CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

Trade Name: Risperdal

Generic Name: Risperidone

Sponsor: Johnson & Johnson

Approval Date: October 6, 2006

Indications: in treatment of the irritability associated with autistic disorder

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APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036, S-041
NDA 20-588/S-024, S-028, S-029
NDA 21-444/S-008, S-015

Johnson & Johnson Pharmaceutical Research & Development LLC
Attention: Harindra R. Abeysinghe, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road, PO Box 200
Titusville, NJ 08560-0200

Dear Dr. Abeysinghe:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) Tablets, Oral Solution, and M-TAB.

We acknowledge receipt of your submissions dated August 10, 2006, September 13, 2006, September 22, 2006, and September 28, 2006, and your secure e-mail transmissions dated September 21, 2006, September 26, 2006, September 29, 2006, October 2, 2006, and October 3, 2006. Your submissions of August 10, 2006 were considered complete, class 2 responses to our July 14, 2006 action letter.

Reference is also made to the following supplemental new drug applications [Changes Being Effected - Labeling]:

NDA	Supplement	Submission Date
20-272	S-041	Submitted February 23, 2005
20-588	S-028 S-029	Submitted February 23, 2005 Submitted February 23, 2005
21-444	S-015	Submitted February 23, 2005

Supplemental new drug applications NDA 20-272/S-036, NDA 20-588/S-024, and NDA 21-444/S-008 provide for the use of Risperdal® in treatment of the irritability associated with autistic disorder.

Supplemental new drug applications NDA 20-272/S-041, NDA 20-588/S-027 and S-028, and NDA 21-444/S-015 provide for revised labeling to strengthen the PRECAUTIONS (Use in Patients with Concomitant Illnesses) section of labeling with new information regarding patients with Dementia with Lewy bodies (DLB) or Parkinson's Disease (PD).

We have completed our review of these applications, as amended. We are superseding all of the above referenced labeling supplements by incorporation into efficacy supplements 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008, respectively. These three efficacy supplements, including final agreed-upon language regarding patients with Dementia with Lewy Bodies (DLB) or Parkinson's Disease

(PD), are approved, effective on the date of this letter, for use as recommended in the attached agreed-upon labeling text [package insert].

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling. These revisions are terms of the supplemental NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved Supplemental NDAs 20-272/S-036, 20-588/S-024, and 21-444/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

Pediatric Rule: Partial Waiver
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. Because your studies have been conducted in children aged 5 to 16 years, we are partially waiving the pediatric study requirements for this application, for children aged 0-2 years [the condition is difficult to diagnose and treat in this age group], 2-4 years, and 17-18 years [efficacy in these age groups can be extrapolated from efficacy demonstrated in the 5-16 year old study population].

Postmarketing Studies: Phase 4 Commitments
We remind you of the following postmarketing commitments [Phase 4 Commitments], agreed upon in your secure electronic communication of September 29, 2006. These commitments are listed below:

Nonclinical Pharmacology and Toxicology: Two Phase 4 Commitments [Juvenile Animal Toxicology Studies: Rat and Dog]
1. Rat Study. You have agreed to perform an additional juvenile rat toxicity study at the requested higher dose of [redacted] This study will include measurement of levels of Insulin-like Growth Factor (IGF-1).

Protocol Submission:	On or before 30 June 2007.
Final Report Submission:	On or before 31 March 2009.

2. Dog Study. You have agreed to perform a juvenile dog toxicity study to evaluate the effects of risperidone on the development of the organs of reproduction; this study will include a recovery period. This study will also include measurement of levels of Insulin-like Growth Factor (IGF-1) and assessment of long bone growth.

Protocol Submission	On or before 30 June 2007.
Final Report Submission	On or before 31 March 2009.

Combined Clinical / Clinical Safety / Clinical Pharmacology Study: Phase 4 Commitment
3. You have agreed to perform a study in autistic children and adolescents to determine the lowest effective dose of risperidone in this indication, and to evaluate the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. This study will be a 6-week, fixed-dose, parallel-group, placebo-controlled design, to be completed three years after approval of the proposed protocol. The hormone assessment section of this study will also incorporate measurement of growth hormone (GH) and Insulin-like Growth Factor (IGF-1).

Protocol Submission	On or before 30 December 2007.
Final Report Submission	On or before 31 March 2010.

For the above Phase 4 Commitments, submit clinical protocols to your IND(s) for this indication. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. (You may cross-reference to avoid duplicate submissions.)

All submissions, including supplemental New Drug Applications, relating to these Phase 4 Commitments must be prominently labeled **"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence".**

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81 (b)(2)(viii), you should include a status summary of each commitment in your annual reports to these NDAs. The status summary should include expected protocol submission, study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, the number of patients entered into each study.

Advice and Recommendations Regarding Studies to Meet Phase 4 Commitments
We have reviewed the outlines you have provided for the studies you propose to conduct to meet the Phase 4 Commitments listed above. While a full review will be performed when the full protocols are submitted, we have the following advice and recommendations at this point:

1. Juvenile rat toxicity study: we recommend that you increase the number of animals to 15/sex/group for each subset in this study, and that you measure motor activity using the Figure 8 Activity Maze during the treatment phase of the study as well as during the recovery period. The proposed design is otherwise generally acceptable.
2. Juvenile dog toxicity study: we have not considered the proposed doses in the dog study in our evaluation of the proposed protocol design. However, the proposed design is otherwise generally acceptable.
3. Clinical / Clinical Safety / Clinical Pharmacology Study: With respect to the third Phase 4 commitment listed above, we recommend that the initial treatment design include three arms [placebo, 0.125 mg risperidone, 1 mg risperidone] with a six week duration of treatment. Study RIS-CAN-25 included 25 patients per group; for this Phase 4 commitment study, 25 patients per treatment arm would be considered adequate. We also note that although the (b)(4) dose could be administered using the commercially available 1 mg/mL solution, accurate measurement of this dose (b)(4) will be challenging for parents and practitioners; you are

therefore advised to [redacted] support dosing at this level.

With regard to the hormone assessment section of this study, we consider that a 6-week study duration may not be sufficient time to allow for capture of significant data on hormone levels and the effects of any changes in these levels. We therefore recommend that you add a three to six month open-label treatment phase to this study, during which additional data on glucose, fasting insulin, IGF-1, and GH levels, as well as insulin resistance, would be collected.

Advice and Recommendations Regarding Other Suggested Studies

The currently available data do not allow adequate assessment of the effect of risperidone on growth hormone levels, or growth itself, in children and adolescents. Further study of this issue would be valuable, particularly in view of the children and adolescents in clinical trials who had elevated growth hormone levels, and the cases of delayed and precocious puberty reported in the post-marketing setting.

Although not necessary in order to meet your Phase 4 Commitments, we recommend that you conduct a study to assess the effect of long-term risperidone treatment on the growth, development, and sexual maturation of children and adolescents. If conducted, we would recommend rigorous and consistent measurement of IGF-1 and growth hormone levels, and a minimum duration of six months (if height velocity is used as an endpoint for the assessment of growth effects); a longer duration would be preferable. Assessment of other metabolic parameters and adverse events in a long-term study in this population could also be useful.

We would be willing to review and provide comments on a study protocol.

Introductory Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. 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(s) 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

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, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301).796.2260, or contact her via secure electronic mail at doris.bates@fda.hhs.gov.

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

Attachment: Final Agreed-Upon Labeling [Package Insert]

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

10/6/2006 01:29:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036, (b) (4) S-043, S-044
NDA 20-588/S-024, (b) (4) S-032, S-034
NDA 21-444/S-008, (b) (4) , S-017, S-018

Harindra R. Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development LLC
1125 Trenton-Harbourton Road, PO Box 200
Titusville, NJ 08560-0200

Dear Dr. Abeysinghe:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) Tablets, Oral Solution, and M-TAB.

We acknowledge receipt of your submissions dated January 16, 2006; February 10, 2006; April 28, 2006; May 4, 2006, June 30, 2006, and July 12, 2006. Your submissions of January 16, 2006 were considered complete, class 2 responses to our May 19, 2005 action letter.

We also acknowledge receipt of your submissions dated June 30, 2006. These submissions were not reviewed for this action. You may incorporate them by specific reference as part of your Complete Response to the deficiencies cited in this letter.

Reference is also made to the following supplemental new drug applications [Changes Being Effected - Labeling]:

NDA 20-272	NDA 20-588	NDA 21-444	Correspondence Dates
(b) (4)			
S-043	S-032	S-017	Submitted October 25, 2005; Amended February 2, 2006
S-044	S-034	S-018	Submitted May 18, 2006

Supplemental new drug applications NDA 20-272/S-036, NDA 20-588/S-024, and NDA 21-444/S-008 provide for the use of Risperdal® in treatment of the irritability associated with autistic disorder.

(b) (4)

(b) (4)

(b) (4)

The above referenced supplements submitted on October 25, 2005 and subsequently amended [S-043, S-032, S-017] provide for changes to the Adverse Reactions and Precautions sections of labeling to add information related to (b) (4) pituitary adenomas and reversible extrapyramidal symptoms in the neonate, respectively.

(b) (4)

We have completed our review of (b) (4) fficacy supplements 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008, respectively.

Before these applications may be approved, however, you must address the following deficiencies:

Nonclinical Pharmacology and Toxicology: Two Phase 4 Commitments Requested [Juvenile Animal Toxicology Studies: Rat and Dog]

1. We have completed our review of your juvenile animal toxicology study [rat]. We consider this study to be less than optimal based on the following information:

> A dose higher than the HD of 0.63 mg/kg could have and should have been used. In a range finding study, a dose of 2.5 mg/kg produced similar toxicity to the next lowest dose of 0.63 mg/kg, the only clear difference being cold body surface and cold/dark extremities transiently (during the first few days of dosing only) at the 2.5 mg/kg dose. Bodyweight gains were decreased at both doses, with the effects at 2.5 mg/kg equal to or slightly *less* than those at 0.63 mg/kg. Plasma AUC values (for parent drug + 9-OH risperidone) at the 0.63 mg/kg dose are estimated to be roughly similar to those in humans receiving the currently proposed maximum dose; based on data from the range finding study achievable levels at 2.5 mg/kg are about 3X greater than those at 0.63 mg/kg.

We are therefore requesting that you perform an additional juvenile rat study, at a higher dose, as a Phase 4 Commitment. This study should be performed using doses greater than 0.63 mg/kg; based on range finding data, it appears that a dose of 2.5 mg/kg would be tolerated. We note that you have been requested to conduct a juvenile rat study for the active metabolite of risperidone, 9-hydroxy-risperidone, under IND (b) (4) we would consider it acceptable for you to add a risperidone arm to this study.

2. In addition, we have evaluated the need for a juvenile dog toxicology study, and have determined that this study also should be conducted as a Phase 4 Commitment. Effects on reproductive organs were seen in both the juvenile rat study submitted here, and in previous adult dog toxicity studies. A

juvenile dog study should therefore be performed to evaluate the effects of risperidone on the development of the organs of reproduction; such a study should include a recovery period.

Please provide an outline of your proposed study designs, and proposed submission dates for the full study reports, as part of your Complete Response to this letter.

Clinical Pharmacology and Biopharmaceutics: Phase 4 Commitment Requested [Fixed Dose Placebo Parallel Controlled Trial for Dose-Response]

We have completed our review of the requested *post hoc* Sheiner analysis [Sheiner et. al., "Study Designs for Dose-Ranging." *Clin. Pharmacol. Ther.* 1989; 46:63-77] as discussed at our December 7, 2005 meeting. We note and have reviewed your use of both Model I and Model II to analyze the data from RIS-CAN-23 and RIS-USA-150. We have the following comments based on our review:

1.These studies, as designed, have subjects experiencing an increase in dose but then later (i.e., for the same subject) experiencing a decrease in dose. This raises questions related to possible carryover to the next lower dose in terms of PD response and questions as to why the dose was decreased. There is no obvious reason to decrease the dose if it is effective; it should be increased only if ineffective. Therefore it is difficult to understand the rationale for decreasing and increasing doses, and this variability renders the Sheiner analysis of the resulting data problematic.

2.The results from your submitted analysis using model II are problematic for two reasons. First, a negative ED50 is not interpretable; the ED50 value for study RIS-CAN-23 is so small, and with such a large standard error, that the 90% CI contains zero - which is an uninterpretable result. The meaning of this result is that in the dose region of 0.25 mg/day, the dose response is flat (i.e., no dose response). This makes it difficult to define the lowest effective dose. Your conclusion " any risperidone dose is more effective than placebo" does not answer the question of what is the lowest effective dose. Therefore, your current explanation for the lowest effective dose is not supported by analysis using the Sheiner method.

3. Based on our review of your submission, the starting dose (or lowest effective dose) and need for titration are not justified for this indication. Our prior concerns still hold. To the extent that the *post* hoc Sheiner analysis can be interpreted, it corroborates this fact. That is, the responses observed across the dose range from lowest to highest doses are not different.

4. Based on the foregoing comments, we are requesting a Phase 4 Commitment in the form of a fixed dose placebo parallel controlled trial to determine the lowest effective dose of risperidone in this indication. For instance, such a trial might consist of three arms (i.e., placebo, 0.125 mg and 1 mg) studied for 6 weeks. RIS-CAN-23 included 25 patients per group; this number per arm would be considered adequate. We also note that although the 0.125 mg dose could be administered using the 1 mg/ml solution, accurate measurement of this dose [1/8 mL] will be challenging for parents and practitioners; you are therefore advised to consider whether a less concentrated solution should be developed to support this dose level.

The Agency is willing to discuss the details of this design further with you. Please include a proposed date for submission of study protocol and final study report in your Complete Response to this letter.

(b) (4)

6. Additional revisions to the proposed labeling are embedded in the attachment [FDA Draft Labeling] and should be addressed in your Complete Response.

Clinical / Clinical Safety: Phase 4 Commitment Requested [Effect Of Risperidone Treatment On Fasting Glucose, Fasting Insulin, And Insulin Resistance in Autistic Children / Adolescents]

(b) (4)

2. We note that your SAE analysis for reported events of akathisia did not include Study US-150, a pivotal autism study, because ESRS was not applied in this trial. An analysis across all studies including this one, combining all terms possibly related to akathisia, should be performed and (b) (4) submitted as part of your Complete Response. With respect to tardive dyskinesia, this term should be searched in long term trials as opposed to short term trials, since in short term trials no event can meet the criteria for this diagnosis.

3. With respect to the question of insulin resistance and diabetes mellitus, we note that the Complete Response does not include new data or a new analysis of data regarding glucose levels or related adverse events. In your prior submission [November 2004], you submitted the result of fasting and nonfasting glucose metabolism from study RIS-INT-79, a then completed study in a Disruptive Behavioral Disorders (DBD) pediatric population. Over 27% (138/506) of these subjects did not have fasting glucose values reported. Though fasting insulin levels were presented in the 2004 submission, there was no proper mathematical transformation of fasting insulin and fasting glucose levels conducted to calculate Insulin Sensitivity.

Recent research in the field of glucose regulation has shown fasting insulin level per se is not a good index for prediction of insulin resistance or diabetes mellitus. Insulin resistance should be calculated from fasting insulin and fasting glucose, not just fasting insulin or fasting glucose per se. Furthermore, the diagnosis of metabolic syndrome in adults requires meeting multiple criteria, including abnormal values for: serum triglyceride, high density cholesterol, fasting glucose, blood pressure, abdominal/central obesity measured as waist to hip ratio, waist circumference, or BMI. Weight gain or BMI is regarded as a very important predictive factor for development of metabolic syndrome.

We note that there is an increasing prevalence of diabetes in children and adolescents in recent years and there are concerns about the validity of fasting glucose levels for establishing a diagnosis of diabetes in this population. Since the precise diagnostic criteria for metabolic syndrome in children and adolescents are not yet established, we consider it premature to conclude that there is no evidence of metabolic syndrome, insulin resistance, or a risk of diabetes mellitus in autistic children and adolescents treated long-term with risperidone.

We therefore request that you perform a study in autistic children and adolescents to determine the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. This study should be considered a Phase 4 Commitment.

You may combine the elements of this Phase 4 Commitment Request with the Clinical Pharmacology and Biopharmaceutics Phase 4 Commitment Request cited above [page 3, Item 5], and meet both sets of requirements with a single study. Please include a proposed date for submission of study protocol and final study report in your Complete Response to this letter.

Request for Regulatory Update
Please provide any new information on the regulatory status of Risperdal® in this indication worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we also ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. It is only necessary to provide information that is more recent than that provided in your January 16, 2006 Complete Response.

Request for Safety Update, World Literature Update, and Foreign Labeling
When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug in the pediatric population. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling for this, or any other pediatric indication, not previously submitted.

Labeling (Package Insert)
In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter. We believe the attached draft labeling presents a fair summary of the information available on the benefits and risks of Risperdal® (risperidone) in the treatment of irritability associated with autistic disorder. You will see that we have proposed a number of changes to the draft labeling submitted in your January 16, 2006 Complete Response, and explanations for these changes are generally provided in the bracketed comments embedded within the proposed text.

Please use the proposed text verbatim, with the exception of revisions in response to comments embedded in the text or presented in this letter. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes. Division staff are willing to discuss this revised labeling in detail and to meet with you to resolve any disagreements you may have with the proposed labeling. Note that if additional information related to the safety or effectiveness of these drug products becomes available, revision of the labeling may be required.

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 application(s) 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 for this indication before approval of these supplemental application(s).

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301).796.1040.

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

Attachment: FDA Draft Labeling

48 Pages Immediately Following Withheld - b(4) Draft Labeling

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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
7/14/2006 01:19:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036
NDA 20-588/S-024
NDA 21-444/S-008

Harindra R Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical R & D
920 US Highway 202, PO Box 300, Room E1349
Raritan, NJ 08869, USA

Dear Dr. Abeysinghe:

Please refer to your supplemental new drug applications dated, received November 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal ® (risperidone) Tablets, Oral Solution and M-TAB.

We acknowledge receipt of your submission dated: March 2, 2005.

This supplemental new drug application provides for the use of Risperdal® in the treatment of the irritability associated with autism.

We completed our review and find the information presented is inadequate. Therefore, the applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

We do not believe that your proposed dosing recommendations will permit prescribers to reliably identify a dose in any particular patient that is both effective and acceptably safe.

In particular, you have not established either that 1) the proposed initial dose (b) (4) is the lowest effective dose. (b) (4)

With regard to the initial dosing recommendation, you have presented no arguments (other than that this is consistent with clinical practice) that establish that doses lower than those you propose might not be as effective. As we noted in our Approvable letter, the fact that a lowest effective dose has not been identified, although never ideal, may be acceptable if the lowest dose studied is not associated with an unacceptable risk. We continue to believe that the lowest doses used (in your analyses, <1 mg/day as a modal dose) are associated with an unacceptably high incidence of important adverse events (e.g., somnolence, "parkinsonism", confusion, fatigue), and may be associated with an

unacceptable risk of long-term consequences (e.g., tardive dyskinesia, sequelae of prolonged increased prolactin).

With regard to the second question, your analyses do not establish that doses greater than the starting doses confer any additional benefit. You assert that some patients required higher doses, but offer no compelling rationale for this conclusion (other than, perhaps, that this is what was done in the studies). In particular, your analyses suggest that the maximum response was seen with the lowest dose (although, again, we recognize that this conclusion cannot be considered definitive, based on the nature of the study design). We acknowledge that in Study 150 patients in the higher dose groups demonstrate an increase in effect later in time, but we fail to see how this observation supports the conclusion that these doses were necessary in any given patient (for one thing, the effect in these patients by the end of the study is no greater than the effect in the lowest dose group). Indeed, you seem to acknowledge this when you state that these results may be confounded by the design, and that it is possible that some patients who ultimately received higher doses might have responded just as well had they been maintained on lower doses (you further conclude, quite rightly in our view, that this question cannot be tested in these trials).

Although we agree with your general view that slower titration to any given higher dose is likely to increase tolerability, this view does not, in our view, speak to the question of whether or not there is evidence that these higher doses are necessary. We do note your finding that patients considered responders had received, in general, slightly higher doses (and achieved higher plasma levels) than patients considered non-responders. Although this finding is consistent with a dose-response, the retrospective nature of these analyses makes the finding preliminary at best.

For these reasons, then, we believe that you must conduct an additional fixed dose trial to adequately evaluate dose response (in particular, of course, we expect that this study would define a lowest effective dose) prior to approval. We believe that approving this application without a full understanding of the dose response would potentially expose patients to unnecessarily high doses that are associated with unacceptable risks.

In addition to these reasons for the Not Approvable action, we have the following additional requests.

1) As noted in our Approvable letter, we request that you perform juvenile animal toxicology studies in the rat and dog. As outlined in that letter, given that you must perform an adequate dose-response study prior to approval, we would expect that reports of these completed animal studies would be included in your resubmission.

2) Although there seemed to be no important EKG changes, there is a discrepancy between the number of patients who presumably had EKG data available (by our count 66) and the number of patients included in your tables (77). Please address this discrepancy.

3) You should analyze your data for adverse events possibly related to loss of glucose control, as well as examine the proportion of patients who met clinically relevant outlier criteria for serum glucose. Further, because there are theoretical reasons for believing that patients with autism might differ in their capacity for loss of glucose control from that of patients with conduct disorder (i.e., first degree relatives of patients with autism have a higher than background risk

for type I diabetes, and there is some evidence that autism may have an autoimmune component), appropriate monitoring of glucose should be performed in the clinical trial.

