6.7 Changes in Body Weight and Height

Schizophrenia Trials

A clinically significant increase (>7%) in body weight was observed for 15% and 16% of subjects receiving risperidone 1-3 mg/day or 4-6 mg/day, respectively, in RIS-SCH-302 (compared with 2% of placebo subjects). This same increase of >7% in body weight was seen in 39% of subjects receiving risperidone 1.5-6 mg/day in RIS-USA-231 (compared with 16% in subjects receiving low-dose risperidone 0.15-0.6 mg/day). None of the adverse events of weight increase were considered serious or led to discontinuation of study drug.

In the long-term open-label study (RIS-USA-234), mean (SD) body weight and BMI increased by 4.21 kg (5.33 kg) and 1.25 kg/m2 (1.83 kg/m2), respectively, from baseline to the Month 6 endpoint. Height showed a small increase over the treatment period with the mean (SD) change from baseline of 0.96 cm (1.55) at the Month 6 end point and 1.10 cm (1.87) at the overall end point.

Bipolar I Disorder Trial

In the risperidone groups, mean increases in body weight were higher than placebo but were not dose related (risperidone 0.5–2.5 mg group, 1.90 kg [SD, 1.68]; risperidone 3-6 mg group, 1.44 kg [SD, 2.41]). A similar trend was observed in the mean change from baseline in BMI.

Team Leader Comment: Increase in body weight is a known and labeled adverse event associated with the use of risperidone.

6.8 Laboratory Findings

Prolactin

Risperidone is known to increase mean prolactin levels and an increase in mean prolactin levels from baseline to end point was observed in the pediatric studies. The increases in mean prolactin appeared to be dose-dependent and the clinical relevance of such increases is unknown.

RIS-SCH-302

In study RIS-SCH-302 the mean increase in prolactin was 25.65 ng/mL (SD, 34.29) in the 1-3 mg dose group and 40.63 ng/mL (SD, 45.61) in the 4-6 mg dose group. The increase in prolactin was most pronounced over the first 4 weeks of treatment and the mean increases were greater in female patients. No potentially prolactin-related adverse events were observed.

RIS-BIM-301

One female subject in the placebo group, 2 subjects (1 female, 1 male) in the risperidone 0.5-2.5 mg group, and 3 subjects (all female) in the risperidone 3–6 mg group experienced prolactin-related adverse events. The main prolactin-related adverse event was lactation nonpuerperal, which was experienced by 4 subjects in the risperidone groups but no subjects in the placebo group. See the table below for more information.

Incidence of Treatment-Emergent Prolactin-Related Adverse Events (RIS-BIM-301; Intent-to-Treat Analysis Set)

AE System Organ Class Adverse Event Preferred Term	Placebo (N=58) n (%)	Risperidone 0.5–2.5 mg (N=50) n (%)	Risperidone 3–6 mg (N=61) n (%)	All Risperidone (N=111) n (%)
Total no. subjects with prolactin-related AEs	1 (2)	2 (4)	3 (5)	5 (5)
Reproductive disorders, female	1 (2)	1 (2)	3 (5)	4 (4)
Lactation nonpuerperal	0	1 (2)	3 (5)	4 (4)
Breast enlargement	1 (2)	0	0	0
Breast pain female	1 (2)	0	0	0
Reproductive disorders, male	0	1 (2)	0	1 (1)
Ejaculation disorder	0	1 (2)	0	1 (1)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events

Team Leader Comment: Risperidone is known to increase serum prolactin, the clinical significance of which is unknown. This information is included in current labeling. Updated labeling (PLR format) will retain this information in the Warnings and Precautions section.

Glucose

RIS-SCH-302

There was a small mean increase in fasting glucose levels from baseline to endpoint in the higher dose group of this study. The magnitude of the change in serum glucose was small; there were a few subjects in each study with post-baseline values above the potentially clinically important upper

limit of 6.4 mmol/L, but no glucose-related adverse events, including new onset diabetes, were reported.

RIS-BIM-301
There were no glucose-related adverse events from this short trial.

Team Leader Comment: The potential for hyperglycemia with risperidone use is included in current labeling and will remain in the Warnings and Precautions section.

6.9 Long-term Open-label Studies

Common adverse events occurring at a greater frequency in the in the long-term study RIS-USA-234 (median treatment duration of 6 months) compared with the 2 short-term studies RIS-USA-231 and RIS-SCH-302 include weight gain and psychosis, but no new adverse events emerged with long-term treatment.

The overall incidence of serious adverse events with risperidone treatment in the long-term study (RIS-USA-234) was higher (15%) than in the 2 short-term studies (RIS-USA-231 and RIS-SCH-302 (2-3.5%)).

6.10 Postmarketing Experience

The sponsor reports 27 million patient-years of cumulative exposure to oral risperidone. The worldwide exposure in pediatric patients (ages 5-17 years) was estimated at 1,117,689 patient-years as of August 31, 2006.

There have been fewer serious adverse events involving pediatric patients in postmarketing reports than in all other age groups. There has been no newly identified pattern of adverse drug reactions specific for the pediatric population on the basis of cumulative review other than weight gain.

6.11 Literature Review

The sponsor has conducted a comprehensive literature search (current as of August, 31, 2006) and summarized the results of articles containing original clinical data on the use of risperidone in children and adolescents as part of this submission. These articles included 17 double-blind, placebo-controlled studies and 6 reference drug-controlled studies in children and adolescents, as well as 75 open-label studies and 30 chart reviews. In total there were data on more than 5,400 pediatric subjects and safety results from 206 articles. Risperidone doses administered ranged from 0.25mg–12 mg/day or 0.01-0.06 mg/kg/day, and the duration of treatment was up to 7 years.

In general, the adverse events reported in the published articles were consistent with the established adverse event profile of risperidone. The most frequently reported adverse events were: weight gain (75 articles), sedation (47 articles), and EPS (32 articles).

Discontinuation of treatment with risperidone was discussed in 67 articles. The most commonly reported reasons to discontinue treatment were: weight gain (18 articles), EPS (11 articles), hyperprolactinemia (8 articles), and sedation (7 articles).

Six nonfatal overdoses were reported, and no deaths were reported in children or adolescents. Serious adverse events were reported for 19 subjects: neuroleptic malignant syndrome (9), tardive dyskinesia (4), pancreatitis (2), acute dystonia (1), probable viral encephalitis (1), worsening mitochondrial disorder (1), and increased carbamazepine level (1).

6.12 Conclusion Regarding Safety

Short-term treatment of pediatric patients with risperidone appears to have been reasonably safe and there were no unexpected adverse events.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS

Three clinical investigator sites were inspected by DSI and it was determined that the data generated to support RIS-BIM-301 and RIS-SCH-302 were acceptable.

9.0 LABELING AND ACTION LETTER

9.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed labeling is presented in the new PLR format and will require some modification as described throughout this review. We will need to re-order the Warnings/Precautions section and include all relevant potential adverse events prominently.

9.2 DMETS

Risperdal™ is an approved trade name.

10.0 PHASE 4 COMMITMENTS

No Phase 4 requirements have been identified.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that risperidone is effective and reasonably safe in the treatment of pediatric schizophrenia and bipolar I disorder, and we should proceed with an APPROVABLE action pending negotiation of labeling. Annotated Draft Labeling as revised by the Division should be attached to the Action Letter.

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/s/

Mitchell Mathis
6/18/2007 04:05:12 PM
MEDICAL OFFICER