4) We continue to have concerns about the adequacy of coding of adverse events. Specifically, for example, with regard to the preferred terms of nervousness, anxiety, or agitation, you state that, in the description of the events coded to agitation, there were no other adverse event terms that were listed that could help you to determine that they were, in fact, cases of EPS. However, we are unsure what other terms you feel could have been helpful in deciding that these cases (for example, in the case of an adverse event listed as "increased fidgeting of right foot") were, or were not, EPS. In another example, many of the events coded as "dyskinesia" seemed, to us, to be more appropriately coded as "tardive dyskinesia". In addition, numerous cases you coded as "agitation" again seemed, to us, to be more appropriately coded as "akathisia". For these reasons, we believe that these specific events should be re-coded. Finally, we request that you specifically analyze the akathisia items in the various relevant rating scales performed in your controlled trials.

5) In the future recommended fixed-dose studies, please elicit formal ratings of severity of somnolence, fatigue and EPS over the duration of treatment. This will help address the question of whether or not patients will habituate to these adverse events with treatment over time.

6) We have some questions about the interpretation of your cognitive testing. It appears that relatively few patients enrolled in the study actually had the testing. In addition, it appears that for some tests, differences from baseline were calculated in the absence of baseline measurements. Please address these issues.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file amendments, 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 application 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.

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

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
5/19/05 12:45:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036
NDA 20-588/S-024
NDA 21-444/S-008

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Megan Zoschg, Pharm.D.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. Zoschg:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal ® (risperidone) Tablets, Oral Solution and M-TAB.

We acknowledge receipt of your submissions dated:

February 19, 2004	April 2, 2004	May 3, 2004	May 17, 2004
March 5, 2004	April 5, 2004	May 11, 2004	June 2, 2004
March 26, 2004	April 14, 2004	May 13, 2004	

These supplemental new drug applications provide for the use of Risperdal ® in the treatment of the irritability associated with autism.

We completed our review of these applications and they are approvable. Before the applications may be approved, however, you must address the following deficiencies:

Although we acknowledge that you have demonstrated the effectiveness of Risperdal in the treatment of the irritability of autism, we believe that the trials, as conducted, resulted in a substantial number of patients receiving doses of risperidone at or near the maximum dose permitted. Of course, given the flexible dose regimen utilized in the studies, we cannot determine whether or not these larger doses are necessary (that is, whether increasing doses are associated with increasing effectiveness). Some preliminary analyses suggest either that effectiveness does not increase with increasing dose (a simple plot of each patient's modal dose against their change from baseline on the Irritability subscale of the ABC) or that there may be a lag in time between the attainment of the final dose and treatment effect size (the estimate of the treatment effect continues to increase over time in Study RIS-USA-150 apparently long after the maximum dose has been attained), suggesting that dose increases were made before the maximum response to any given dose could have been adequately observed. Although we recognize that these analyses cannot be considered definitive, they do suggest that the dosing regimen in the trials was sub-optimum, and may have resulted in inappropriately high doses in many patients.

Although it is never ideal to provide dosing recommendations in labeling for regimens that may result in patients receiving unnecessarily high doses, it is particularly problematic when, as is the case here, the incidence of important adverse events are particularly high, and are likely to be dose related. In the controlled trials in patients with autism, there were significant and substantial rates of somnolence, increased appetite, fatigue, extrapyramidal symptoms, weight gain and constipation. Further, although the rates for dizziness, confusion, automatisms, and tachycardia were lower, they still represented a considerable increase over the rates of these events seen in the placebo patients.

Although we acknowledge that few patients discontinued treatment in the controlled trials because of an adverse event, and that the overall rate of adverse dropouts in the open-label experience was about 8% (with no single adverse event responsible for discontinuation in more than 1.6% of patients), this does not necessarily mitigate the risk of these adverse events in the long-term.

We are particularly concerned about the risk of adverse events that may be more likely to occur with long-term treatment with risperidone, and that would be expected to be dose-related. Specifically, we are concerned about the possible occurrence of tardive dyskinesia, as well as any long-term sequelae of chronic elevation of prolactin (clearly significantly increased compared to placebo patients in the 8 week controlled trials). In addition, the long-term risks of some of the adverse events seen at high rates in the controlled trials may be significant (e.g., significant weight gain, tachycardia, etc.).

For these reasons, we believe it is critical for you to adequately explore the dose response relationship for risperidone in this population. We believe this can be done definitively only in a multiple, fixed-dose controlled trial. However, to support approval before such a trial is conducted, we would be willing to entertain the possibility that you could (b) (4) [redacted] (b) (4) we would require that you perform an adequate dose response study in Phase 4.

In addition to this concern, we have the following requests:

1. Juvenile animal toxicity studies in both rat and dog must be conducted. Please refer to our email dated May 26, 2004 for specific recommendations on the draft protocols submitted April 2, 2004 and May 17, 2004. If we determine that you do not need to perform a dose-response study prior to approval, the animal studies may be completed and submitted in Phase 4. If we determine that a dose-response study must be performed prior to approval, the juvenile animal studies should be performed while that study is on-going, and the reports should be submitted with the re-submission to the application.

2. We believe the analyses of part III of study USA-150 are problematic, because different relapse criteria are described in different parts of the protocol (the results of one analysis are significant

and the results of the other are not). In our view, including global measures in the relapse criteria would be inappropriate, given the restricted nature of your proposed claim. Therefore, we request that you re-analyze the study using a Kaplan-Meier survival analysis and the definition of relapse based only on the 25% worsening of ABC Irritability subscale change.

3. Height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores). This analysis of height and weight data is accomplished by computing the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time (e.g., at least 3 months).

4. Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose (b) (6) These discrepancies should be explained.

5. Provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of the drug:placebo odds of each common, drug-related (occurring in at least 5% of drug-treated patients and at least twice as frequent than the placebo rate) adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

6. Provide an analysis of quantitative ECG data from study CAN-23.

7. It was noted that you collected PK samples in the pivotal trial RIS-USA-150 and a population pharmacokinetic analysis was planned. Requests for submitting the PK data were previously sent; however, it appears that these data were not submitted to the Agency. Please submit the analysis of this population PK data.

8. You should examine glucose metabolism (at a minimum, evaluating fasting blood sugars) in a cohort of children that includes substantial numbers of patients with Autistic Disorder. You should also perform an adequate assessment of cognitive function in patients with Autistic Disorder. If it is determined that a fixed dose controlled trial will be required prior to approval, these measures may be assessed at that time. If the fixed dose study is not required prior to approval, these assessments may be performed in Phase 4.

9. You should examine the verbatim terms coded as "somnolence" and "fatigue" to determine if these terms represent a similar clinical phenomenon; if they do, of course, the incidence of this event should be re-calculated. In addition, you should perform a re-analysis of verbatim terms subsumed under the various preferred terms that represent abnormal movements and extrapyramidal symptoms to ensure that we have a complete understanding of the incidence of these specific events. We are particularly concerned that events coded as "nervousness", “agitation”, and "anxiety" may represent akathisia.

10. You should fully evaluate the time course of the important adverse events, including the time of onset and the duration of their persistence.

Because we have fundamental questions about whether the current data support approval, and, if so, what dosing recommendations should be provided, we are not including draft labeling with this letter.

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

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should be limited to the pediatric population but include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug in the pediatric population. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling for this, or any other pediatric indication, not previously submitted.

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 these changes before approval of these supplemental applications.

If you have any questions, call Melina Griffis, R.Ph., Senior Regulatory Project Manager, at (301) 594-5526

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
6/18/04 01:12:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-272/S-036
NDA 20-588/S-024
NDA 21-444/S-008

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Megan Zoschg, Pharm.D.
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. Zoschg:

Please refer to your December 19, 2003 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal® Tablets, Oral Solution and M-Tab.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 16, 2004 in accordance with 21 CFR 314.101(a). The User fee goal date for this application is June 19, 2004.

In our filing review, we have identified the following potential review issues and/or requests for additional information:

1. It is noted that in some clinical studies including study RISUSA- 150 (the pivotal clinical trial), the formulation used is not the marketed formulation. It is claimed that bioequivalence studies in healthy volunteers and psychotic patients demonstrated that the risperidone research tablets are bioequivalent to the marketed tablets. Please provide the bioequivalence studies indicated or refer to their location.

2. Please provide the status of the pharmacokinetic analyses in study RIS-USA-150 Part 1.

3. Please submit the required four drop out case report forms for the USA-150.

4. Please submit more detailed narratives for the two suicidal reports in the two ongoing studies, INT-79 and INT-84.

5. Please redo the tables number 25 and 27 in the ISS to compare with the rates with the placebo groups and patient-year of exposure for each group. Also, please clarify and

make sure that the tables do include all the studies, as the footnotes of these tables don't include any of your pivotal studies.

6. Since you intend to market Risperdal for (b) (4) in young children as well as in adolescents, two studies in juvenile animals (rodent and non rodent) need to be conducted. We recommend that you start these studies as soon as possible.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Melina Griffis, R.Ph., Senior Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
2/25/04 07:45:31 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

LABELING

JANSSEN, L.P.

RISPERDAL®
(risperidone)
TABLETS/ORAL SOLUTION

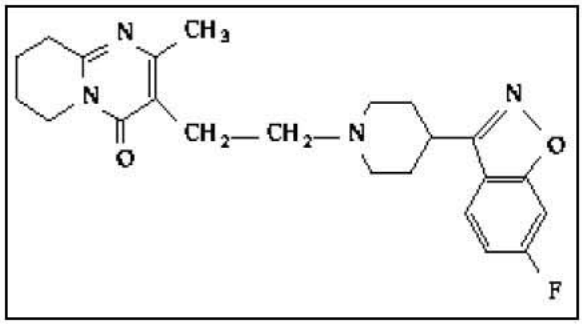
RISPERDAL® M-TAB®
(risperidone)
ORALLY DISINTEGRATING TABLETS

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.

DESCRIPTION

RISPERDAL® (risperidone) is 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. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

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

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.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that 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. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_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.

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 BID). 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, risperidone 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

(e.g., the active moiety) 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 the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTIONS – Drug Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. 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 risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. 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.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) 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% (see PRECAUTIONS -Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Administration of RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) 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 risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see PRECAUTIONS – Drug Interactions).

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety.

In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

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

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 the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

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

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.

CLINICAL TRIALS SCHIZOPHRENIA

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 (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

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

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

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

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic

medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 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 (Y-MRS), 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 Y-MRS 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 Y-MRS 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 Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in 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 Y-MRS 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 Y-MRS 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.

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).

INDICATIONS AND USAGE

Schizophrenia

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

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

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

physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

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.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Irritability Associated with Autistic Disorder

RISPERDAL® is indicated for the treatment of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

The efficacy of RISPERDAL® 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. The benefit of maintaining patients with irritability associated with autistic disorder on therapy with RISPERDAL® after achieving a responder status for an average duration of about 140 days was demonstrated in a controlled trial (see CLINICAL PHARMACOLOGY - Clinical Trials.)

Physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

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).

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.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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

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

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

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 WARNING**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

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.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period,

probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

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

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone 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 PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

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

Thrombotic Thrombocytopenic Purpura (TTP)

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

Antiemetic Effect

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

Body Temperature Regulation

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

Suicide

The possibility of a suicide attempt is inherent in 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.

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).

Information for Patients

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

Orthostatic Hypotension

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

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

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

Nursing

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

Concomitant Medication

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

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

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.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

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

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

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

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%.

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

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone 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 risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) 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.

Lithium

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

Valproate

Repeated oral doses of risperidone (4 mg QD) 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 risperidone.

Digoxin

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

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). 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 ($n \cong 70$) 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.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

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, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum 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 PRECAUTIONS, General -Hyperprolactinemia).

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.

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 risperidone during the last trimester of pregnancy.

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

The safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or bipolar mania 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, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years (see CLINICAL PHARMACOLOGY - Clinical Trials, INDICATIONS AND USAGE, and ADVERSE REACTIONS). 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 other psychiatric disorders who were of similar age and weight, and who received similar dosages of RISPERDAL® as patients who were treated for irritability associated with autistic disorder.

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

Tardive Dyskinesia

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of risperidone treatment (see WARNINGS – Tardive Dyskinesia).

Weight Gain

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. When treating patients with RISPERDAL®, weight gain should be assessed against that expected with normal growth. (See also ADVERSE REACTIONS.)

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. (See also ADVERSE REACTIONS.) Patients

experiencing persistent somnolence may benefit from a change in dosing regimen (see DOSAGE AND ADMINISTRATION – Irritability Associated with Autistic Disorder).

Hyperprolactinemia, Growth, and Sexual Maturation

Risperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS - Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) 49% of patients who received risperidone had elevated prolactin levels compared to 2% of patients who received placebo.

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, galactorrhea was reported in 0.8% of risperidone-treated patients and gynecomastia was reported in 2.3% of risperidone-treated patients.

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

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 and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is 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).

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 risperidone

when compared to patients treated with risperidone 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, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)**

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania, and are followed by a description of adverse events and other safety measures in short-term, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder. In patients with Bipolar I Disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania and pediatric patients with autistic disorder.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

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

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal

symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

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

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients - Schizophrenia

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

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

Table 1: Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials in Schizophrenia [1]

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

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

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

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2: Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3: Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placebo + Mood Stabilizer (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

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

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism

score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

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

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

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

Other Adverse Events

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

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

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

Laboratory Changes

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

ECG Changes

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

Adverse Events and Other Safety Measures in Pediatric Patients With Autistic Disorder

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

In addition to spontaneous reporting, in one of the studies, adverse events were also elicited from a checklist for detecting selected events, a method that is more sensitive than spontaneous reporting.

The most common adverse events with RISPERDAL® that occurred at an incidence equal to or greater than 5% and at a rate of at least twice that of placebo are shown in Table 4.

Table 4 Incidence of Treatment-Emergent Adverse Events in Two 8-Week, Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

Body System Preferred Term	RISPERDAL® (n=76)	Placebo (n=80)
Psychiatric		
Somnolence	67%	23%
Appetite increased	49%	19%
Confusion	5%	0%
Gastrointestinal		
Saliva increased	22%	6%
Constipation	21%	8%

Dry mouth	13%	6%
Body as a whole - general		
Fatigue	42%	13%
Central & peripheral nervous system		
Tremor	12%	1%
Dystonia	12%	6%
Dizziness	9%	3%
Automatism	7%	1%
Dyskinesia	7%	0%
Parkinsonism	8%	0%
Respiratory		
Upper respiratory tract infection	34%	15%
Metabolic and nutritional		
Weight increase	5%	0%
Heart rate and rhythm		
Tachycardia	7%	0%

Weight increase was reported more frequently with RISPERDAL® than with placebo. The average weight increase over 8 weeks was 2.6 kg in patients treated with RISPERDAL® compared with 0.9 kg in patients treated with placebo. (See also PRECAUTIONS – Pediatric Use – Weight Gain.)

There was a higher incidence of adverse events reflecting extrapyramidal symptoms (EPS) in the RISPERDAL® group (27.6%) compared with the placebo group (10.0%). In addition, between-group comparison of the severity of EPS were assessed objectively by the following rating instruments: the Simpson-Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS) in one study, and the Extrapyramidal Symptom Rating Scale (ESRS) in the other study. The mean changes between baseline and endpoint in the total ESRS score were –0.3 in the RISPERDAL® group and –0.4 in the placebo group. The median change from baseline to endpoint was 0 in both treatment groups for each EPS rating scale.

Somnolence was the most frequent adverse event, and was reported at a higher incidence in the RISPERDAL® group compared with the placebo group. The vast majority of cases (96%) were either mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first 2 weeks of treatment, and median duration was 16 days. Patients experiencing persistent somnolence may benefit from a change in dosing regimen (see DOSAGE AND ADMINISTRATION – Irritability Associated with Autistic Disorder – Pediatrics [Children and Adolescents]).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 adult patients with schizophrenia and 1923 pediatric patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 adult or 1923 pediatric patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it. Serious adverse reactions experienced by the pediatric population were similar to those seen in the adult population (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

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

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare*: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent*: dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare*: aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

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

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent*: edema, rigors, malaise, influenza-like symptoms. *Rare*: pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

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

Skin and Appendage Disorders

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

Cardiovascular Disorders

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

Vision Disorders

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

Metabolic and Nutritional Disorders

*Infrequen*t: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare*: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

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

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare*: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina* *Infrequent*: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare*: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare*: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare*: normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction* Infrequent: ejaculation failure.

White Cell and Resistance Disorders

Infrequent: granulocytopenia. *Rare*: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pituitary adenomas, pulmonary embolism, and precocious puberty. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

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

OVERDOSAGE

Human Experience

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

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

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.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

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

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Pediatric Use

The safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia have not been established.

Bipolar Mania

Usual Dose

Risperidone 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 PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

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 risperidone. 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 risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use

The safety and effectiveness of RISPERDAL® in pediatric patients with bipolar mania have not been established.

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 weighed 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 PHARMACOLOGY – Clinical Trials) 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 1.0 mg in patients < 20 kg, 2.5 mg in patients ≥ 20 kg, or 3.0 mg in patients > 45 kg. No dosing data are available for children who weigh 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.

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.

Dosage in Special Populations

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

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have

increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

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 risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

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.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

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

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

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

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

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

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

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

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

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", and "R4", respectively. 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 per box, NDC 50458-395-28, long-term care packaging of 30 tablets NDC 50458-395-30.

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

2 mg light coral, round, biconvex tablets: 7 blister packages 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.

Keep out of reach of children.

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

Keep out of reach of children.

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.

[INSERT NEW COMPONENT CODE]

Revised October 2006

RISPERDAL® tablets are manufactured by:

JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy
RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

OFFICE DIRECTOR MEMO

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 14, 2006

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

SUBJECT: Recommendation for approvable action for Risperdal (risperidone) for the treatment of irritability associated with autistic disorder

TO: File NDAs 20-272/S-036, 20-588/S-024 and 21-444/S-008
[Note: This overview should be filed with the sponsor's 1-16-06 response to FDA's 5-19-05 not approvable letter.]

The original supplement was submitted 12-19-03 and an approvable letter was issued 6-18-04. A major concern noted in this letter was the failure to establish the optimal dosing strategy for treating this new indication. The concern was that patients might be receiving higher doses than needed. This concern was based in part on a finding of a somewhat higher incidence of various adverse events in the autism studies than was seen in other studies with this drug. The letter noted that there would be a need for a dose response study to better establish the dose response relationship for this drug, but did, nevertheless, offer the sponsor the opportunity to try to establish reasonable dosing recommendations for labeling based on existing data. The letter also included a request for juvenile animal toxicity studies in 2 species, and for various other information.

The sponsor responded to the 6-18-04 approvable letter on 11-18-04. This response included a (b) (4) acknowledging that the flexible dose design of these trials precluded reaching any definitive conclusions about the dose response relationship. The division (DNDP) considered and rejected these arguments and maintained it's position that the sponsor had not identified a lowest effective dose and had not justified the use of the higher doses recommended in labeling. The basic concern again was unacceptable adverse effects. Thus, a not-approvable letter was issued 5-19-05.

The sponsor requested a meeting to discuss the 5-19-05 NA letter, and the psychiatry division (DPP) met with the sponsor on 12-7-05. In a background package for this meeting, the sponsor made several arguments:
-Regarding the concern about unacceptable adverse events, the sponsor noted that adverse events were largely mild to moderate in severity, similar qualitatively to those seen in adults, transient, and led to discontinuation very infrequently (1.3%). They further argued that the somewhat higher

incidence of adverse events was partly an artifact of using a questionnaire to elicit adverse events and partly due to the fact that many of these patients were naïve to risperidone, unlike patients in other programs.
-They argued that a recoding of certain adverse events as suggested by FDA led to even less of a signal for unacceptable adverse events for risperidone.
-They also argued that the expressed concern about unacceptable longer-term risks, in particular, TD, hyperprolactinemia, and delayed growth and maturation, was not justified based on available data.
-Finally, they argued that, although the dose/responses relationship for efficacy was admittedly not understood, dosing in current practice for this disorder is more aggressive than that proposed for labeling based on the available data from these trials.
-FDA agreed with many of these arguments and encouraged the sponsor to submit a response to the NA letter. However, we did ask that they try to apply approaches developed by Sheiner, et al, to try to better understand the dose response relationship from the available data. We also asked for additional safety information.

The sponsor responded to the 5-19-05 NA letter in a 1-16-06 submission that included responses to all of our requests. This was reviewed by the clinical group, pharm/tox, and biopharm.
-Andre Jackson, Ph.D., from OCP reviewed the sponsor's attempt to apply a Sheiner approach to the efficacy data. His major concern was that the studies in question (USA-150 and CAN-23) were not conducted in a manner required to apply the Sheiner approach. Thus, the results are not interpretable and still do not provide support for the proposed starting dose and the need for titration. He and the biopharm group conclude that a phase 4 fixed dose study is still needed, e.g., placebo, 0.125 mg and 1 mg.
-The pharm/tox group (Drs. Elayan and Rosloff) conclude that the juvenile rat study will need to be repeated because the high dose was not adequate (they recommend 2.5 mg/kg as the high dose). They also recommend that we ask for a juvenile dog study. They agreed that these studies could be conducted in phase 4.
-Drs. Cai and Khin also agree that the supplement is approvable, but have a number of recommendations for additional data requests and for a phase 4 commitment to conduct a fixed dose study to better establish the lowest effective dose and a need for titration.

CONCLUSIONS AND RECOMMENDATIONS

I agree with the review team that the sponsor has still not adequately established an optimal starting dose and adequately justified a need for titration to higher doses. However, I also agree that additional data to address these questions could reasonably be submitted following approval of this supplement (b) (4). A major justification, as noted, is that current prescribing practice for this indication is even more aggressive than that proposed in this supplement. There are several labeling issues that need to be resolved prior to final approval, and these will likely require some discussion with the sponsor. In addition, we have several requests for clarification and further information that need to be addressed prior to final approval. Thus, I will issue an approvable letter with our proposed labeling, along with our requests for additional data and a commitment to conduct a fixed dose study post-approval.

cc:
Orig NDAs 20-272/S-036, 20-588/S-024 and 21-444/S-008
HFD-130/TLaughren/NKhin/JCai/DBates

DOC: Risperdal_Autism_Laughren_AE Memo.doc

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
7/14/2006 08:04:10 AM
MEDICAL OFFICER

MEMORANDUM

DATE: May 19, 2005

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-272/S-036; NDA 20-588/S-024; NDA 21-444/S-008

SUBJECT: Action Memo for NDA 20-272/S-036 Risperdal (Risperidone) (b) (4) NDA 20-588/S-024 Risperdal Solution, & NDA 21-444/S-008, Risperdal Orally Disintegrating Tablets, in the treatment of irritability in patients with autism

NDA 20-272/S-036, NDA 20-588/S-024, & NDA 21-444/S-008, Risperdal (Risperidone) (b) (4) Solution, and Orally Disintegrating Tablets, respectively, as treatment of irritability in patients with autism were submitted by Johnson and Johnson Pharmaceutical Research and Development, L.L.C., on 12/19/03. The application contained the results of controlled trials, as well as open-label safety data. The division issued an Approvable letter on 6/18/04. The issues raised in that letter were:

1) Although we acknowledged that effectiveness had been demonstrated, we were concerned that a substantial number of patients had received unnecessarily high doses (these were flexible dose trials). This was of particular concern because the incidence of numerous adverse events (e.g., somnolence, fatigue, extrapyramidal symptoms, weight gain) was high. In addition, we were concerned about the potential long-term consequences presumed to be dose-related (e.g., tardive dyskinesia, chronic elevation of prolactin). For this reason, we asked the sponsor to perform a fixed-dose study to determine true dose response (in particular, to identify a lowest effective dose). We did, however, offer the sponsor the opportunity to develop a dosing regimen, from the available data, that would ensure that patients received the lowest effective dose.
2) We asked that juvenile animal studies be conducted in rat and dog. We informed them that these studies could be done in Phase 4 if they were able to convince us that appropriate dosing recommendations could be offered without a new controlled trial, but that if they were required to do a dose response study, the animal studies should be conducted while that new controlled trial was on-going.
3) We asked for a re-analysis of the randomized withdrawal study.
4) We asked for a re-analysis of the height and weight data.
5) We asked for additional financial disclosure information from 4 investigators.
6) We asked for demographic analyses to be done for the adverse event data.
7) We asked for a quantitative EKG analysis for Study 23.
8) We asked for an analysis of the population pharmacokinetic (PK) data.
9) We asked for analyses of glucose levels and cognitive function.
10) We asked for analyses of the adverse events “somnolence” and “fatigue” to ensure that the appropriate verbatim terms were appropriately categorized, and for similar analyses of extrapyramidal adverse events.
11) We asked for analyses of the time course of the important adverse events.

The sponsor responded to the Approvable letter on 11/18/04. The response has been reviewed by Dr. June Cai, medical officer, Dr. John Duan, Office of Clinical Pharmacology and Biopharmaceutics, and Dr. Paul Andreason, psychiatric drugs team

leader. The review team has concluded that the sponsor has not adequately addressed the primary issue of identifying appropriate dosing recommendations. I will briefly review the response, and offer the rationale for the division's action.

Dosing Recommendations

(b) (4)

As Dr. Duan has noted in his extensive and detailed review, the sponsor had attempted to justify these revised recommendations in several different ways. The sponsor's fundamental task, from our point of view, has been two-fold: 1) to establish that the proposed starting doses are the lowest effective doses, and 2) to establish that some patients need higher doses than these starting doses (that is, that there is dose response).

(b) (4)

(b) (4)

First, they agree that formal dose-response cannot be determined from studies that utilize flexible dosing regimes. However, to address this question, they examined the responses in patients according to three groups, based on their modal doses: < 1 mg/day, > 1 mg-<2 mg, and greater than or equal to 2 mg/day.

According to the sponsor (see Dr. Duan's Tables 1 and 2, page 8), in Study 150, patients in the < 1mg/day group had a better response at Week 2 than those in the higher dose groups, but by the end of the study, patients in all three dose groups had approximately the same difference from placebo. In Study 23, although the lowest dose group showed a better response at Weeks 1 and 2 than the higher dose groups (as in Study 150), by the end of the study, there was a monotonically negative dose response (higher doses fared worse than lower doses). Although the sponsor concludes that "The

length of time that individual subjects are maintained on a dose appears to have a relationship to measured effect." (which presumably supports (b) (4) to keep patients on a given dose for 14 (b) (4) days, before continuing to titrate), this analysis does not establish that these higher doses are needed. Indeed, at the end of the study, there is no evidence that doses greater than < 1 mg/day confer any additional benefit. The "relationship" of time on dose to increased benefit, if there was one (and these analyses, again, do not seem to support this), could easily be due to a lag in time between receiving a dose and achieving a response, and have nothing to do with the dose increase (a phenomenon that was suggested by earlier analyses, and noted in the Approvable letter).

In addition, the sponsor acknowledges that "These results may be confounded by the flexible-dose study design, …", and that, "It is possible that some patients in the higher mode-dose groups would have improved with continued treatment at a lower dose, although that cannot be tested with the results of these studies.".

The sponsor has also looked at predicted steady-state plasma levels in Study 150 in responders and non-responders (variously defined). They demonstrate slightly greater doses and steady-state plasma levels in responders compared to non-responders (see Tables 4 and 5, Dr. Duan's review, page 11). Although this is somewhat suggestive of a dose response, these analyses, given the retrospective nature of the analyses, cannot be considered nearly definitive.

(b) (4)

Finally, the sponsor has examined the incidence of adverse events by the previously described modal dose groups (Table 6, Dr. Duan's review, page 13). Again, the incidence of adverse events is not strictly dose related, likely due to the design of the trials. Nonetheless, the incidence of certain adverse events is quite high in the low-modal dose group, as described below:

	Drug (N=17)	Placebo (N=80)
Somnolence	82%	23%
Appetite Increased	33%	19%
Confusion	12%	0%
Fatigue	29%	13%
Constipation	24%	8%
Parkinsonism	24%	0%

Although the number of low dose patients is small, the increase in these significant adverse events is of considerable concern.

Regarding the other requests in the Approvable letter:

2) Juvenile animal studies: Given that we will not approve the application until an adequate dose response study is performed, the sponsor should perform the requested juvenile animal studies.

3) Re-analysis of Phase III of Study 150: The sponsor has done this adequately.

4) Re-analysis of the height and weight data. The sponsor has performed these analyses adequately.

5) Financial disclosure issues: These have been adequately addressed.

6) Demographic analyses of adverse events: The sponsor has adequately performed these analyses; there is little effect of any demographic variables on the incidence of specific adverse events.
7) Quantitative EKG analyses: Although there seemed to be no important EKG changes, there is a discrepancy in the number of patients for whom EKGs were available, and this should be addressed by the sponsor.
8) Population PK analyses: According to Dr. Andreason, these analyses document that pediatric patients with autism metabolize risperidone similarly to other pediatric patients.
9) Re-analyses of glucose metabolism and cognitive function: Although no glucose levels were obtained in these studies of autistic patients, the sponsor presented glucose data in patients with conduct disorder, and argued that there is no reason to expect differential effects on glucose metabolism in these populations. Dr. Cai is unconvinced, stating that both autism and type I diabetes are both autoimmune diseases, and that there is a higher incidence of first degree relatives of autistic patients with type I diabetes, which in her view raises the possibility that there might be autism-specific changes in glucose metabolism. Dr. Andreason agrees that this should be further explored, but that it can be done in Phase 4. Apparently, in the study presented, about 27% of patients did not have glucose data available, and the sponsor seems not to have analyzed the data for outliers, nor did they examine the data for adverse events related to loss of glucose control. Although I am not aware that autism is accepted to be an auto-immune disease, and I am inclined to accept the sponsor's argument, given that they will need to perform another controlled trial, we can ask them to evaluate glucose metabolism in more detail both in the conduct disorder study as well as in the study to be done.

Regarding cognitive function, the sponsor has performed a battery of tests in Study 150. As Dr. Cai notes, there are questions about this study. For example, there appear to have been very few patients in this study who actually took the specific tests. Further, the sponsor appears to have calculated change from baseline in patients without baseline scores. We will ask them to address these issues.

10) Re-coding of adverse events: For "somnolence" and "fatigue", Dr. Cai notes some residual concerns about the appropriateness of the sponsor's coding, but there were relatively few cases giving rise to these concerns.

Regarding re-coding of extra-pyramidal symptoms, the sponsor also asserts that their original coding was adequate. Dr. Cai, however, notes relatively frequent potential mis-coding. For example, "hyperkinesias" included terms related to increased activities; most symptoms coded to "dyskinesia" seemed to be related to tardive, but there were only four cases coded as tardive dyskinesia; there were several cases that probably should have been coded to "dyskinesia" but weren't; "extrapyramidal disorder" was not used as a general term that subsumed other terms, as we would expect it to be.

Further, we asked the sponsor to specifically examine their coding of verbatim terms to akathisia, given the potential for these terms to be coded to either agitation, nervousness, or anxiety. As Dr. Cai notes, there are residual concerns. She notes that the sponsor asserts that, in some cases, there were no other adverse events that were indicative of akathisia or other EPS (for example, for a patient with "increased fidgeting of right foot" there were no other terms indicative of EPS, and this event was coded as "nervousness"). She rightly notes that the sponsor does not explain what terms they feel might have helped convince them that this was, in fact, a case of akathisia. She also notes that in the controlled trials, the sponsor used various scales that had specific akathisia items, and that these items were not specifically analyzed; they should be. Finally, she also notes that many of the verbatim terms coded to "agitation" seemed more appropriately probably akathisia; the sponsor should be requested to re-code these events.

11) Analyses of the time course of selected adverse events: The sponsor assessed the time to onset, the total number of days of the event, and the percent of total treatment time that the event was present. As Dr. Cai notes, the duration analyses were done only on the controlled trial data, which may not have been adequate to fully assess the entire duration of the event. In addition, Dr. Cai notes that the sponsor did not examine, in effect, the hazard for these events during the trials, and should be asked to do so.

COMMENTS

The sponsor argues, in this submission, that their revised dosing recommendations can reliably result in patients with autism being treated with a dose that is effective and that is associated with an acceptable risk of adverse events.

There is no question that the sponsor has demonstrated that the treatment is effective, and that an effective dose (range) can be determined. The question remaining for us is whether we believe that the sponsor's arguments and re-analyses support that such

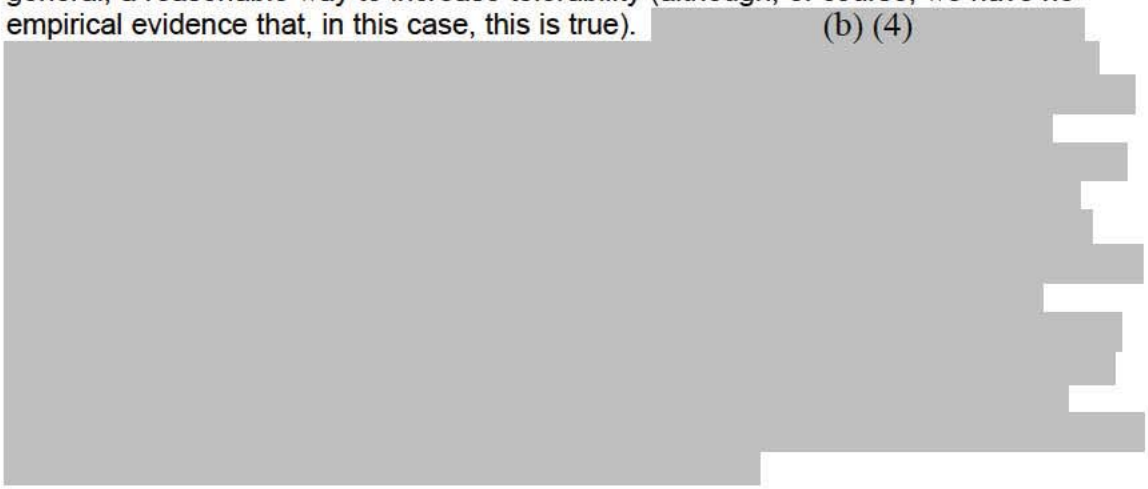
doses can be acceptably tolerated. Whether or not a particular dose is sufficiently well tolerated is, of course, a personal judgment. However, I do believe that certain principles can be applied to address this question.

As I noted in my original memo, the lack of identification of the lowest effective dose can be acceptable (although it is never ideal) if the doses found to be effective are well-tolerated. Our original review of the data revealed two important findings: most patients received doses near or at the highest end of the permitted dose range, and there was, in our view, an unacceptable risk associated with the use of these doses (both for events seen and, we concluded, unseen). Has the sponsor's re-examination of the data convinced us that, despite these findings, dosing recommendations can be written that adequately address these concerns?

I believe the issue can be broken into two parts. First, has the sponsor identified a lowest effective dose, and second, do the revised slower titration recommendations accomplish any important goal? Implicit in the second question is the question of whether or not the sponsor has demonstrated any dose response (that is, have they demonstrated that these higher doses are "necessary" in any patients).

Regarding the first question, clearly the sponsor has provided no evidence that the lowest doses studied are, in fact, the lowest effective doses. Patients were initiated at a particular dose (based on weight), and were all increased on Day 3/4. This particular regimen (a number of patients remained on this "final" dose) was associated with a particular outcome. Indeed, in both studies, this dose appeared to be the maximally effective dose, although, again, this cannot be a definitive conclusion because of the design of the trial. Nonetheless, all the evidence in the trial suggests that this lowest dose was quite effective (again, perhaps maximally effective), which strongly suggests that possibility that lower doses may be (equi-) effective. As far as I can tell, the sponsor makes no attempt to address the question of what is the lowest effective starting dose. Critically, however, the incidences of important adverse events at this lowest dose are quite high, and are unacceptable, given that lower, better tolerated doses may exist (see below).

Regarding the second question, I agree with the sponsor that slower titration is, in general, a reasonable way to increase tolerability (although, of course, we have no empirical evidence that, in this case, this is true). (b) (4)



In summary, I do not believe that the sponsor has provided evidence either that they have identified the lowest effective (starting) dose, or that higher doses than the lowest dose used in the studies are associated with an increase in effectiveness, either in individual patients or in the group.

Does either of these two conclusions preclude the approval of the application? Could we not simply permit dosing recommendations similar to those offered by the sponsor? After all, we have determined that the drug is effective in this dose range. Could we not reasonably recommend that patients be started on the lowest doses used, (b) (4)

I do not believe that this approach would be acceptable.

My primary concern is that the recommended starting dose itself may be unacceptably high. As noted above, this dose is associated with an array of significant adverse events that occur with very high frequency compared to the frequency in the placebo group. In addition, we have been concerned about the incidence of significant long-term sequelae that has not been fully assessed in this database (e.g., tardive dyskinesia, effects of increased prolactin). In my view, we would be remiss if we did not require the sponsor to more fully explore the lower end of the effective dosing range, in particular. Given the evidence described above, (b) (4)

Indeed, we are not willing to reach this decision at this time in the absence of this additional dosing information. In addition, of course, the sponsor should examine (to the extent that they are tolerated), fixed higher doses as well, titrated appropriately. (b) (4)

In the absence of this information, I do not believe that prescribers would be in a position to adequately dose patients. Indeed, I believe that patients would receive doses (far?) in excess of those that they actually need, as seemed to be the case in these controlled trials. For these reasons, then, the sponsor must perform an adequate dose-response study before the application can be approved. In addition, we will ask the sponsor to address the remaining issues discussed above.

Because the sponsor has not made a convincing argument that the available data support adequate dosing recommendations, and, therefore must perform a new trial, I consider the application Not Approvable, and I will issue the attached Not Approvable letter (our original letter was an Approvable letter because there remained the possibility that no additional data would be needed; because that is no longer the case, a Not Approvable action is appropriate at this time).

Russell Katz, M.D.

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

/s/

Russell Katz
5/19/05 12:51:53 PM
MEDICAL OFFICER

MEMORANDUM

DATE: June 15, 2004

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-272/SE1-036

SUBJECT: Action Memo for NDA 20-272/SE1-036, for the use of Risperdal (risperidone) Tablets/Oral Solution in the treatment of symptoms of irritability in pediatric patients with autism

NDA 20-272/SE1-036, for the use of Risperdal (risperidone) Tablets/Oral Solution in the treatment of symptoms of irritability in pediatric patients with autism, was submitted by Johnson and Johnson Pharmaceutical Research and Development, L.L.C. on 12/19/03. The application contains the results of two short term randomized controlled trials in pediatric (b) (4) In addition to these effectiveness studies, the application contains longer term, open label safety data.

The application has been reviewed by Drs. June Cai and Greg Dubitsky, medical officers (review dated 6/7/04), Dr. Kun He, statistician (review dated 5/3/04), Dr.John Duan, Office of Clinical Pharmacology and Biopharmaceutics (review dated 6/8/04), Dr. Ikram Elayan, pharmacologist (review dated 6/1/04), Dr. Ni Khin, Division of Scientific Investigations (review dated 5/25/04), and Dr. Paul Andreason, Psychiatric Drugs Team Leader (memo dated 6/7/04). The clinical review team recommends that the application be considered Approvable. I will briefly review the relevant data, and offer the basis for the Division's decision.

EFFICACY

As noted above, the sponsor has submitted the results of (b) (4) randomized, placebo controlled trials.

STUDY RIS-CAN-23

This was a randomized, double blind, parallel group, multi-center controlled trial in which patients aged 5-12 years with Autism (N=52) and other Pervasive Developmental Disorders (PDDs; N=23) were randomized to treatment with either risperidone 0.02-0.06 mg/kg/day or placebo. The duration of the study was 8 weeks, and patients were started on 0.01 mg/kg, and titrated (according to investigator decision) up to a maximum of 0.06 mg/kg/day (details of the dosing regimen will be described later). The primary outcome measure was the change

from baseline on the Irritability subscale of the Aberrant Behavior Checklist (ABC). This subscale consisted of 15 items (the total scale consists of 58 items), measuring various behaviors all related in some measure to what can reasonably be considered Irritability (see, for example, Dr. He's review, page 8 for a complete list of the items in this subscale). Each item is rated from 0 (no problem) to 3 (severe problem). The primary analysis was to be an ANCOVA with baseline score as the covariate.

The following chart displays the results on this outcome for all patients; the results for the patients with autistic disorder were essentially the same:

	Baseline	End	Change (LS Mean)	P-value
Risperidone (N=37)	18.9	6.9	-11	<.001
Placebo (N=38)	21.2	14.7	-4.8	

A Clinical Global Impression was a secondary outcome. At Week 8, 54% of risperidone patients and 18% of placebo patients were in the "very much improved" or "much improved" categories (p<.001).

Study RIS-USA-150

This was a study of similar design to that of RIS-CAN-23, although in this study, only patients with autistic disorder were enrolled. The details of the dosing regimen will be described later. In this study, both change from baseline in the Irritability subscale and the CGI-C (Clinical Global Impression of Change) were co-primary outcomes.

The following chart displays the results on the Irritability subscale:

	Baseline	End	Change (LS Mean)	P-value
Risperidone (N=49)	26.1	11.3	-14.6	<.001
Placebo (N=52)	25	21.6	-4.0	

For the CGI-C, 75.5% of the risperidone and 11.5% of the placebo patients were in the "very much improved" or "much improved" categories at Week 8 (p<.001).

(b) (4)

(b) (4)

SAFETY

The sponsor presents safety data in 821 pediatric patients (including a total of 83 patients with autism) who received at least one dose of risperidone. Over 300 patients received treatment for at least 12 months, and over 550 patients received treatment for at least 6 months. Over 600 patients received a modal dose of at least 1 mg/day, and over 200 received a modal dose of at least 2 mg/day.

In controlled trials (including trials of patients with disorders other than autism), 1.4% (3/222) of risperidone treated and 1.7% (4/237) of placebo treated patients experienced a serious ADR. In the risperidone patients, one patient experienced extrapyramidal syndrome (he received 2 mg, instead of the intended 0.2 mg) which resolved with drug discontinuation.

In the entire safety database (open and controlled data), 9.4% of 821 risperidone treated patients experienced a serious ADR. In this experience, 4 patients experienced a suicide attempt, and there were no other serious ADRs that appeared significant and/or drug related (see Dr. Cai's review, page 55-6).

In autism controlled trials, 2 patients in each treatment group discontinued due to ADRs. In the risperidone group, 1 was the patient described above with EPS, the other was a patient who experienced ineffectiveness and increased crying and irritability.

With regard to other ADRs, the following table presents the incidence of ADRs in the pooled short-term autism trials that occurred at 5% or greater, and were at least twice the incidence on drug compared to placebo (this is a reproduction of Dr. Cai's Table, page 58-9):

ADR	Risp (N=76)	Placebo (N=80)
Somnolence	67%	23%
Appetite Increased	49%	19%
EPS*	43%	10%
Fatigue	42%	13%
URI	34%	15%
Saliva Increased	22%	6%
Constipation	21%	8%
Dry Mouth	13%	6%
Dizziness	9%	3%
Automatism	7%	1%
Tachycardia	7%	0%
Confusion	5%	0%
Weight Increase	5%	0%

? Includes tremor, hypotonia, dyskinesia, extrapyramidal disorder, involuntary muscle contractions, ataxia, hypokinesia, hypotonia, akathisia, apathy, abnormal gait, dystonia, bradykinesia, hyperkinesia, oculogyric crisis, parkinsonism, tongue disorder.

A table of all ADRs occurring at an incidence greater than that in the placebo group seen in these two controlled trials can be found in Dr. Cai's review on pages 109-11.

The following chart displays the frequency of specific extrapyramidal symptoms in the autism controlled trials (again taken from Dr.Cai's review, page 66):

ADR	Risp (N=76)	Placebo (N=80)
Dystonia	12%	6%
Tremor	12%	1%
Parkinsonism	8%	0%
Dyskinesia	7%	0%
Akathisia	1%	1%
Tardive Dyskinesia	0%	1%

In these trials, between treatment differences on two scales that assess EPS were not significant.

In the entire safety database, there were 25 cases of akathisia, as coded by the sponsor.

There were no important laboratory abnormalities save for prolactin (including EKG measures), although risperidone was associated with an increase in heart rate compared to placebo (43% vs 15% reached PCS criteria for increased pulse) in the autism trials, with a 7.4 bpm mean increase in pulse in risperidone patients compared to a 0.7 bpm decrease in placebo patients.

Prolactin was not measured in the autism studies, but in the other controlled trials, risperidone patients (N=91) had a mean change in prolactin of about 20 ng/ml (baseline 8 ng/ml), while the placebo patients (N=108) had no mean change. A total of 43% of risperidone patients had a change for normal to elevated, compared to 2% of the placebo patients.

In the controlled trials, about 6% of risperidone patients experienced an ADR considered possibly related to prolactin increase, compared to about 2% in the placebo patients (see Dr. Cai's review, page 68-9).

Dr. Cai provides more details about the occurrence of somnolence, given the rate at which it occurred in the autism controlled trials.

Recall that the rate in these studies was 67% in the risperidone group and 23% in the placebo group. In all controlled trials, the rate in the risperidone group was 50% and 14% in the placebo patients. Two risperidone patients discontinued due to somnolence. The incidence was greatest in the first two weeks of treatment, and the mean duration was about 19 days (range 1-57 days; the trial was 8 weeks in duration).

Patients treated with risperidone experienced significant weight gain. Recall that 5% of risperidone and 0% of placebo patients reported weight gain as an adverse event. In the autism trials, 67% of risperidone and 11% of placebo patients experienced a 7% or greater increase in weight.

There were no other significant, clearly risperidone-related ADRs in the clinical database.

In the post-marketing experience, a total of 241 reports describing 444 ADRs seen in 14 countries were described. There is an increasing number of reports in recent years (see Dr. Cai's table, page 77), with 34 reports describing serious ADRs; she does not describe use data. As she notes, the most common serious ADRs were tardive dyskinesia (N=4), dystonia (N=4), EPS (2), tremor (1), and NMS (1). A few additional reports of these events were described in the literature. More recent literature and safety updates did not identify any previously unreported serious clearly drug-related ADRs.

Dose

As described above, the dosing regimen in the autism trials utilized a flexible dosing regimen. In study CAN-23, the dose was to be given once in the morning (which could be divided into a BID regimen or given in the evening if clinically indicated). The initial dose was .01 mg/kg/day, increased to .02 mg/kg/day on Day 3, and then increased to .04 mg/kg/day by Day 8, with a maximum dosing increment of .02 mg/kg/day. After Day 8, the dose could be increased by no more than .02 mg/kg/day at weekly intervals to a maximum daily dose of .06 mg/kg/day.

In Study RIS-USA-150, the dose was given on a BID regimen, starting at .25 mg/day or .5 mg/day, depending upon the patient's body weight, and then titrated to clinical response. In the higher weight patients (above 20 kg), the daily dose was increased to 1 mg/day (given as .5 mg BID) on Day 4; thereafter, by Day 22-23, the dose could be increased to 2.5 mg/day in the 20-<45 kg group, and to 3.5 mg/day in the >45 kg group.

In the autism trials, 75% of patients were treated with a maximum daily dose of 2.5 mg or less (50% of patients achieved a maximal daily dose of about 2.0 mg) and 75% of patients had a modal dose of 2 mg/day (50% achieved a modal dose of 1.5 mg/day). Dr. Duan presents a table in his review (page 23) of the percentage of patients in the autism trials who received various maximum/modal doses, displayed by various weight categories. From this table, and the dosing regimens employed in the two studies, it appears that many patients received close to the maximum doses permitted (it is difficult to know this with great confidence, because the dosing regimens in the trials were different, and the data in Dr. Duan's table are not presented by individual study).

For example, in study CAN-23, the maximum daily dose was to be 0.06 mg/kg, and in USA-150, the maximum dose was an absolute dose, dependent upon the patient's weight. In a 20 kg patient, this translates to a maximum daily dose of 1.2 mg in CAN-23 and 2.5 mg in USA-150, and in a 30 kg patient this translates to a maximum daily dose of 1.8 mg in CAN-23 and also 2.5 mg in USA-150. We can see from Dr. Duan's table, the modal dose for the median number of patients who weighed between 20-30 kg was 1.5 mg/day (this means, of course, that half of the patients in this weight range had this dose or less, and that half of the patients in the study had this dose or higher). This is mid-way between the maximum dose for 20 kg patients (1.2 mg) and that for the 30 kg patients (1.8 mg), as calculated from the dosing regimen in CAN-23 (as would be expected when the data are presented for the 20 and 30 kg patients together, if they achieved their maximum doses), and somewhat less than the maximum allowable dose in this weight group in USA-23. The modal dose for the 75th percentile in this weight range was 2 mg/day, even closer to the maximum dose permitted in USA-150.

For patients in quantiles below the median, the maximum daily dose was generally greater than the modal dose, for any given weight range. This suggests that many patients had their dose decreased at some point during the study. It is tempting to conclude that this happened because of intolerable adverse events.

It is difficult, if not impossible, to correlate either effectiveness or the occurrence of adverse events with dose, given the flexible dosing regimen employed.

Nonetheless, Dr. Duan has attempted to do both. To examine the dose response for effectiveness, he has produced a graph (found on page 13 of his review) in which he plots the modal dose for all patients against the percent change in the primary outcome measure. When placebo is included in the graph, there appears to be a dose response. However, with the placebo data removed, there is no trend of increasing improvement with increasing dose.

Further, the sponsor has presented the results of the drug-placebo comparisons on the primary outcome by study week.

In Study Can-23, statistically significant between-treatment differences in the autism patients (N=24-26 depending upon the week) first emerge at about Week 2, and persist throughout the remainder of the study. In Study USA-150, statistically significant differences emerge at Week 2 and persist throughout the remainder of the trial. The between treatment differences (drug-placebo differences in the mean change from baseline scores) by week in each study are presented below for the observed cases analyses:

CAN-23		USA-150	
Week 2	-3.7	Week 2	-5.9
Week 3	-4.5	Week 4	-6.5
Week 5	-4.5	Week 6	-9.8
Week 7	-3.9	Week 8	-11
Week 8	-5.4		

In Study CAN-23, as far as I can determine, the maximum dose was to have been achieved by Weeks 2-3, and in USA-150, the maximum dose was to have been achieved by Week 3. In CAN-23, there seems to be no obvious increase in effectiveness over time, although there does seem to be somewhat of an increase in effect over time in USA-150 (although the dose presumably was no longer increasing beyond Week 3). This does suggest that there may be a lag in the amount of time it takes for the drug to have its maximum effect.

In any event, although these analyses are crude, and the effect (if any) of dose is difficult if not impossible to tease out, certain disturbing questions are clearly raised.

As a result of the dosing regimens employed in the trials, it appears that patients were often titrated to doses close to the maximum allowable doses. These maximums were presumably achieved within 2-4 weeks of treatment initiation, and in Study CAN-23, there is no obvious increase in effect beyond this early timepoint, and in Study USA-150, there appears to be an increase in effect over time, also beyond the time that the maximum dose has been reached. Further, as Dr. Duan has demonstrated, there is no obvious relationship between dose and effect (again, see his scatter plot, page 13). Taken together, these observations suggest that there is no evidence for dose response. If it is true in Study USA-150 that the treatment effect continues to increase after the maximum dose has been achieved, this suggests a lag in time between the attainment of an effective dose and the maximum treatment effect associated with that dose. If this is true, the sponsor has employed a dosing regimen that inappropriately increased the dose before a patient's maximum response could have been observed. Such a regimen (unfortunately not uncommonly employed in clinical trials) will have the effect of titrating patients to unnecessarily high

doses. Further, as described, the data actually do suggest that these higher doses may not increase response.

Reaching unnecessary high doses in a trial is never appropriate, but it may be considered to be acceptable if these doses are not associated with unacceptable risks. In these trials, however, a number of observed risks, and potential risks not observed, raise questions about the acceptability of the doses achieved in the trials.

In particular, there was an extremely high rate (importantly increased compared to placebo) in these trials of somnolence, increased appetite and weight gain, extrapyramidal symptoms, fatigue, and constipation. Additionally, the rates for automatisms, dizziness, tachycardia, and confusion, although considerably lower than those events previously listed, were importantly greater than those in the placebo patients (although it is true that the number of patients with these latter events was small). Further, there was a considerable increase in plasma levels of prolactin in risperidone-treated patients, the long-term consequences of which are not well known. It is, however, important to note that only 2 patients discontinued the studies because of these adverse events.

Of considerable concern also is the potential risk of tardive dyskinesia (TD), a potentially irreversible and devastating complication. There have been post-marketing reports of TD in pediatric patients being treated with risperidone, including at least one case that persisted after discontinuation of the treatment (at least for one week, which is the maximum follow-up we have), and several cases occurred in the NDA database.

COMMENTS

The sponsor has submitted the results of (b) (4) randomized controlled trials that they believe establish the effectiveness of risperidone as a treatment for the irritability associated with autism. Two of these trials were randomized parallel group placebo controlled trials of 8 weeks duration, and one used a randomized withdrawal design. The two parallel group 8 week studies clearly demonstrate statistically significant differences between drug and placebo on their primary measures as well as on various secondary outcomes.

As the review team notes, however, interpretation of the randomized withdrawal study is problematic, because it is unclear what the primary outcome was, and the results of the analyses the sponsor performed on the endpoint defined in different ways were inconsistent (one was significant, one was not). The review team recommends that the trial be re-analyzed, using only the “failure” criterion related to the “Irritability” subscale of the ABC, given that this is the primary claimed effect of the drug. I agree.

However, several other issues need to be addressed before we can conclude that substantial evidence of effectiveness has been demonstrated.

First, as Dr. Cai notes, we had previously raised the issue of pseudospecificity. That is, we have been concerned that any effects seen on measures of what has been called Irritability in patients with autism might be a manifestation of a more global effect of risperidone on other functions in these patients (and so the claim would be inappropriately narrow). Of at least equal concern in this regard, risperidone's effect, if any, on this symptom, might not in truth be restricted to autistic patients, but it might have an effect on Irritability in other clinical settings, so that concluding that it is effective (and, therefore, granting a claim) for use in autistic patients **specifically** might be considered an artifact of the fact that it has been studied only in autistic patients (hence the **pseudo**specific nature of such a claim).

On further reflection, I believe it is appropriate, all other things being equal, to approve a treatment for the Irritability of autism, without requiring a sponsor to perform studies in other settings in which “Irritability” occurs (in other words, to assess the specificity of the claim). The behaviors assessed in this study are clearly troublesome and patients would benefit by their control. Further, recent Agency precedent is consistent with granting claims for particular psychiatric symptoms for specific clinical settings (e.g., agitation in schizophrenia and in bipolar mania). Further, it is not immediately obvious that what is being called “Irritability” in this setting is identical to those behaviors that may resemble it in the context of other clinical settings; this would argue for, at least at this time, restricting such a claim to the specific behaviors studied.

In addition, we had discussed with the sponsor the likelihood that we would take this application to the Psychiatric Drugs Advisory Committee (PDAC), given the fact that this is the first application for this novel indication. Again, on further reflection, the team decided that this was not necessary, given our conclusion regarding the pseudospecificity issue and the clear positive findings on an outcome measure that appears, on face, to assess the domain of interest.

However, I am concerned that patients in these studies were exposed to doses that were unnecessarily high. As I have discussed earlier, the data at least suggest that 1) response does not increase with increasing dose and/or 2) there may be a lag in time between receiving a dose and achieving a maximum response to that dose, and 3) the doses in these studies appear to have been increased according to protocol before the maximum response was obtained, resulting in doses greater than necessary.

Although approving doses that are too high is always problematic, it is particularly problematic when those doses give rise to a significant risk of adverse events. In this case, patients experienced high rates of somnolence, fatigue (it is of particular concern that these terms may have been used to

describe, in some proportion of patients, the same clinical event; if this is true, the true rate of somnolence may be considerably greater than that reported), increased appetite, weight gain, extrapyramidal symptoms, and constipation. Rates of tachycardia, dizziness, confusion, and automatisms were lower, but considerably greater than those in patients on placebo. In addition, mean plasma levels of prolactin were significantly elevated in the drug-treated patients; the (long-term) clinical consequences of this are not known.

It is true that there were almost no patients who discontinued treatment secondary to an adverse event in the controlled trials of patients with autism. In longer term open label experience, about 8% of patients discontinued treatment secondary to adverse events. The most common single ADR responsible for discontinuations in the open label cohort was weight gain, which was the reason for discontinuation in 11/695 (1.6%) open-label patients. Next most frequent was headache (6/695; 0.9%), depression, and gynecomastia, each of which occurred in 5/695 patients (0.7%), and appetite increased and condition aggravated, each of which occurred in 0.6% of patients. No other single ADR was responsible for discontinuation in more than 0.4% (about 3) patients. However, it is not clear how many patients discontinued open-label treatment because of extrapyramidal symptoms. The sponsor reports that 0.4% of patients discontinued due to "extrapyramidal disorder", and 0.3% of patients discontinued for each of the following: dyskinesia, dyskinesia tardive, hyperkinesia, and hypertonia. I cannot tell if these represent distinct patients. Further, 0.4% of patients discontinued due to "anxiety" and 0.3% of patients discontinued secondary to "nervousness" and 0.1% due to "agitation". I cannot tell if any or all of these terms represent akathisia.

Of perhaps even greater concern, however, is the possible risk of TD. There were at least 2 cases of TD reported in the NDA database (both in open-label, non-autism studies, and which resulted in drug discontinuation), and several reported from the post-marketing experience. It is generally believed that drugs in this class can be associated with TD, and that the incidence is likely to increase with increasing dose.

Clearly, the appropriate way in which to adequately answer the question of what dose(s) is (are) effective is for the sponsor to perform a well-designed, multiple fixed dose study. Only with such a design can the effectiveness of various specific different doses be assessed. In my view, such a study must be done. Must such a study be performed prior to the approval of risperidone for this indication?

There are several factors in favor of approving the treatment prior to the performance of such a study.

First, risperidone is unequivocally effective in the treatment of the irritability of autism, and there is nothing currently approved for this indication. Although there were numerous adverse events seen at quite high rates, the number of patients who discontinued treatment as a result of these events is quite small, even in the longer term open label experience (one might expect that certain adverse events might have been tolerated in the relatively short term controlled trials, but not tolerated in the long term; this appeared to be somewhat true [less than 2% of patients discontinued the controlled trials because of an ADR, compared to about 8% in the open label experience]). Further, the division has obviously been aware of the design of these controlled trials (indeed, we had two pre-NDA meetings with the sponsor), and never raised an objection to the flexible dosing regimen. (b) (4)

Arguing in favor of requiring an adequate fixed dose study prior to approval are several factors.

First, and primarily, approving the application at this point, with dosing recommendations based on the regimen used in the trials (b) (4) will very likely result in many patients receiving excessive doses. Not only will this result in unacceptable rates of acute adverse events, but it will likely also increase the risk of TD, a totally unacceptable risk if it can be avoided. Further, we would expect that plasma levels of prolactin will be elevated chronically, with unknown clinical consequences. Further, although it is true that there are currently no approved treatments for the irritability associated with autism, risperidone is obviously an approved drug. Consequently, not approving the application at this time will not prevent practitioners from prescribing it as they see fit.

In my view, the critical factor in deciding whether or not the application can be approved at this time is whether or not we can write labeling that can reasonably ensure that patients will be treated with a dose that is both effective and associated with an acceptable risk of adverse events. Is this possible at this time?

First, I do not believe that providing dosing recommendations that closely mirror the dosing regimens used in the trials is acceptable. As discussed above, I believe that these regimens will likely result in the use of unnecessarily high doses, with attendant risks (especially in the long-term).

(b) (4)

(b) (4)

Will such a dosing regimen reliably provide patients with a dose that is both safe and effective? There are a number of questions that need to be answered in this regard.

First, it is not obvious how long the period of observation should be at each dose before one could be sure that the maximum (or no) response has been attained. The results of Study RIS-USA-150 can be interpreted to mean that response continues to improve for many weeks after titration has stopped, although the results of CAN-23 do not necessarily suggest this. It is not obvious to me, at this point, that we can know what such a duration should be.

In addition, if the rate of (observed and potentially worrisome unobserved) adverse events is unacceptable with the dosing employed in the trials, how can we be sure that the alternate proposal described above will result in a more acceptable adverse event profile?

In my view, a dosing regimen that starts at a low dose that is increased quite slowly (and only if it is necessary to do so) can reasonably be expected to produce a lower incidence of adverse events than a more rapid regimen that might result in higher doses being attained. Of course, we cannot know with certainty what incidence of any (particular) adverse event will be associated with any particular (low) dose (that is, we do not have evidence that lower doses than those studied will be associated with a lower incidence of ADRs than was seen in the trials, and, even if we presumed that these lower doses would result in lower incidences of adverse events, we cannot know what this lower rate of ADRs would be [and, therefore, whether this lower rate would be acceptable]).

Ultimately, I believe that a dosing regimen of the sort being discussed can be expected to result in a lower rate of adverse events than was seen in the trials, but it is still difficult to know if the rate seen (of any particular ADR of concern) will be acceptable. However, before we consider the acceptability of the ADRs seen with such a regimen, it is critical to determine if such a regimen can be expected to reliably produce an effective dose (assuming the duration of observation question raised above can be adequately addressed).

Given the dosing regimen used in the trials, it is difficult to know what the effective dose is. This is unfortunately true for almost all studies that utilize a

flexible dosing regimen. The regimens used in these studies both presumably directed prescribers to titrate the dose according to clinical effect. Of course, we have no idea what criteria the investigators actually used to decide whether or not to increase (or decrease) the dose. (b) (4)

the sponsor would need to address the questions raised here before we could find this an acceptable proposal. If we were to find such dosing recommendations acceptable, the sponsor must still perform a fixed dose study in Phase 4.

The review team has identified several other issues they believe the sponsor should address prior to approval (e.g., they request the sponsor re-analyze growth data, obtain more data on the effects of the drug on glucose metabolism and cognitive function, provide more detailed pharmacokinetic data, re-code particular verbatim adverse event terms, and provide information on the time course of certain significant adverse events). I agree that these requests should be forwarded to the sponsor.

I believe one additional request for data needs discussion.

Several members of the team have recommended that juvenile animal studies be completed prior to approval. A review of the record shows that we have never insisted that the sponsor perform these studies prior to approval, although we have had numerous communications with them on this matter. Further, I believe that, if we can be convinced that the current data can support appropriate dosing recommendations, we should not delay approval for the (potentially substantial) amount of time it would take to complete these studies. On the other hand, if a new controlled trial will be required prior to approval, I believe the animal studies should be completed before the re-submission is made, and I believe that the clinical study can commence before the animal studies are completed.

In summary, although the sponsor has clearly demonstrated the effectiveness of risperidone as a treatment for the irritability associated with autistic disorder, it appears that many patients received doses at or near the maximum permitted doses. Given that the studies utilized flexible dosing, we cannot determine if these higher doses were necessary; that is, we have no good dose response data. Importantly, there were high rates of significant adverse events, and concerns raised about the risk of these and other adverse events (e.g., TD) in the long term that might be dose related. Because we believe that patients may

have received unnecessarily high doses and that chronic treatment with these doses may be deleterious, the sponsor will need to perform a multiple fixed dose study in order to adequately characterize the dose response. I am willing, however, to entertain the possibility that the current data can support adequate dosing recommendations at this time, although there are a number of questions that would need to be addressed before we could come to that conclusion. If we can be convinced of this, the sponsor will be required to perform an adequate dose response study in Phase 4.

For these reasons, then, I will issue the attached Approvable letter.

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/s/

Russell Katz
6/18/04 02:14:33 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M

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

DATE: October 5, 2006

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products (DPP)
HFD-130

TO: NDA 20-272/SE1-036 (Risperdal Tabs)
NDA 20-588/SE1-024 (Risperdal Oral Solution)
NDA 21-444/SE1-008 (Risperdal M-TAB)

SUBJECT: Recommendation to take Approval Action for Risperdal (risperidone) in the Treatment of the Irritability associated with Autistic Disorder in Children and Adolescents
(This memo should be filed with the August 10, 2006 Response to Approvable Letter of the above referenced NDA)

1. BACKGROUND

Johnson & Johnson PR&D, LLC (JNJPRD) submitted above referenced supplemental NDAs for use of risperidone in the treatment of autistic disorder in children and adolescents (5-16 years of age) on December 19, 2003. On July 14, 2006, the Division issued an approvable letter following our review of the sponsor's January 2006 submission in response to the items listed in the non-approvable letter dated May 19, 2005. A teleconference meeting with the sponsor was held on July 26, 2006 and discussed proposed draft labeling and other components of their planned response to our July 14, 2006 letter. On August 10, 2006, JNJPRD submitted a complete response to the Division's July 2006 approvable letter.

This August 10, 2006 submission was reviewed by Ikram Elayan, Ph.D., Pharmalogy/Toxicology Reviewer (review dated 9/27/06), Andre Jackson, Ph.D., the Office of Clinical Pharmacology (OCP) reviewer (review dated 9/11/06), Lourdes Villalba, M.D., Safety Reviewer, DNP, (review dated 9/27/06), and June Cai, M.D., Medical Officer, DPP (review dated 10/04/06).

2. PHARMACOLOGY/TOXICOLOGY

We asked that the sponsor perform an additional juvenile rat study using a higher dose (eg. 2.5 mg/kg) and a juvenile dog toxicology study as a Phase 4 commitment. The sponsor has agreed to conduct these studies and included protocol outlines in their approvable response. Dr. Elayan concluded that the proposed study designs of the juvenile animal studies appear acceptable. As recommended by Dr. Villalba, we would ask the sponsor to include measurement of Insulin-like

Growth Factor (IGF-1) levels and assessment of long bone growth in the dog study. I refer to Dr. Villalba's review for detailed discussion on available hormonal data in clinical trials. See also a brief overview of this issue in clinical data section below.

3. CLINICAL PHARMACOLOGY

We requested a Phase 4 Commitment in the form of a fixed dose, placebo-controlled, parallel study to determine the lowest effective dose of risperidone in this indication. Dr. Jackson judged the sponsor's commitment to conduct this Phase 4 study is a complete response. The sponsor also agreed (b) (4)

4. CLINICAL DATA

4.1 Efficacy Data

The Division, in prior action letter, has acknowledged that JNJPRD demonstrated efficacy of risperidone for this indication, but asked for a fixed dose study to identify the lowest effective dose. As stated in clinical pharmacology section above, the sponsor has agreed to conduct a fixed dose, placebo-controlled study as part of their Phase 4 commitment.

4.2 Safety Data

Glucose Metabolism

In terms of glucose data, we asked the sponsor to conduct a phase 4 glucose metabolism study including insulin sensitivity and the sponsor has agreed to do so. The sponsor plans to conduct this in combination with the clinical pharmacology study. The glucose metabolism part of the study will evaluate the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. As stated by Dr. Cai in her review, the sponsor's response is acceptable to her and I agree as well. We have obtained the sponsor's commitment for submitting a protocol on or before December 30, 2007 and also for submitting the final study report by March 31, 2010.

Hyperprolactinemia and Growth Hormone Data

Dr. Villalba reviewed labeling changes on hyperprolactinemia subsection and available clinical data (b) (4) measurements in pediatric trials. As she suggested, the team has concurred that the labeling should comprise a statement noting the percentage of risperidone treated patients with hyperprolactinemia (b) (4) The sponsor has agreed to include a labeling statement that 49% of risperidone treated patients showed elevated prolactin level compared to 2% of patients who received placebo in the pediatric clinical trials (b) (4)

Although the sponsor indicated 12 subjects had GH excess, there seemed to have limitations in interpreting the GH data as the collection methodology was not well controlled and these levels were not age adjusted levels. In addition, there could be a wide range of variation in GH in this age population. The (b) (4) .

(b) (4)

. We have asked the sponsor to incorporate measurement of growth hormone (GH) and Insulin-like Growth Factor (IGF-1) in the hormone assessment section of the Phase 4 study and the sponsor has agreed to do so.

In addition, we will recommend the sponsor to conduct a separate study to assess the effect of long-term risperidone treatment on the growth, development, and sexual maturation of children and adolescents. This is not part of the Phase 4 Commitments.

Brain edema and Cardiac death cases

Dr. Cai reviewed the sponsor's response on additional clinical information of those cases with brain edema and of 4 cardiac deaths, mostly from the post-marketing reports. Based on the information provided, no further judgment or conclusion can be made on these cases at this time. As previously planned, we have initiated consultation with the Office of Surveillance and Epidemiology (OSE) on the issue of brain edema and should also consult with OSE on the cardiac death cases as Dr. Cai categorizes her underlying concerns on these 4 cases.

Safety Update and Pharmacovigilence Data

As can be seen in Dr. Cai's review, she reviewed and commented safety update information on SAEs from ongoing and completed pediatric trials, and pharmacovigilence data from the period of 3/1/05-2/28/06.

Based on the reviews of the information provided in this submission, there were no additional significant safety concerns that would preclude an approval action for this sNDA.

5. FOREIGN REGULATORY ACTION

According to the sponsor, the autistic indication has been approved in Sweden and Switzerland since January 16, 2006. (b) (4)

6. LABELING

The sponsor has included the language in the labeling based on our comments for suggested labeling changes in the July 14, 2006 letter and discussions during the July 28, 2006 teleconference. In the approvable letter, we asked the sponsor to calculate the average number of days for responders who remained stable, to provide definition of responder and relapse, and to insert the change in weight, height and BMI in the labeling. We also asked the sponsor to insert new SAEs experienced by children and adolescents in the adverse reactions section of the labeling. Specifically, we asked the sponsor to include two cases of tardive dyskinesia (TD) in the pediatric use section of the labeling. The sponsor agreed and included the TD information in this August 10, 2006 version. In addition, we asked the sponsor to revise the language in pediatric use section on hyperprolactinemia and galactorrhea. The majority of the labeling changes made by the sponsor in the August 10, 2006 submission were acceptable, but we did make additional changes.

Our additional changes include some modification of the labeling language in pediatric use section, subsection hyperprolactinemia, and inclusion of SAEs (eg. granulocytopenia) which were not in the last approved version in the adverse events section of the labeling. (b) (4)

(b) (4)

6. CONCLUSION AND RECOMMENDATION

I conclude that the sponsor has submitted sufficient data to support the efficacy and safety of risperidone in treatment of the irritability associated with autistic disorder in children and adolescents. The sponsor has provided commitment to conduct the required Phase 4 studies. We have reached agreement on the labeling. The review team is in agreement that the Division approves this supplemental NDA.

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/s/

Ni Aye Khin
10/5/2006 03:06:12 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: July 6, 2006

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products (DPP)
HFD-130

TO: NDA 20-272/SE1-036 (Risperdal (b) (4)
NDA 20-588/SE1-024 (Risperdal Oral Solution)
NDA 21-444/SE1-008 (Risperdal M-TAB)

SUBJECT: Recommendation of Approvable Action for Risperdal (risperidone) in the Treatment of Irritability associated with Autistic Disorder in Children and Adolescents
(This memo should be filed with the January 16, 2006 submission of the sNDA)

1. BACKGROUND

Risperdal (risperidone) is currently approved for the treatment of schizophrenia and for the short-term treatment of acute manic and mixed episodes associated with Bipolar I Disorder in adults. It is available as oral tablets (strength of 0.25, 0.5, 1, 2, 3, or 4 mg), oral solution (1mg/mL, minimum calibrated volume of 0.25mL) and M-TAB oral disintegrating tablets (0.5, 1 or 2 mg).

Johnson & Johnson PR&D, LLC (JNJPRD) submitted above referenced supplemental NDAs for use of risperidone in the treatment of (b) (4) in children and adolescents (5-16 years of age) on December 19, 2003. The application included positive results from two short-term, 8 weeks, placebo-controlled trials with the irritability subscale of the Aberrant Behavior Checklist (ABC-I) as the primary efficacy end point. The co-primary efficacy measures of the study RIS-USA-150 was the change from baseline to end point in a clinical global impression change (CGI-C) scores. The study RIS-CAN-23 which was conducted at Canadian sites enrolled pediatric patients (ages 5-12 years) with pervasive developmental disorder (total N=79) including Autistic Disorder subset (N=55) while the pivotal U.S. study RIS-USA-150 (Part 1) enrolled solely pediatric patients (total N=101; ages 5-17 years) who met the DSM-IV criteria for Autistic Disorder.

In the study RIS-USA-150 (Part 1), subjects received either placebo or a starting dose of risperidone 0.25 mg or 0.5 mg at bed time depending on subject's baseline weight of <20 kg (15-20 kg) and ≥20 kg, respectively, titrated up to a total daily dose of 0.5 to 3.5 mg by Day 4 to a twice daily dosing schedule. Following this part, 63 subjects were maintained on an open label phase treatment with risperidone for 4-6 months depending on responder status (Part 2). 39 subjects who maintained a positive response participated in the 8-week, double-blind, randomized withdrawal part of the study (Part 3). Responder status was defined as: demonstrated ≥25% improvement in Irritability subscale (ABC-I) from baseline of the Part 1 double-blind treatment phase, and "much improved" or "very much improved" on the CGI-C scale. In both parts (2 & 3) of this study,

risperidone was given once or twice daily as a flexible dose according to weight (up to 4 mg/day for subjects weighing <45 kg and up to 6 mg/day for subjects weighing ≥45 kg). The Part 3 results (N=32) demonstrated a significantly lower relapse rate in the risperidone group (12.5%) compared with the placebo group (68.8%). Relapse was defined by the occurrence of both of the following events: Clinical Global Impression of Change (CGI-C) score of much worse or very much worse than baseline ratings (week 16) for 2 consecutive weeks and an increase of ≥25% in the ABC-I score from baseline entry into the randomized withdrawal phase.

On June 18, 2004, the Division (DNDP at that time) issued an approvable action letter outlining our concerns about identification of a minimally effective dose and the risk of adverse events that may be more likely to occur with long-term treatment with risperidone (eg. tardive dyskinesia, persistent hyperprolactinemia, weight gain, etc.). In November 2004, the sponsor submitted a response to the FDA comments. The Division then issued a non-approvable (NA) letter on May 19, 2005, stating that JNJPRD response was inadequate in terms of their proposed dosing, specifically, the initial dosing recommendation and if doses greater than the starting doses confer any additional benefit for this patient population. The Division asked for an additional fixed dose trial to adequately evaluate dose response.

On December 7, 2005, the Division held a meeting with the sponsor acknowledging that the Division was persuaded by the arguments, as stated in the August 16, 2005 Briefing Documents, by the sponsor in response to the NA letter. In the meeting minutes, it was documented that the FDA found JNJPRD's position on adverse events acceptable in that the AEs reported in the autism studies were largely mild to moderate in severity, and qualitatively similar to AEs reported in adults. The Division indicated that the sponsor would need to conduct a fixed dose study to explore a dose response but offered to discuss labeling based on the available data. It was recommended to the sponsor to conduct additional analyses for the dose response as suggested in a publication by Sheiner et. al., while the Division acknowledged that this post-hoc analysis may not provide any new information given the limitations of the clinical trial design.

On January 16, 2006, JNJPRD submitted a complete response to the Division's May 19, 2005 Not Approvable Action letter incorporating the Division's agreement at the December 7, 2005 meeting.

This January 16, 2006 submission was reviewed by Ikram Elayan, Ph.D., Pharmalogy/Toxicology Reviewer (review dated 6/12/06) on the Juvenile Rat Toxicity Report. June Cai, M.D., Medical Officer, DPP (review dated 6/29/06; addendum dated 7/5/06) reviewed the efficacy dose analyses and dosing recommendation, the sponsor's response to safety concerns cited in the NA letter and safety information including glucose and prolactin data. A consultative review (dated 6/1/06) was done by Andre Jackson, Ph.D., from the Office of Clinical Pharmacology (OCP) on the biopharmaceutic issues in this submission.

There were no CMC issues requiring reviews for this set of supplemental NDA. DSI clinical site inspections for pivotal clinical studies were conducted during the first review cycle of the sNDA.

2. PHARMACOLOGY/TOXICOLOGY DATA

Pharm/Tox review has concluded that the rat juvenile toxicology study was less than optimal as the sponsor could have used a dose higher than 0.63 mg/kg. It is recommended that the sponsor should perform an additional juvenile rat study using a higher dose (eg. 2.5 mg/kg). This could be

conducted as a phase IV study and may be added as a study arm to the other IND study (active metabolite of risperidone). In addition, it is also recommended that we ask for a juvenile dog toxicology study conducted as a Phase IV commitment. These items should be included in the action letter.

3. CLINICAL DATA

Dose-Response Analyses and Dosing recommendation:

The Division, in prior action letter, has acknowledged that JNJPRD demonstrated efficacy of risperidone for this indication, but was concerned that most study patients received doses near the maximum allowable dose. As recommended by the Division, the sponsor conducted the dose-response analyses including dose over time (mean dose by week), Sheiner analyses and made dosing recommendations based on the two short-term pivotal efficacy and safety studies, study RIS-USA-150 (Part 1) and RIS-CAN-23 (autistic disorder subset).

When mean dose by week is plotted superimposing on the mean ABC-I scores for study RIS-US-150, mean dose of both treatment groups increased through Week 4 and then reached to a plateau correlating with significantly improved ABC-I score during the same period; mean ABC-I score from Week 4 to 8 in the risperidone group continued to show improvement while no improvement was seen in placebo. In both treatment groups of study RIS-CAN-23, mean dose increased throughout the study. It correlates with the improvement of mean ABC-I score over time. The results showed that 90% of patients who showed a response received doses of risperidone between 0.5 mg and 2.5 mg per day.

As expected, it is still unable to determine the minimal effective dose due to the limitation of the study design which is different from the design used in Sheiner's method. Dr. Jackson pointed out in his review that the starting dose and the need for titration are not justified based on available data. I understand the clinical concern discussed by Dr. Cai that the patients will receive doses higher than effective and even higher than tested doses if the labeling does not provide the best information for prescribers on the effective doses. I also note her comment about the ideal situation that the starting dose and the titration intervals be established prior to approval. As the sponsor states in this submission, it is known that psychiatric treatment community has been prescribing this medication off-label. There is sufficient data to support that the efficacy of risperidone in treating irritability associated with Autistic Disorder. Given there is no treatment approved for this indication, I do not feel that lack of a minimal effective dose precludes approval of this application. I therefore believe that this indication should be approved provided that the description in the labeling reflects available trial data.

While I acknowledge (b) (4) In the pivotal study RIS-USA-150, the study drug was titrated up to a total daily dose of 0.5 to 3.5 per day by Day 4 to a twice daily dosing schedule. I have no objection to the sponsor's proposed dosing interval of (b) (4) However, I agree with both Drs. Jackson and Cai that the sponsor should conduct a fixed dose study in this patient population to give a better understanding in the lowest effective

dose, the dose titration schedule and interval. We should obtain the sponsor's commitment to conduct this as a phase IV study. We should also convey to the sponsor with Dr. Jackson's recommendation regarding the study design (i.e., a 6-week fixed dose study which consists of placebo, 0.125 mg and 1mg risperidone treatment arms using the 1 mg/mL oral solution). Given the fact that the minimum calibrated volume for the oral solution is 0.25mL, the sponsor may need to consider development of a lower dose strength for the 0.125 mg dose. We should mention this in the letter.

Safety Data

Adverse events, vital sign measurements, ECG data and other safety data submitted in the sNDA and in subsequent submissions were reviewed. I refer to Dr. Cai's reviews for detail. Her review dated June 2006 includes item by item comments on the sponsor's responses to safety concerns, in particular, clarification of EKG data, reanalyses of dyskinesia events, glucose related data and SAEs from ongoing pediatric studies (cut-off date of November 2005). I generally agree with her assessments and recommendations.

I would briefly describe prolactin data. In study RIS-USA-150 Part 1, the mean changes of prolactin level from baseline to endpoint (week 8) showed a significant elevation of prolactin level in the risperidone group compared to those in the placebo group, i.e., mean change of 0.79 (SD 6.016) ng/mL from 10.88 ng/mL at baseline (N=48) to 10.12 ng/mL at endpoint (N=38) for placebo group; mean change of 29.70 (SD 19.24) ng/mL from 9.39 ng/mL at baseline (N=46) to 39.36 ng/mL at endpoint (N=45) in risperidone group.

The Part 2 open label study consisted of subjects who received placebo in the double-blind period of the Part 1. The placebo non-responders (PNR) went to receive a 4 month open label treatment of risperidone; the placebo responders exited the study. In those subjects who received placebo in the Part 1 and then continued to the open-label part of risperidone, their prolactin levels were found to be 11.64 ng/mL at baseline (N=34), 10.91 ng/mL (N=30) at end of the double-blind Part 1, then increased to 33.55 ng/mL after 8 weeks of open-label risperidone in the PNR group (N=30); remained elevated at 29.15 ng/mL at the 4-month open-label endpoint (N=25). In those subjects who received risperidone in the Part 1 and then continued to the open-label part of risperidone, their prolactin levels were found to be 9.21 ng/mL at baseline (N=31), 44.66 ng/mL (N=29) at end of the double-blind Part 1, 36.5 ng/mL at the 4-month open-label endpoint (N=22). For all subjects in the open-label phase regardless of their status in Part 1, their mean prolactin level was elevated at 32.59ng/mL at the endpoint of the open-label Part. The sponsor reported that no subjects in RIS-USA-150 had a prolactin level above 100 ng/mL.

The sponsor also analysed prolactin data from two other studies in which risperdone was used in treatment of disruptive behavior disorder (DBD): RIS-INT-79 (a longer term study with a 3-month double blind phase) and RIS-INT-84 (1 year open-label extension). The sponsor notes the mean prolactin level at baseline for RIS-INT-79 was 8 ng/mL, and for RIS-INT-84 was 15 ng/mL. The sponsor reports that the level returned to near baseline levels at month 6 and month 9 in subjects who withdrew from the study RIS-INT-79, but increased again with the readministration of risperidone treatment in study RIS-INT-84. The sponsor further states that the mean prolactin levels are similar in those who were treated for 12 months in RIS-INT-84 and those treated for 21 months continuously. Despite these statements, I did not see any specific information on how they

reach this conclusion. Based on the limited information provided, it is difficult to interpret the meaningfulness of prolactin data from these risperidone DBD studies.

Recently, the published results from the NIMH sponsored multicenter, multiphase, multi-drug CATIE study showed elevation of prolactin levels in association with use of antipsychotics. In particular, a greater increase from baseline in prolactin levels was observed with risperidone compared to olanzapine, quetiapine ziprasidone and perphenazine. This is considered by the Division as significant finding and should be reflected appropriately in the labeling.

In terms of glucose data, I agree with Dr. Cai that we ask the sponsor to conduct a phase IV glucose metabolism study including insulin sensitivity. I refer to Dr. Cai's reviews for more detailed review of glucose and weight gain data. As pointed out by Dr. Cai in her review regarding the updated SAE data from the ongoing risperidone trials, brain oedema was listed as one of the findings in a subject who experienced neuroleptic malignant syndrome. Based on the limited information available for this case, it is difficult to determine the causal relationship of this event to the study drug. I agree with Dr. Cai's recommendation that we request the Office of Surveillance and Epidemiology (OSE) to conduct a search in post-marketing data.

Overall, there was no unexpected AE data in this submission. Based on the reviews of the information provided in this submission, no particular patterns of safety signal were raised.

3. LABELING

The sponsor's proposed language in the labeling needs to be modified. In particular, the sections that will need modifications are as follows:

(b) (4)

Our proposed labeling and our comments for the suggested labeling changes should be included in the action letter.

4. CONCLUSION AND RECOMMENDATION

The sponsor has been able to establish the efficacy and safety of risperidone in treatment of irritability associated with autistic disorder based on the available study results. I recommend the Division issue an approvable action letter with our proposed labeling for this claim.

The Division may consider approval of this supplemental NDA provided that an agreement is reached between the sponsor and the Agency regarding the language in the labeling. In addition, a postmarketing commitment from the sponsor should be obtained in that they conduct the phase IV studies for nonclinical pharmacology/toxicology (juvenile rat and dog toxicity studies) and a fixed dose study in combination of a clinical pharmacology/biopharmaceutics study to identify the lowest effective dose and a clinical safety study to assess glucose metabolism in this patient population. Given the fact that the minimum calibrated volume for the oral solution is 0.25mL, the sponsor may need to consider development of a lower dose strength for the 0.125 mg dose.

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/s/

Ni Aye Khin
7/7/2006 03:25:05 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: May 19, 2005

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for a Not Approvable Action for Risperdal for the Treatment of (b) (4)

TO: 20-272/SE1-036
20-588/SE1-024
21-444/SE1-008
[Note: This memo should be filed with the November 18, 2004 original submission of these NDAs.]

BACKGROUND

NDA 20-272 Supplement 36 and its associated risperidone formulation supplements presented data in support of a new claim Risperdal for the treatment (b) (4) The Division issued an Approvable Action letter on June 18, 2004 without labeling. Though not completely clear in the action letter, the Division will not approve risperidone for the treatment of (b) (4) Though the initial review established that risperidone was effective at reducing irritability compared to placebo, labeling was not included because the clinical trials showed that children had received doses that were associated with adverse events that could likely be reduced at a lower dose. The two studies that were submitted in the original supplement were both flexible dose studies. In these studies, doses were increased every three days to what was considered a maximally effective dose, but there was evidence that this schedule did not allow for patients to show therapeutic response to a dose prior to the next incremental increase. Hence children likely received doses that were too high and suffered adverse events that were likely unnecessary even though efficacy was established.

The first submission failed to identify a minimum effective dose or provide an empirical basis for a starting dose of 0.5-mg. Generally speaking, solving the problem of identifying a minimum effective dose and a dose relationship between the effective doses and co-incident adverse events requires the performance of a fixed dose trial where a minimum effective dose can be identified along with the adverse events that might be associated with that dose level. Even so, the sponsor was afforded the opportunity of making an argument that they could identify a minimum effective dose and an optimally safe and effective dose titration based on the data that they had already collected.

The sponsor was also asked to respond to seven other points:

1.-Juvenile animal toxicity studies in both rat and dog must be conducted. Please refer to our email dated May 26, 2004 for specific recommendations on the draft protocols submitted April 2, 2004 and May 17, 2004. If we determine that you do not need to perform a dose-response study prior to approval, the animal studies may be completed and submitted in Phase 4. If we determine that a dose-response study must be performed prior to approval, the juvenile animal studies should be performed while that study is on-going, and the reports should be submitted with the re-submission to the application.

2. We believe the analyses of part III of study USA-150 are problematic, because different relapse criteria are described in different parts of the protocol (the results of one analysis are significant and the results of the other are not). In our view, including global measures in the relapse criteria would be inappropriate, given the restricted nature of your proposed claim. Therefore, we request that you re-analyze the study using a Kaplan-Meier survival analysis and the definition of relapse based only on the 25% worsening of ABC Irritability subscale change.

3. Height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores). This analysis of height and weight data is accomplished by computing the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time (e.g., at least 3 months).

4. Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose (b) (6) These discrepancies should be explained.

5. Provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of the drug:placebo odds of each common, drug-related (occurring in at least 5% of drug-treated patients and at least twice as frequent than the placebo rate) adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

6. Provide an analysis of quantitative ECG data from study CAN-23.

7. It was noted that you collected PK samples in the pivotal trial RIS-USA-150 and a population pharmacokinetic analysis was planned. Requests for submitting the PK data were previously sent; however, it appears that these data were not submitted to the Agency. Please submit the analysis of this population PK data.

8. You should examine glucose metabolism (at a minimum, evaluating fasting blood sugars) in a cohort of children that includes substantial numbers of patients with Autistic Disorder. You should also perform an adequate assessment of cognitive function in patients with Autistic Disorder. If it is determined that a fixed dose controlled trial will be required prior to approval, these measures may be assessed at that time. If the fixed dose study is not required prior to approval, these assessments may be performed in Phase 4.

9. You should examine the verbatim terms coded as "somnolence" and "fatigue" to determine if these terms represent a similar clinical phenomenon; if they do, of course, the incidence of

this event should be re-calculated. In addition, you should perform a re-analysis of verbatim terms subsumed under the various preferred terms that represent abnormal movements and extrapyramidal symptoms to ensure that we have a complete understanding of the incidence of these specific events. We are particularly concerned that events coded as "nervousness", “agitation”, and "anxiety" may represent akathisia.

10. You should fully evaluate the time course of the important adverse events, including the time of onset and the duration of their persistence.

June Cai, MD was the primary Clinical Reviewer, and John Duan, PhD was the primary Office of Clinical Pharmacology and Biopharmaceutics (OCPB). There was no new studies submitted supporting safety or efficacy with this response. There were however, several analyses of the previously submitted data for supplement 036. There were no preclinical data submitted with this response though the sponsor must ultimately submit juvenile animal studies for risperidone. There were, likewise, not CMC data submitted with this response. My comments on each item in the June 18, 2004 action letter follow the format of that letter below.

Summary of Sponsor Response and Reviewer Recommendations

(b) (4)

[redacted]

This re-analysis of the previously submitted data fails to provide a clear rationale for starting autistic children at 0.5-mg/day. The 0.5-mg starting dose is associated with toxicity that may not be necessary. I agree with Dr Duan that the uncertainties pertaining to the dosing recommendations still remain.

The sponsor makes the argument that further studies should not be required prior to approval because of the lack of an approved treatment for autism. This is a rhetorical argument that fails to be compelling in the face of large rates of drug related somnolence and fatigue combined with lack of information on a minimum effective dose and optimum titration for the following reasons:

1. (b) (4)
2. (b) (4)
   risperidone is marketed and widely available to all clinicians on an unrestricted basis that care for autistic children.
3. The studies on which the sponsor wishes to base the approval for autism are already published and widely known.

Therefore, I recommend that the Division take a Not Approvable Action on Supplement 36 because it appears that the questions about minimum effective dose and dose titration require further studies. I

believe that approving risperidone without empirical information on a minimum effective dose or an optimal dose titration scheme would not better inform clinicians or provide an otherwise unavailable treatment to this patient population. If risperidone was not available (b) (4) then perhaps speculation on dosing recommendations in labeling along with a phase IV commitment to perform such studies could be acceptable; however, this is not at all the case. Risperidone use in the treatment of (b) (4) is widely known, widely used and there is little known about its safe use beyond the information in these two already published studies. In fact, contrary to the sponsor's opinion, I believe that withholding FDA approval of risperidone better serves autistic children than approving it now and getting the information later. I therefore recommend that the sponsor perform one or more fixed dose studies to establish the minimum effective dose and optimal dose titration scheme for the use of risperidone in patients with (b) (4) prior to its approval for this indication.

1. **Juvenile animal toxicity studies in both rat and dog must be conducted**- No studies were included. I concur with the previous instructions to the sponsor on this point.
2. **Re-analyze part III of study USA-150 using a Kaplan-Meier survival analysis and the definition of relapse based only on the 25% worsening of ABC Irritability subscale change** -I believe that the sponsor adequately responded to this question. Using the new definition of time-to-relapse, the mean time to relapse was 14 days for the placebo group and 55 days for risperidone group (p=0.008, Chi-square [1 df]=6.94). Study USA 150 part II was a 4-month open-label treatment phase. (b) (4)
3. **Height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores)**.-I believe that the sponsor adequately addressed this question. There appears to be an increase in the weight z-score with treatment with Risperdal. Autistic children have slightly numerically greater increases in weight than Disruptive Behavior Disordered (DBD) children, but the changes appear to be roughly similar for the 180-day period over-which the autistic children were observed. There was a smaller but consistently positive change in height z-score for both the autistic and DBD children. The change in height z-score was not great enough to offset the increases in BMI that essentially mirrored the changes in weight z-score.

Baseline and End Point Z-Scores for Weight, Height, and Body Mass Index (BMI)						
Exposure Days	**Change in Z-Scores**					
	Autistic Patients			**DBD Patients**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
≥ 90 Days						
Weight (kg)	57	0.44	0.66	846	0.41	0.48
Height (cm)	55	0.16	0.34	646	0.15	0.43
BMI (kg/m^2)	54	0.45	0.73	669	0.40	0.63
≥ 180 Days						
Weight (kg)	28	0.55	0.49	676	0.43	0.50
Height (cm)	26	0.19	0.28	501	0.16	0.45
BMI (kg/m^2)	26	0.55	0.61	523	0.42	0.67

4. Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements - I believe that the sponsor adequately addressed this point. It appears that the four investigators in question were placed on the "missing information list" in error. Their financial disclosure information was apparently available and they had no significant conflicting interests.

5. Provide a reanalysis of the effect of demographic variables on adverse event reporting rates-I believe that the sponsor adequately addressed this point in their response. As Dr Cai notes, except for somnolence, gender effect didn't impact the incidence of adverse events listed in the above table. Based on Breslow-Day *p*-value (0.03), there was gender effect on incidence of somnolence: Female subjects were significantly more predisposed to somnolence than males in risperidone treated group. There were no detectable differences between racial groups in the incidence rates of adverse events based on the small numbers of subjects in the respective ethnic groups.

6. Provide an analysis of quantitative ECG data from study CAN-23- Additional clarification on this point is still necessary. Dr. Cai notes that only 66 ECG tracing values were reported as available for analysis, yet the tables in the response account for 77 patients. There were 79 subjects in the study (risperidone n=40; placebo n=39). The sponsor stated that tracings from Dr Shea's site (n=12) were not available, plus 1 subject refused to consent to an ECG at Dr Leisher's site. This should leave 66 available ECG tracings for analysis.

7. Please submit the analysis of this population PK data. -I believe that the sponsor adequately responded to this point. The data were not submitted with the previous supplement and are presented in this submission. The sponsor's analysis supports their contention that risperidone metabolism in the autistic population is similar to that of children with DBD. Dr Duan's review details this data. He contends that there is still an outstanding question about the volume of distribution appearing higher in extensive metabolizers.

8. You should examine glucose metabolism (at a minimum, evaluating fasting blood sugars) in a cohort of children that includes substantial numbers of patients with Autistic Disorder. You should also perform an adequate assessment of cognitive function in patients with Autistic Disorder. If it is determined that a fixed dose controlled trial will be required prior to approval, these measures may be assessed at that time. -Dr Cai states that this point was not adequately addressed by the sponsor.

There were no fasting glucose data available on autistic subjects. The sponsor presented a cohort of fasting glucose data from DBD patients and stated that this should suffice and that "Since no important safety profiles were observed between DBD patients and autistic patients, a separate study of glucose metabolism doesn't appear to be warranted." Dr Cai states, "Considering both autism and diabetes mellitus, especially type I diabetes, are autoimmune related diseases and that first degree relatives of autistic patients have higher incidence of type I diabetes, I don't think one can assume or conclude that glucose metabolism in autism is the same as that in DBD patients based on this preliminary assessment from one study on DBD."

I agree with Dr Cai; however, I do not believe that such a study needs to be performed prior to a potential approval. Type I diabetes is autoimmune and attacks pancreatic islet cells. Atypical antipsychotic exacerbated or induced diabetes appears to affect insulin sensitivity and is largely reversible with discontinuation. Therefore, potentially disturbed glucose metabolism in the treatment

(b) (4) with atypical antipsychotics should likewise be reversible with discontinuation of treatment. It is important to study the effects of glucose regulation in autism with this treatment but I think that this could be done as a phase 4 commitment.

Cognitive data from RIS USA 150 was submitted but appears un-interpretable. Dr Cai states that the numbers of subjects at endpoint were more than those at baseline for all tests. In addition, from the original submission, a total of 101 subjects were in the study: 49 in risperidone group and 52 in placebo group. Thus, the percentage of subjects who had these assessments was small. She concludes that it is difficult to make any meaningful interpretation of the cognitive assessment presentation. I concur.

9. You should examine the verbatim terms coded as "somnolence" and "fatigue" to determine if these terms represent a similar clinical phenomenon; if they do, of course, the incidence of this event should be re-calculated. In addition, you should perform a re-analysis of verbatim terms subsumed under the various preferred terms that represent abnormal movements and extrapyramidal symptoms to ensure that we have a complete understanding of the incidence of these specific events. We are particularly concerned that events coded as "nervousness", "agitation", and "anxiety" may represent akathisia. I believe that the sponsor has adequately addressed this point with regard to somnolence and fatigue. Dr Cai staes that the problems with coding of extrapyramidal events is still present.

When combined, the incidence of these two adverse events (fatigue or somnolence) was 88% in the risperidone group versus 29% in the placebo group. The relative risk of the combination was unchanged from the relative risk of 3.1 for somnolence by itself. This re-enforces the need for further studies at lower doses.

Dr Cai notes the following problems with coding extrapyramidal effects:

- Akathisia is coded to "hyperkinesias." In addition, all terms related to restlessness were also coded under "hyperkinesias." –Hyperkinesia included terms related to increase activities as well as terms of akathisia and restlessness.
- Akinesia is coded to "hypokinesia."
- Terms related to slowness were coded to either "bradykinesia" or "hypokinesia." –Hypokinesia included akinesia, terms related to decrease movement as well as those related to slowness.
- Most symptoms coded under "dyskinesia" seem to be typical symptoms of "tardive dyskinesia." -- Currently, only four events of "tardive dyskinesia" are recorded.
- Terms already coded under "dystonia" seemed appropriate; however, many events that probably should be coded as "dystonia" were coded under other terms. For example, three cases of "stiff tongue" and one case of "tongue stiffness" were coded as "tongue paralysis," which probably should be considered as "dystonia." Another example is "jaw stiffness" which is coded as "tetany" instead of "dystonia." In addition to rigidity of limbs and muscles, "stiffness" and "stiff neck" were also coded as "hypertonia" which could likely be coded as "dystonia" since these subjects received benztropine for their symptoms of stiffness.
- Many items in the category of "muscle contractions involuntary," such as grimacing, lip smacking or repeatedly wipes inner lip, facial movement or tics, head tilting or rocking, and eye blinking or winking of eyelid, should be considered as "tardive dyskinesia" as well.
- Parkinsonism is not listed but coded under the term "extrapyramidal disorder." – The preferred term, "extrapyramidal disorder" is not used as a general term to include other symptoms in this category as it should be.

- Most tremor related terms were appropriately coded as “tremor” except for “lip tremor.”

I agree with Dr Cai that these terms should be recoded and re-analyzed with attention to the above critique. Dr. Cai also suggests using the akathisia subscales from the ESRS, Simpson-Angus and AIM scales to examine differential effects on akathisia.

10. You should fully evaluate the time course of the important adverse events, including the time of onset and the duration of their persistence-I do not believe that the sponsor has adequately responded to this point. It appears that they have analyzed relative risk differences over time and translated these differences into conclusions about durations of the events in question on relatively short studies. I am particularly concerned about somnolence and EPS associated with atypical antipsychotic use in autism. We would be less concerned about acute somnolence or EPS if patients habituated to them. This analysis appears to discuss rates of spontaneously reported adverse events and not solicited events. Events of longer duration may not be reported spontaneously if the patients or parents have already reported them on one or more previous visits. Somnolence as well as EPS should be formally measured in the future fixed-dose study that I recommend.

Safety Update-This safety update review did not produce evidence of adverse events that were likely drug related and either unexpected or unlabeled. I do not believe that there are any changes that need to be made to labeling based on this particular safety update.

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/s/

Paul Andreason
5/19/05 08:17:13 AM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: June 7, 2004

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation of Approvable Action for Risperdal in the Treatment of the Symptoms of Irritability in Children Autistic Disorder

TO: File, NDA 20-272 Supplements SE1-036
[Note: This memo should be filed with the December 19, 2003 original submission of this NDA and likewise filed with 20-588/SE1-024 and 21-444/SE1-008.]

1.0 BACKGROUND

Autistic Disorder (autism) is a syndrome of mental retardation that begins in early childhood and persists throughout life. Its prevalence is estimated at from 2-20 per 10,000 individuals. The causes of autism are unknown. There are no approved treatments for autism and many current off-label treatments focus on relief of the irritability that is part of the autistic syndrome. Many of the atypical antipsychotics are used off-label to treat the irritability-like symptoms of autism; however, this is the first drug to present an application for the use of an atypical antipsychotic drug for the treatment of the irritability-like symptoms of autism.

There is no evidence that risperidone treats the mental retardation or pervasive disruption of childhood development that are the core features of Autistic Disorder. The focus of this application was on whether or not Risperdal was safe and effective for the relief of the irritability-like symptoms that are associated with autism. It is usually not the habit of the Division to approve drugs based on what might appear to be pseudo-specific effects of a drug on a disorder that is poorly understood; however, since there were no treatments for autism, the drug class was regularly used off-label for these symptoms, and there was little controlled trial data to support treatment for any part of autism, the Division decided to accept applications for the treatment of the irritability-like symptoms associated with autism based on the same logic that the Division (b) (4) We therefore decided not to take this particular supplement to the Psychopharmacological Drugs Advisory Committee (PDAC) at this time.

2.0 CHEMISTRY

As risperidone tablets are already approved, there were no CMC issues requiring review for this NDA.

3.0 PHARMACOLOGY

The Pharmacology-Toxicology Team review pointed out that sponsor had not performed juvenile animal studies in risperidone. The sponsor acknowledged this is and proposed outlines for juvenile rodent and non-rodent studies. The sponsor suggests that they perform these animal studies as a phase 4 commitment. The Pharmacology Toxicology Team recommends that these studies be completed prior to approval.

4.0 BIOPHARMACEUTICS

John Duan, PhD was the primary OCPB reviewer. A single dose PK study in 6 pediatric patients with autistic disorder was provided. Dr. Duan judged that the PK in general seemed to be consistent with that in adults. However, the sponsor concluded that the relative bioavailability of the active moiety is 3-fold higher than that in adults and other pediatrics. He noted that the sponsor collected PK samples in the pivotal trial RIS-USA-150 and a population analysis was planned. Requests for submitting the PK data were sent to the sponsor. However, he states that these data were not submitted to the Agency. I concur with Dr Duan that the sponsor should submit the analysis of this population PK data for review prior to approval of the Clinical Pharmacology section of labeling.

(b) (4)

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5.0 CLINICAL DATA

The primary clinical reviewers were June Cai, MD and Greg Dubitsky, MD.

The sponsor submitted two trials in support of this application. These studies were designated USA-150 and CAN-23. Both of these studies were double blind, placebo controlled, multi-center, randomized controlled trials. Both studies used the Irritability symptom subscale of the Aberrant Behavior Checklist (IS-ABC) as the primary efficacy variable.

5.1 Efficacy Data

Study USA 150

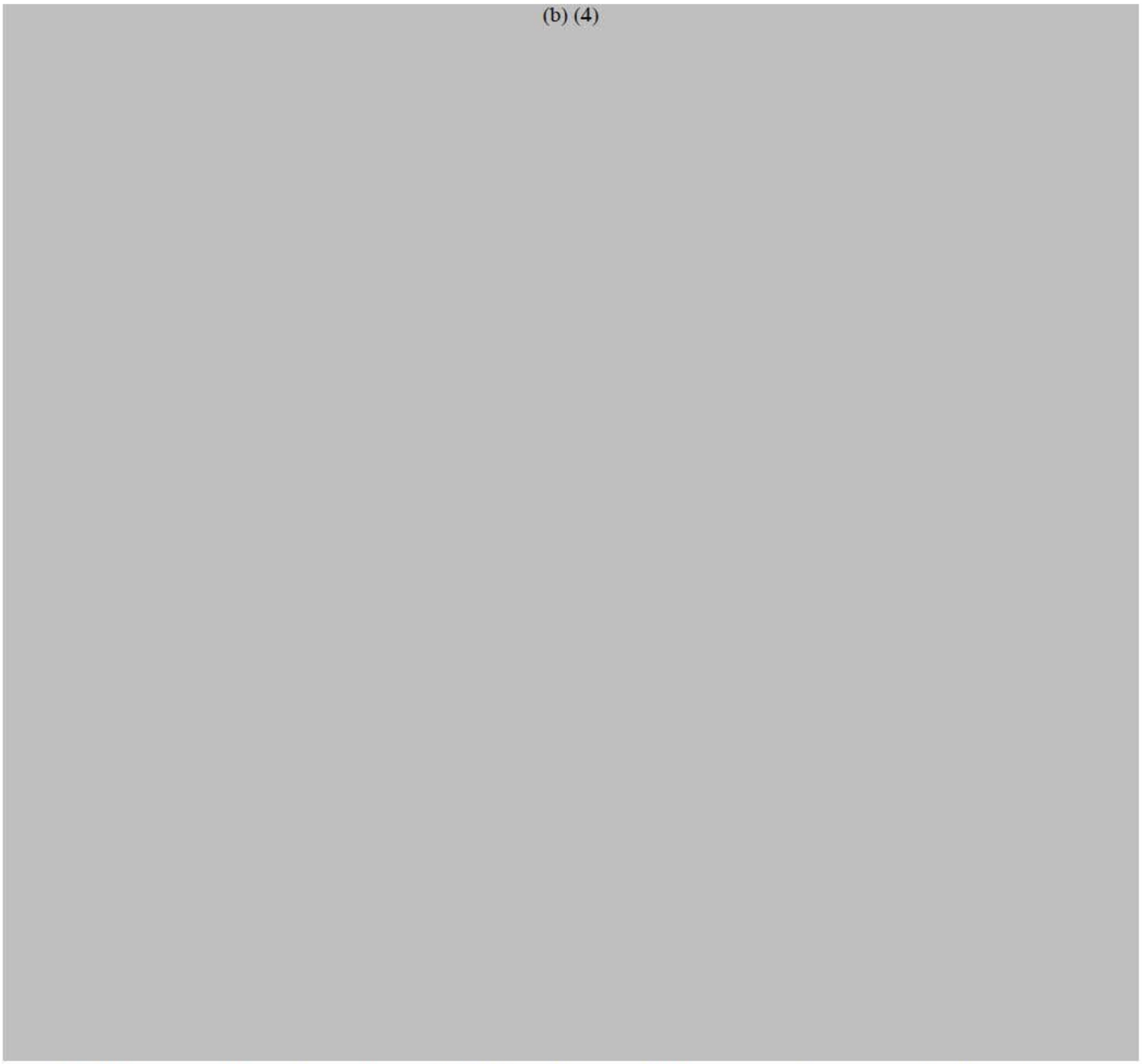
USA-150 had two controlled trial phases that can be considered as two separate clinical trials. Part I was a short term treatment phase and part III was a randomized withdrawal phase that was preceded by an open-label treatment phase of 4-months' duration.

USA-150-Part I was an 8-week, randomized, double-blind, parallel group, multi center trial. The study medication dosage was flexible, based on weight categories, ranging from 0.25mg to 2.5mg (for weight between 20kg and 45kg) or 0.5mg to 3.5 mg/day (for 45kg and over) of risperidone tablets versus placebo. This phase of the trial included 101 autistic children aging 5-16 years (Risperdal n=49; placebo n=52). The primary efficacy analysis was based on the change from baseline in the IS-ABC of the ITT population using LOCF to impute for missing data.

Results from part I of USA-150 showed that Risperdal was superior to placebo in reducing symptoms on the IS-ABC (treatment difference of -11.4 units in favor of Risperdal on a 45 point total possible scale, $p<0.001$). OC analysis produced similar results even with a third of the placebo patients

dropping out versus only 6% of the risperidone treated patients discontinuing from study. Based on these results, I believe that USA-150 part I represents a positive study in support of the claim that risperidone is effective in treating the irritability-like symptoms associated with Autistic Disorder.

(b) (4)



CAN-23 was an 8-week, randomized, double-blind, parallel group, multi-center trial. The study medication dosage was flexible (based on weight), ranging from 0.02 to 0.06 mg/kg/day of risperidone oral solution (concentration 1mg/ml) versus placebo. This study included patients with both Autistic and Pervasive Developmental Disorder (PDD). Enrollment included 79 total patients divided into the two treatment groups of placebo and risperidone (placebo n=39, risperidone n=40). The primary efficacy variable was the IS-ABC. The primary analysis was an ANCOVA using LOCF imputation of missing data in the ITT population.

Results from CAN-23 showed that risperidone was superior to placebo in the treatment of irritability-like symptoms associated with autism. The treatment effect difference between placebo and risperidone on the IS-ABC was -5.6 units ($p<0.001$). Sub-group analyses for autistic and PDD patients showed similar treatment effect sizes and both were statistically significant despite the small number of representative patients. I therefore believe that CAN-23 represents a second positive trial in support of the claim that risperidone is effective in the treatment of the irritability-like symptoms associated with autism.

Conclusions on Efficacy

The sponsor presents two positive 8-week trials that support a claim that risperidone is effective in the treatment of irritability -like symptoms associated with autism. (b) (4)

5.2 Safety Data

The safety review by Drs Cai and Dubitsky was based on data from 821 pediatric patients who received risperidone in completed Phase 2/3 studies: 83 of these patients were autistic and 738 had disruptive behavior disorders (DBD) or other PDD (Pervasive Developmental Disorders). A total of 331 patients were exposed for 13 months or longer and 565 were exposed for 7 months or longer. In all, 625 patients received modal doses of 1.0 mg/day or more and 217 received a modal dose of 2.0 mg/day or greater. Mean exposures to risperidone, on a mg/kg basis, were roughly two times higher in the non-autistic children, so conclusions drawn from the non-autistic group for autistic children will likely err on the side viewing adverse events occurring more frequently and severely than in reality might be expected.

Their safety review revealed no previously unrecognized, significant safety findings associated with risperidone therapy in pediatric patients that would preclude approval of this supplement or require a major revision to Risperdal labeling. There were no deaths or serious unlabeled/unexpected serious adverse events in the studies of autistic children. There was one case of "extrapyramidal disorder" that resulted from a 10-fold accidental overdose (2-mg instead of 0.2-mg in a 5-year-old) and was considered serious as he experienced an oculogyric crisis; however, acute dystonia is a recognized and labeled adverse event with risperidone. There was no evidence of drug related treatment emergent suicidality or aggression.

I concur with the primary reviewers that conclusions regarding growth and sexual maturation during 3 years of open-label treatment are difficult to reliably verify based on the data provided in this submission. Tanner Stage progression has to be interpreted in terms of expected progression, which varies with age and gender. I agree that height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores). The sponsor may not be aware of our current approach to doing this using historical growth data. The Drs Cai and Dubitsky suggested that the sponsor analyze height data by computing the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time (e.g.,3 months). I concur.

(b) (4)

They note that there appeared to be no glucose analytes drawn or reported in the studies of autism. I concur with their recommendation that the sponsor make a phase 4 commitment to study glucose metabolism in this population given the new warnings in the adult population.

6.0 World Literature
A world literature review and mid-cycle literature update were provided. This produced over 600 references. These references were reviewed by both the sponsor and Drs. Cai and Dubitsky who felt that they did not reveal any previously unreported serious adverse events likely to be causally associated with risperidone.

7.0 Foreign Regulatory Action
To my knowledge, risperidone is not approved for the treatment of children with autism anywhere at this time.

8.0 Psychopharmacological Drugs Advisory Committee (PDAC) Meeting
As noted above we did not take this supplement to PDAC.

9.0 DSI Inspections
The following sites were inspected by the Division of Scientific Investigations (DSI):

- RIS-USA-150: Dr. McDougle (Indiana) and Dr. Aman (Ohio).
- RIS-CAN-23: Drs. Fleisher (Winnipeg), Shea (Halifax) and Turgay (Scarborough).

The DSI inspection actions are not final at this time; however, DSI provided us with a preliminary clinical inspection summary. There were several record keeping inaccuracies that if they represent isolated occurrences appear to be minor.

At the McDougle site in Indiana, Dr Khin stated that they found that the study site has made several data entry errors while creating the data listing for patient 5090 from the CRF. Dr Khin stated that there were approximately 20 errors for subject's 5090 baseline ABC score. She suggests the review division check the SAS data sets in comparison with correct ABC score for subject 5090. Her report was not completely clear about her concerns over other patients' data but in an e-mail she explained that she was only concerned about the effect that patient 5090 might have on the study outcome and that the remainder of her audit was acceptable.

The cause of this error with patient 5090 remains unknown. A re-analysis of the data from USA-150 excluding patient 5090 is not necessary as excluding this particular patient could not possibly change the overall outcome of this study. Other inaccuracies in reporting adverse events by some of the audited investigators do not effect the overall action for this supplement.

10.0 Labeling and Approvable Action

10.1 Labeling for Approvable action Letter
Draft labeling for approvable claims along with imbedded recommendations to the sponsor for draft labeling modifications are attached to this action letter.

10.2 Foreign Labeling
To my knowledge, risperidone is not approved for the treatment of children with autism anywhere at this time.

11.0 Conclusions and Recommendations

I recommend that the Division take an approvable action for this supplement. I recommend that the following items must be addressed to reach final approval:

- Perform a re-analysis of part III of study USA-150 using a Kaplan-Meier survival analysis and the definition of relapse based only on the 25% worsening of ABC Irritability subscale change
- Height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores). This analysis of height and weight data is accomplished by computing the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time
- Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose ((b) (6) .). These discrepancies should be explained.
- The sponsor should provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of the drug:placebo odds of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.
- An analysis of quantitative ECG data from study CAN-23 should be submitted for our review.
- It was noted that the sponsor collected PK samples in the pivotal trial RIS-USA-150 and a population pharmacokinetic analysis was planned. Requests for submitting the PK data were sent however we can not find that these data were not submitted to the Agency. The sponsor should submit the analysis of this population PK data for review prior to approval of the Clinical Pharmacology section of labeling.
- The Pharmacology-Toxicology Team review points out that the sponsor had not performed juvenile animal studies in risperidone. The sponsor acknowledged this is and proposed outlines for a rodent and non-rodent study. The sponsor suggests that they perform these animal studies as a phase 4 commitment. The Pharmacology Toxicology Team recommends that these studies be completed prior to approval.
- Commit to performing a phase 4 study of glucose metabolism in children that includes substantial numbers of patients with Autistic Disorder
- Commit to performing a closely monitored phase 4 study of cognitive function in patients with Autistic Disorder who are treated with risperidone.
- Reach agreement on draft labeling with the Division.

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/s/

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MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA #20272/S-036
(Cross References 20588/024 and 21444/008)

Sponsor:	Johnson & Johnson
Drug:	Risperidone
Indication:	Autistic Disorder in Children
Material Submitted	Response to July 14, 2006 Approvable Letter
Corresponding Date	August 10, 2006
Date Received	August 15, 2006

I. Background

The sponsor submitted NDA#20272/S-036 for the approval of risperidone in the treatment of irritability associated with autistic disorder in children and adolescents on December 19, 2003. The Division issued an Approvable (AE) Letter on June 18, 2004 after the review and subsequently, a Not-Approvable (NA) Letter after reviewing the sponsor's response to AE letter on May 19, 2005. The sponsor's response to the NA letter resulted in the issue of another AE letter on July 14, 2006. A teleconference was held between the sponsor and the Division on July 26, 2006 and the sponsor agreed to submit additional safety information and proposed labeling.

In this re-submission, the sponsor includes the following data:

- Protocol outlines of the Phase IV commitment for the proposed fixed dose placebo parallel controlled study and measurement of glucose metabolism and insulin resistance
- Additional clinical information of those with brain edema and cardiac deaths that we requested after our last review
- Safety Update on SAEs in all ongoing and recently completed pediatric trials
- Pharmacovigilance data of two consecutive six-month periods (March 1, 2005 to August 31, 2005 and September 1, 2005 to February 28, 2006)
- As requested, the sponsor also provides explanations about the purpose of obtaining growth hormone levels in this response despite there is no new data on growth hormone other than previously submitted.
- Worldwide regulatory update
- Proposed US labeling, with acceptance of the Agency requested changes in the most recent AE letter.

Our Safety Team will share part of the review work for this submission, (b) (4) The following of my review will focus on the rest of the information submitted.

Additionally, the Agency Pharmacology-Toxicology team will review the nonclinical juvenile rat toxicology study with higher dose which is also part of the sponsor's Phase IV commitments (please see Dr. Ikram Elayan's review for details).

II. Review of Clinical Data

1. Clinical study of Phase IV commitment: This will be a six-week, fixed-dose, parallel-group, placebo-controlled trial. Safety measure will include the metabolic parameters to assess glucose, fasting insulin, and insulin resistance. The sponsor plans to submit the protocol on December 15, 2006 and complete the study three years after the approval of the protocol.

   Reviewer's Comment: This plan appears reasonable. However, the short term study is probably not sufficient to reveal clinical meaningful changes in glucose metabolism. Data from long term study is probably needed. Also, the sponsor needs to make sure that the glucose obtained will also be fasting, at the same time they obtain the fasting insulin. When submitting to the Agency, the sponsor needs to submit the results of calculated "Insulin Sensitivity (SI)."

2. Additional clinical information of those with brain edema and of cardiac deaths, mostly in postmarketing reports, that we requested after our last review

   1) Information on cases of brain edema:

      For the two patients from the postmarketing database who died from neuroleptic malignant syndrome with coexisting brain edema or increased intracranial pressure, there is no new information added based on my examination of the re-submitted case descriptions. The sponsor provides the published literature on one of these postmarketing cases, Case #US-JNJFOC-20040908713. However, the referenced article (Litovitz TL, etc. 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. American Journal of Emergency Medicine Sept. 2004; 22 (5): 335-404) does not provide more detailed and helpful information.

      According to the CRF obtained from the sponsor, the subject who had cerebral edema in an ongoing trial (US-RIS-231), Subject #RO JNJFOC-20050700284, has a history of possible head concussion five years prior to the trial. Her baseline physical exam, including neurologic exam, was normal and urine toxicology was negative. The patient received starting dose of 0.5ml of risperidone (0.1mg/mL per sponsor's submission) and the dose was increased by 0.5ml daily. On the fourth day of the study, the

subject was taking 2.0ml (=0.2mg) of risperidone. The dose was stopped on the fifth day (b) (6) due to adverse events. The recorded AEs during this period are listed in the following table.

Table 1. Summary of the Recorded Adverse Events of the Brain Edema Case in Trial US-RIS-231

Dates	Adverse Events
(b) (6)	Insomnia Loss of appetite Dry mouth Skin rashes Orthostatic hypotension (first time) Nausea Block of thinking, delusions, palpitations, change of taste, and hypomnezia Orthostatic hypotension (second time) Disorientation, confusion, obmubilation Suicidal attempt Cerebral edema Delusional thinking (exacerbation of psychosis)

No concomitant medication was given during the first four days but the following medications were used afterwards:

Table 2. Summary of the Concomitant Medications Reported by the Sponsor in the Brain Edema Case in Trial US-RIS-231

Dates	Additional Treatment
(b) (6)	Zolpidem 5.0 mg for insomnia 5% glucose, saline and $NaHCO_3$ Lorazepam 1.0 mg for agitation Furosemide 10mg bid and Diazepam 20mg bid for cerebral edema Manitol 200mg for cerebral edema 5% Glucose plus saline iv Zyprexa 5mg/day, Zoloft 25mg/day, Xanax 0.25mg tid

The sponsor reports that after she had mental status changes, CT scan showed dilated ventricles and blunted cerebral contours and she was diagnosed as cerebral edema. There were no signs of infectious process and no prior CT scan is available. Her blood urea nitrogen was elevated at 44mg/dL, but creatinine was normal. Other lab tests (not specified) were also reportedly normal (not included in CRF). The subject was treated with manitol and subsequently given lorazepam and olanzapine. Her condition was described as "stabilized" but "continued to show signs of aggravated psychosis with no suicidal ideation." The investigator

considered this to be probably related to the study drug and informed the sponsor that the patient was "stable on treatment with olanzapine" after following up the patient in late July 2006. The sponsor states, "The patient's cognitive status has not been formally assessed, but there is no clinical evidence of cognitive or neurological deterioration." No follow-up tests or imaging study is mentioned in the submission. The sponsor explains that with further review, it is a case "likely due to a toxic metabolic encephalopathy secondary to dehydration."

Reviewer's Comment: The reason for increased BUN is not quite clear as serum creatinine usually increases during dehydration but it was within normal range in this patient. It is unclear to me what exact toxic metabolic process the sponsor was referring to with regard to the encephalopathy. It is also unclear when cerebral edema actually started. Although the rate of iv perfusion on (b) (6) is unknown, the iatrogenic cause of cerebral edema from iv fluid overload cannot be ruled out. This further confounds this case as to whether cerebral edema is drug related or not. There are no follow-up head CT scan and no discharge diagnosis submitted at this point despite the CRF indicates that the discharge date was (b) (6). As previously recommended, OSE review is in process for brain edema events in relation to risperidone use.

2) Information on the four cases of cardiac deaths:

These cases were reviewed again in this submission. Little information has been added for these cases. For case #AU-JNJFOC-20040305038, the sponsor only added a statement that autopsy results are being pursued. For another case (#ES-JNJFOC-20040706670), the sponsor provides follow-up information received on May 18, 2006 reporting negative serology to all microorganisms studied and pyrexia as added AE.

The rest of the two cases (Case #JAOCAN2000001168 and Case #NL-JNJFOC-20040907839) had no additional information at all in this submission.

Reviewer's Comment: The re-submitted information for these cases is not satisfactory. There is an additional cardiac death case in the Pharmacovigillance reports submitted by the sponsor (see Section 4). As discussed before, a consult to the OSE is needed for these cases.

3. Safety Update on SAEs in all ongoing and recently completed pediatric trials:

The sponsor reports that although no new pediatric studies have been initiated since the submission of January 16, 2006, three trials in children and adolescents (RIS-BIM-301 for bipolar disorder, RIS-SCH-302 and RIS-USA-231 for

schizophrenia) have completed treatment phases but the analyses are still in process. A long term trial in pediatric patients with schizophrenia is still ongoing.

Death

The only death reported in these trials was a subject in the ongoing open-labeling trial in adolescents with schizophrenia, RIS-USA-234, who committed suicide after being treated with Risperidone 4mg for 60 days. This case was reviewed in the Addendum of my previous review as mentioned above.

SAEs

SAEs by November 30, 2005 were included in the previous submission of January 16, 2006. The sponsor reports that the updated SAEs from additional pediatric trials were also included in their previous communication to the Agency on June 20, 2006 and June 26, 2006 (see Addendum of my previous review dated July 5, 2006). Compared to previous submissions in June, no new SAEs is reported for the three trials (RIS-SCH-302, RIS-BIM-301, and RIS-USA-231) recently completed.

More detailed information on a subject with cerebral edema is reviewed and summarized in the previous section.

With regard to the SAEs in the ongoing trial, RIS-USA-234, the sponsor summarizes those that were available as of March 31, 2006 in the following table (see Table 3 on next page).

Table 3. Incidence of Treatment-Emergent Serious Adverse Events in an Ongoing Long-Term Safety Study in Adolescents With Schizophrenia (Subjects Completed or Discontinued as of 31 March 2006) (JNJPRD--TRIAL RIS-USA-234 (31 March 2006): Intent-to-Treat Analysis Set)

AE System Organ Class Preferred Term	PLA/RIS (N=41) n (%)	RIS/RIS (N=256) n (%)	Total (N=297) n (%)
Total no. subjects with serious AEs	3 (7)	43 (17)	46 (15)
Psychiatric disorders	2 (5)	39 (15)	41 (14)
Psychosis	1 (2)	24 (9)	25 (8)
Suicide attempt[a]	1 (2)	13 (5)	14 (5)
Aggressive reaction	0	5 (2)	5 (2)
Depression	0	4 (2)	4 (1)
Anxiety	0	1 (<1)	1 (<1)
Emotional lability	0	1 (<1)	1 (<1)
Schizophrenic reaction	0	1 (<1)	1 (<1)
Body as a whole - general disorders	0	4 (2)	4 (1)
Injury	0	3 (1)	3 (1)
Lab values abnormal	0	1 (<1)	1 (<1)
Centr & periph nervous system disorders	0	1 (<1)	1 (<1)
Convulsions	0	1 (<1)	1 (<1)
Respiratory system disorders	0	1 (<1)	1 (<1)
Pharyngitis	0	1 (<1)	1 (<1)
Secondary terms	0	1 (<1)	1 (<1)
Inflicted injury	0	1 (<1)	1 (<1)
Gastro-intestinal system disorders	1 (2)	0	1 (<1)
Vomiting	1 (2)	0	1 (<1)

Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
'PLA/RIS' includes subjects who were in the placebo group of RIS-SCH-302 before entering RIS-USA-234.
Adverse events reported during treatment or within 30 days of end of treatment are included.
[a] Includes suicidal ideation (7), suicide attempt (6), and completed suicide (1), as described previously (Table 4).
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As of July 25, 2006, a total of 367 subjects had been enrolled and 339 of them had either completed or discontinued from the ongoing trial, RIS-USA-234. The sponsor reports additional 18 SAEs that were not reported. They are shown in the table below (see next page).

Table 4. Serious Adverse Events in an Ongoing Long-Term Safety Study in Adolescents With Schizophrenia (Subjects Ongoing or Enrolled *After* 31 March 2006)[a]

Adverse Event	USA-234
Schizophrenia	5
Schizophrenia paranoid	1
Suicide attempt	1
Depression	1
Depressed mood	1
Psychotic disorder NOS	1
Delusion	1
Abnormal behavior NOS	1
Bone sarcoma	1
Diabetes mellitus	1
Gastrointestinal hemorrhage	1
Nonspecific reaction	1
Overdose	1
Treatment noncompliance	1

Among them, the following two cases are relatively unexpected with this drug:

i) Bone sarcoma: The sponsor did not provide any detail information including the length of treatment of this subject in the submission. The possibility of drug-relatedness cannot be ruled out. However, this is the only case in the study. Considering this disease is relatively common in this age group, this possibility of drug relatedness is low.

ii) Gastroenteric hemorrhage: Subject FR-JNJFOC-20040303269 is a 14 year-old female with Tourette's syndrome and a history of asthma and weight gain from Pimozide. She also experienced intermittent rectal bleeding while on pimozide 2mg per day which was stopped and switched to risperdione 2mg twice daily in July 2003. However, she experienced diarrhea, abdominal pain, and rectal bleeding again in March, 2004 when her dose of risperidone decreased to 3mg per day. Gastric fibroscopy showed mamillated antral gastritis with helicobacter pylori and colonoscopy, subacute inflammatory lesions, most significant on the rectum, with presence of eosinophils on various biopsies. She was treated with omeprazol for one month and antibiotics for 7 days for gastritis as well as mesalasine 50mg/kg/day and hydrocortisone enema for 8 weeks for colitis. Her risperidone treatment didn't stop despite this and her condition improved (not recovered at the time of report). The physician hesitated between a diagnosis of inflammatory or drug-induced colitis. The reporter considered this possibly related to risperidone -- *I agree that the possibility of drug-induced colitis cannot be totally ruled out.*

With regard to the case of diabetes mellitus (Subject US-JNJFOC-20060205279), she is an 18-year-old female with schizophrenia who took Risperidone 3 mg/day for about four months (October 27, 2005 to (b) (4)). On the next day (b) (4) of

her last dose, the patient presented to the site for Visit 8 complaining of headache, blurred vision, polydipsia, polyphagia, and polyuria. A stat glucose was reported as 580 mg/dL. Concomitant medications included benztropine mesylate. The patient was treated with subcutaneous injections of regular insulin sliding scale after she was sent to the emergency room. On the following day (b) (6) she was admitted to the hospital due to elevated glucose. The subject was treated with intravenous insulin therapy while hospitalized. Her condition improved, she was considered recovered without sequelae four days later (b) (6) and discharged to go home.

Prior to her entry to RIS-USA-234, the patient participated in RIS-SCH-302 (risperidone 4 to 6 mg). While in RIS-SCH-302, the patient's blood glucose results were as follows: Visit 1 – 114 mg/dL, Visit 2 - 139 mg/dL, Visit 4 - 107 mg/dL Visit 5 - 109 mg/dL and Visit 6 - 190 mg/dL (normal values not provided). Review of her laboratory results during RIS-USA-234 showed that the patient's blood sugar was 167 mg/dL on Visit 2, and 190 mg/dL on Visit 4. The patient was referred for medical assessment of her blood sugar but did not follow through with these appointments.

The event has been changed from elevated blood glucose level to diabetes mellitus. The investigator considered this event severe in nature and the causality as possible.

Reviewer's Comment: Though it's unclear whether the glucose levels absolutely fasting, as it seems relatively high during her 2nd visit even in the first study she participated, and the initial glucose level seems borderline, considering the potential of risperidone to cause impaired glucose metabolism and the length of time she was on study drug, it is possible that this event is related to risperidone or was exacerbated by risperidone.

AEs Led to Discontinuation

Adverse events that led to discontinuation in these trials were submitted on June 30, 2006 (see Addendum of my previous review dated July 5, 2006 for details).

Other AEs of Clinical Interest

1) Concerning "Tardive Dyskinesia," we asked the sponsor to search this term in long term trials as opposed to short term trials. We also requested the sponsor to add these cases to the label. The sponsor again reports that there were 2 reports of tardive dyskinesia among the 1348 risperidone-treated patients in the pooled studies, including long-term ones, and agrees to add them to the label under PRECAUTIONS – Pediatric Use – Tardive Dyskinesia subsection.

2) With regard to growth hormone data, the sponsor reports that they were collected in several clinical trials for children or adolescents with disruptive behavior disturbances to investigate drug effects on growth and sexual maturation in this population. However, they were not explicitly described in the study protocols. Thus, there were no interpretations or commentary in their study reports. Detailed data is being reviewed by our safety team.

No other information is included in the Safety Update.

4. Pharmacovigillance (PV)

The sponsor's last PV report covers period through April 30, 2005. In this submission, the sponsor has submitted two PV reports of two consecutive periods as follows:

- Period of March 1, 2005 to August 31, 2005:

The sponsor estimated worldwide pediatric exposure from multiplying the percentage of risperidone prescriptions written for the age group of 5 to 17 years in June 2005 (b) (4) by the total person years of exposure for the period (b) (4) person months). Prescriptions in children ages 0-4 years accounted (b) (4) of prescription market share in June 2005, as risperidone was not approved for use in this age group. Hence, children ages 0-4 years of age are not included in the pediatric exposure estimate.[1] The total pediatric exposure for the 6-month period was approximately (b) (4) person-months or (b) (4) person-years. The sponsor believes that this estimation essentially reflects use of oral risperidone because the actual off-label use in this population is believed to be negligible and the intramuscular formulation of risperidone is not approved for any pediatric indication.

Death

There was one death in this age group reported during this 6-month period. Subject GB-JNJFOC-20050606265 was a 16 year-old male who received risperidone 1 mg daily for abnormal behavior (duration of treatment was not reported). On an unknown date, he experienced a 2-minute seizure from which he recovered. He then went to sleep and was found dead. Other concomittent medications were carbamazepine 1200 mg daily, clobazam 20 mg daily, and topiramate 50 mg daily for epilepsy. The CIOMS states "The death was unexpected and unexplained." Risperidone is regarded as suspected drug and others are "co-suspects".

Reviewer's Comment: This case was not included in the previous PV report, cut-off date, April 30, 2005. There were three cases in my previous review (see my previous review dated July 17, 2006). Thus, there have been four cases of deaths among children and adolescents with history of seizure that were treated with risperidone. Conclusions as to the cause of these deaths cannot be drawn clearly. Incidence of such sudden and unexplained deaths is reported as 0.0035 per patient year in epilepsy patients (Prod Info Lamotrigine, 2006). However, we don't know how many patients with epilepsy were treated with risperidone, and thus, the incidence of these patients who died. Currently, history of seizure disorder is listed as a precaution in risperidone labeling.

[1] Pediatric group mentioned hereafter refers to children and adolescents age 5 to 17 year-old.

SAEs

The numbers of spontaneously reported cases and serious cases in pediatric group and the all other age groups during this reporting period are shown in the table below. Cases of unknown ages were excluded. (Note: It is somewhat confusing that the sponsor refers the percentage of "serious cases" as serious adverse events in the text but later regards these serious cases actually include non-serious events as well. However, no definition for these "serious cases is provided in the submission. Thus, the numbers of serious cases here include more than the actual SAEs defined by the regulation.)

Table 5. Spontaneously Reported Cases and Serious Cases in Pediatric Group and Other Age Groups from March 31, 2005 to August 31, 2005

Age Group	Number Serious Cases	Total Number Cases	% of Cases Coded as Serious
5-17 years	65	210	31%
All other ages	726	1325	55%

The next table shows the rates and types of spontaneously reported cases by System Organ Class (SOC) in pediatric and all other age groups during this reporting period (see next page).

Table 6. Spontaneously Reported Cases by SOC in Pediatric Group and Other Age Groups from March 31, 2005 to August 31, 2005

System Organ Class	Number of Spontaneous Serious Cases		Percentage of Spontaneous Serious Cases		Proportional Ratio of Serious Cases[a]
	5 to 17 Years	All Other Ages	5 to 17 Years	All Other Ages	
Blood & Lymphatic System Disorders	1	22	1.54	3.03	0.51
Cardiac Disorder	6	81	9.23	11.16	0.83
Congenital, Familial & Genetic Disorders	1	4	1.54	0.55	2.79
Ear and Labyrinth Disorder	0	7	0.00	0.96	0.00
Endocrine Disorder	1	15	1.54	2.07	0.74
Eye Disorder	6	20	9.23	2.75	3.35
Gastrointestinal Disorder	4	51	6.15	7.02	0.88
General Disorders & Administration Site Conditions	10	174	15.38	23.97	0.64
Hepatobiliary Disorders	0	17	0.00	2.34	0.00
Immune System Disorders	1	4	1.54	0.55	2.79
Infections and Infestations	1	40	1.54	5.51	0.28
Injury, Poisoning & Procedural Complications	5	45	7.69	6.20	1.24
Investigations	17	115	26.15	15.84	1.65
Metabolism & Nutrition Disorders	10	61	15.38	8.40	1.83
Musculoskeletal & Connective Tissue Disorders	2	37	3.08	5.10	0.60
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	0	18	0.00	2.48	0.00
Nervous System Disorders	24	272	36.92	37.47	0.99
Pregnancy, Puerperium and Perinatal Conditions	0	5	0.00	0.69	0.00
Psychiatric Disorders	9	130	13.85	17.91	0.77
Renal & Urinary Disorders	1	25	1.54	3.44	0.45
Reproductive System & Breast Disorders	7	35	10.77	4.82	2.23
Respiratory, Thoracic & Mediastinal Disorders	4	44	6.15	6.06	1.02
Skin & Subcutaneous Tissue Disorder	3	34	4.62	4.68	0.99
Social Circumstances	1	1	1.54	0.14	11.17
Surgical and Medical Procedures	1	3	1.54	0.41	3.72
Vascular Disorders	1	40	1.54	5.51	0.28
Total Number of Serious Cases	**65**	**726**			

a: % of spontaneous serious cases in ages 5-17 years divided by the % of spontaneous serious cases in all other ages

Disproportionality was noted for children and adolescents with regard to the SOCs Congenital Familial and Genetic Disorders, Immune System Disorders, Surgical and Medical Procedures, and Social Circumstances, but there was only one case in each of these SOC categories among patients ages 5-17. Other SOC categories that show disproportionality are: Eye Disorders, Reproductive System, Breast Disorders, Metabolism and Nutritional Disorders, Injury Poison and Procedural Complications. Finally, the ones remain in Investigations are also higher in pediatric group.

The sponsor reveals that the 6 serious cases among pediatric patients in the Eye Disorders SOC contained the following preferred terms: Oculogyration (3 cases), Visual disturbance (2 cases), and Mydriasis (1 case). Considering oculogyration as extrapyramydal disorder rather than eye disorder, the sponsor excluded these events from both age groups (3 cases in pediatrics and 5 reports in all other age groups), there was still a slight disproportionality observed among pediatric patients for the Eye Disorders SOC. The sponsor reports, however, no

disproportionality was observed for this SOC in the cumulative dataset through April 30, 2005.

The sponsor reports that the 7 serious cases of the Reproductive System and Breast Disorders SOC include the following preferred terms: Priapism (4 cases), Gynaecomastia (1 case), Galactorrhea (1 case), Penile size reduced and Cryptorchism (1 case). Since priapism, galactorrhea, and gynecomastia are listed as possible adverse reactions in the current safety labeling for risperidone, the sponsor doesn't describe further details here. Events related to Reporductive System, including gynecomastia and galactorrhea. (b) (4)

As for priapism, the sponsor reports that the boys' ages were 10, 11, 14 year-old, but one with unknown age. The treatment indications of risperidone for these boys are attention deficit/hyperactivity disorder (2), bipolar disorder (1), and post-traumatic stress disorder (1). The duration of risperidone therapy before the onset of priapism was 3 months in 2 cases, and unknown in the other two. In two cases, the patients required hospitalization for the event. One case also had leukocytosis but there was no report of other blood cell abnormalities. The sponsor further reports that a cluster analysis of the 4 cases during this period (3 from the US and 1 from France) did not reveal a particular trend with respect to reporting source or related signs or symptoms, and none provided a batch or lot number. The sponsor also conducted cumulative analysis through April 30 2005 that showed 15 cases of priapism in pediatric patients and 138 cases of priapism in adults. The sponsor believes that based on the estimated (b) (4) person-years exposure to risperidone during this 6-month review period, and cumulative exposure through December 2004 of greater than (b) (4) patient-years in children and adolescents, the event of priapism has been reported very rarely both during this period and during cumulative postmarketing experience in pediatric patients overall.

As for the 10 serious cases of Metabolism and Nutritional Disorders, the sponsor doesn't present details in the result section but discusses 7 cases in the section of Area of Special Interest in the submission: Six of these reported are considered "serious" and one is "non-serious." (Since the sponsor includes both serious and non-serious events in the "serious cases," it is unclear whether the non-serious one presented is one of the so-called serious cases.) These six "serious" cases that include five reports of diabetes mellitus and one reports of hypoglycemia are summarized below.

- Subject BE-JNJFOC-20050303382 is a 9-year-old girl with a history of congenital hypothyroidism who was receiving risperidone 2 mg daily for abnormal behavior for approximately 6 months. She was also treated with levohyoxine supplement for less than a week at the time of reporting. Her weight gain was significant (17 kg) and she developed diabetes mellitus.
- Subject CA-JNJFOC-20050403212 is a child of unknown age and sex and with no relevant history reported who received risperidone 3 mg daily for

an unspecified indication and duration. No concomitant medications were reported. The patient developed non-insulin-dependent diabetes mellitus. Risperidone was discontinued and the patient "no longer required medication to manage the diabetic symptoms."

- Case US-JNJFOC-20050500070 is a male child of unknown age with no relevant history or concomitant medications reported, who received risperidone (dose and indication unspecified) for 7 years. The patient developed insulin dependent diabetes mellitus. It was unclear when the adverse event occurred.
- Case PT-JNJFOC-20050602672 is a 10-year-old boy who received risperidone 1.5 mg daily for the treatment of fragile X syndrome. No concomitant medication was reported. He developed insulin-dependent diabetes mellitus approximately 20 months after the treatment. At the time of the report, risperidone was being gradually discontinued and he was not recovered.
- Subject US-JNJFOC-20050701389 is a 6 year-old boy with a family history of type I diabetes mellitus. Concomitant medication was Adderall (dextroamphetamine/amphetamine). The patient was receiving risperidone 1 mg daily for aggression for 6 weeks when he developed polydipsia and polyuria. He was hospitalized and glucose levels were "in the 200-500 range" (units not provided) and hemoglobin A1C was 10.1. Urinalysis was positive for glucose and ketones and he is diagnosed with insulin-dependent diabetes mellitus. Outcome is unknown but the sponsor reports "action was taken with risperidone."
- Case DE-JNJFOC-20050900296 is a 16-year-old male, with no relevant history reported, who received risperidone 2 mg daily for an unknown indication and duration. Concomitant medication was methylphenidate., He reportedly had hypoglycemia (no laboratory values were reported). The patient also described focal seizures that were unobserved; EEG showed "no arguments for the occurrence of seizures". Risperidone was continued and the event outcome was unknown.

The sponsor further discusses other seven cases categorized as non-serious adverse events. These seven cases include the following Preferred Terms: Increased appetite (3 cases), Nausea and/or Vomiting plus Decreased appetite or Anorexia (2 cases), Hyperphagia and Hypoglycemia (1 case), and Dry mouth and Polydipsia (1 case). The sponsor states that the report of hypoglycemia (FR-JNJFOC-20050401016) was not documented by a glucose value, but was suspected by the treating physician after a reported event of malaise and asthenia in a 15-year-old male with psychotic disorder. The report of dry mouth and polydipsia was reported by a consumer, and involved an 11-year-old male with "abnormal behaviour" on concomitant desmopressin acetate for an unknown indication. Other cases also exhibited weight changes.

Reviewer's Comment: Potential change of glucose metabolism associated with risperidone has been a concern. The five patients presented by the sponsor in this

report developed diabetes mellitus after 6 weeks to years of risperidone treatment. Still, details of other 4 of the 10 "serious cases" are not unclear. Nonetheless, this further underlines the importance of the need of long term studies for glucose metabolism.

2) Period of September 1, 2005 to February 28, 2006:

For this reporting period, the sponsor also estimated worldwide pediatric exposure from multiplying the percentage of risperidone prescriptions written for the age group of 5 to 17 years from July to December 2005 (b) (4) by the total person years of exposure for the period (b) (4) person-months). Prescriptions in children ages 0-4 years accounted only for about (b) (4) of prescription market share from July to December 2005, as risperidone was still not approved for use in this age group. Hence, like the PV report of the previous 6-month period, children ages 0-4 years of age are not included in the pediatric exposure estimate. The total pediatric exposure for this 6-month period was approximately (b) (4) person-months or (b) (4) person-years. Again, the sponsor believes that this estimation essentially reflects use of oral risperidone because the actual off-label use in this population is believed to be (b) (4) of written prescriptions for risperidone and the intramuscular formulation of risperidone is not approved for any pediatric indication.

Deaths

There were 6 deaths in pediatric patients during this 6-month reporting period. Three of them were suicide: Overdosing resulted in hepatic necrosis (2) and death from hanging (1) – The sponsor reports these subjects did have risk factors for suicide and other three death cases lack sufficient clinical detail for clinical assessment. Below are case narratives for all 6 reports are provided.

The two deaths from hepatic necrosis cases (US-JNJ-FOC-20050901959 and US-JNJFOC-20050902338) are case reports from a single literature source (Watson WA, Litovitz TL, Rodgers Jr GC, et al. 2004 annual report of Poison Control Centers Toxic Exposure System. Am J Emergency Medicine 2005;23(5):589-666). They were both 14-year-old girls, with a history of suicide attempts.

- Subject US-JNJFOC-20050901959 was found minimally responsive by her mother, several hours after last being seen in her usual state of health. Her mother's bottles of olanzapine, risperidone, fluoxetine, and zolpidem were found lined up in front of the patient. Amounts ingested were unknown. no concomitant medications were reported. The patient was hospitalized and treated but died on the second day of hospitalization. Cardiac blood drawn approximately 16 hours following death revealed fluoxetine 2,500 mcg/L; norfluoxetine 600 mcg/L; mirtazapine <100 mcg/L; olanzapine 600 mcg/L; and zolpidem 200 mcg/L.

- Subject US-JNJFOC-20050902338 was presented to the hospital obtunded after being found with empty bottles of zolpidem, risperidone, and fluoxetine. There was one drug listed as concomitant medication, benzodiazepine (dose unknown). Although the primary suspect medication was listed as acetaminophen, laboratory studies revealed negative acetaminophen concentration. The patient was treated but died 2 days after presentation. Cause of death was suicide due to the combined effects of benzodiazepines, fluoxetine (2,500 ng/ml), and zolpidem (200 ng/ml).

Risperidone was not listed as prescribed for the patient in either case. In both cases, post-mortem examination revealed liver necrosis; Negative iron staining was mentioned in pathology report for the first case as well.

The third suicide case was subject US-JNJFOC-20060202084 who was a 12-year-old boy, died by hanging after approximately 4 years of treatment with risperidone. He had a history of depression and ADHD and was reportedly treated with oral risperidone 0.5 mg daily for "hyperactive compulsive disorder" and post-traumatic stress disorder. Concomitant medications (duration unknown) included sertraline 50 mg daily and methylphenidate hydrochloride (dose unknown). The patient had no history of illicit drug use and was reported to abstain from alcohol. Post-mortem blood results indicated the presence of sertraline hydrochloride but not risperidone.

The following two cases were treated with unknown dosage of risperidone for unknown indications for unknown durations and no concomitant medications were reported:

- Patient US-JNJFOC-20050902683 was a 6-year-old boy who was treated with risperidone. He experienced cardiac arrest and death. No further information was supplied.
- Patient DE-JNJFOC-20050906788 was a boy of unknown age with a history of mental retardation. He received presumably "low dosage" oral risperidone. His parents found him dead in his bed. The emergency physician ticked the box "suspected unnatural cause of death" on the death certificate. An autopsy was not done and the cause of death was unknown.

Finally, case 20060201308 describes a 17-year-old male with a history of bipolar disorder, bedwetting, and previous marijuana use (use of other illicit substances was denied) but family medical history was unknown. The patient was given the following medications: 1) Risperidone 0.5 mg daily (duration, and indication unspecified), 2) OROS methylphenidate 36 mg for for ADHD for unknown duration, 3) lithium 600 mg per day, and 4) ddAVP for bedwetting for several months. The patient was reported to be very athletic and enjoyed sports. He collapsed and was not able to be resuscitated despite "open heart massage." (event coded to Preferred Term Sudden death) while playing basketball. Five or six days before the fatal event, the patient's routine electrolytes and TSH were all normal

except for the lithium level being 0. It was reported that the patient had stopped all three psychotropic medications. His family physician told him to restart risperidone and lithium, and the patient reportedly had been on OROS methylphenidate, risperidone, and lithium during the 5 days prior to his death. The primary suspected drug was OROS methylphenidate and risperidone was considered co-suspect in this case.

Reviewer's Comment: There have been sudden death cases reported before (see my previous review) but many with unclear history or confounding factors, including cardiac history in some of these cases. Again, I recommend a consult survey by OSE for cases involving cardiovascular deaths.

SAEs

A total of 246 spontaneous case reports for risperidone involving pediatric patients age 5 to 17 year-old. One-third of these case reports involved serious adverse events. Case reports for other age groups (cases with age specified) during the same period are compared in the table below, half of which involved serious adverse events. (Like the PV report of the previous 6-month period, it is somewhat confusing that the sponsor refers the percentage of "serious cases" as serious adverse events in the text but later regards these serious cases actually include non-serious events as well. Nevertheless, from safety point of view, the numbers are not discounted but more inclusive instead.)

Table 7. Spontaneous Case Reports and Serious Cases in Pediatic Group and All Other Age Groups From September 1, 2005 to February 28, 2006

Age Group	Number Serious Cases	Total Number Cases	% of Cases Coded as Serious
5-17 years	81	246	33%
All other ages	865	1741	50%

The sponsor reports a total of 4070 spontaneous case reports for risperidone involving pediatric patients (ages 5 to 17 years) for the life of the product through February 28, 2006. Among them, 20.7% (844) are serious adverse events. For all other age groups, there were 28,796 completed case reports of which 10,147 are serious adverse events within the same cut-off date period.

The next table displays the distribution of cases considered serious by the sponsor (including events categorized as SAE and non-serious AE according the regulation) by SOC in pediatric group and all other age group. Disproportionality is noted for pediatric patients with regard to the SOCs Eye Disorders, Gastrointestinal Disorders, Endocrine Disorders, Metabolism and Nutritional Disorders, Reproductive System and Breast Disorders, Psychiatric Disorders, as well as Surgical and Medical Procedures. Nerveous System Disorder, Hepatobiliary Disorders, and Injury Poison and Procedural Complications are also

slightly more common in pediatric group. Additionally, more pediatric cases are pending investigations than those of all other age group.

Table 8. Distribution of Serious Cases by SOC in Pediatric Patients and in Patients of All Other Age Group from September 1, 2005 to February 28, 2006

System Organ Class	Number of Spontaneous Serious Cases		Percentage of Spontaneous Serious Cases		Proportional Ratio of Serious Cases[a]
	5 to 17 Years	All Other Ages	5 to 17 Years	All Other Ages	
Blood & Lymphatic System Disorders	4	45	4.94	5.20	0.95
Cardiac Disorders	6	94	7.41	10.87	0.68
Congenital, Familial & Genetic Disorders	0	2	0.00	0.23	0.00
Ear and Labyrinth Disorders	0	3	0.00	0.35	0.00
Endocrine Disorders	1	7	1.23	0.81	1.53
Eye Disorders	6	17	7.41	1.97	3.77
Gastrointestinal Disorders	13	62	16.05	7.17	2.24
General Disorders & Administration Site Conditions	12	197	14.81	22.77	0.65
Hepatobiliary Disorders	2	20	2.47	2.31	1.07
Immune System Disorders	0	4	0.00	0.46	0.00
Infections and Infestations	1	36	1.23	4.16	0.30
Injury, Poisoning & Procedural Complications	9	95	11.11	10.98	1.01
Investigations	18	156	22.22	18.03	1.23
Metabolism & Nutrition Disorders	13	95	16.05	10.98	1.46
Musculoskeletal & Connective Tissue Disorders	3	36	3.70	4.16	0.89
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	0	23	0.00	2.66	0.00
Nervous System Disorders	28	292	34.57	33.76	1.02
Pregnancy, Puerperium and Perinatal Conditions	0	8	0.00	0.92	0.00
Psychiatric Disorders	22	207	27.16	23.93	1.13
Renal & Urinary Disorders	0	26	0.00	3.01	0.00
Reproductive System & Breast Disorders	4	36	4.94	4.16	1.19
Respiratory, Thoracic & Mediastinal Disorders	3	69	3.70	7.98	0.46
Skin & Subcutaneous Tissue Disorders	2	30	2.47	3.47	0.71
Social Circumstances	1	12	1.23	1.39	0.89
Surgical and Medical Procedures	1	6	1.23	0.69	1.78
Vascular Disorders	1	43	1.23	4.97	0.25
Total Number of Cases	81	865			

The sponsor reports that the 6 serious cases among pediatric patients in the Eye Disorders SOC included the following preferred terms: Accommodation Disorder (1), Diplopia (1), Eye Disorder (1), Gaze Palsy (1), Oculogyration (1), Saccadic Eye Movement (1), and Visual Acuity Reduced (1). The sponsor agrees that case reports within this SOC do not suggest a particular pattern of concern; however, disproportionality is also observed among serious events for this SOC in the cumulative dataset (total 46 cases in pediatric patients) through February 2006, with Preferred Terms within the Eye Disorders SOC suggesting oculomotor disorders (Blepharospasm, Eye movement disorder, Eye rolling, Gaze palsy, Oculogyration, or Saccadic eye movement). Among them, the most commonly reported event was Oculogyration (12 events), followed by Miosis (6 events), Eye

disorder (5 events), and Visual disturbance (4 events). There were 1 or 2 serious reports each of Blepharospasm, Eye movement disorder, Eye rolling, Gaze palsy, Saccadic eye movement, or Strabismus. Documented risperidone doses (in 41 cases) range from 0.25– 85 mg, with 11 patients receiving doses of 4 mg or more. Only 2 cases are documented risperidone use for autism.

The 13 serious cases of the Gastrointestinal Disorders SOC included: Vomiting or Projectile vomiting (3), Abdominal pain (2), Pancreatitis or Acute pancreatitis (2 cases), Dysphagia (2), Constipation (1), Diarrhoea (1), Gastric disorder (1), Mouth ulceration (1), Salivary hypersecretion (1), and Swollen tongue (1). The 2 dysphagia cases were both reported in the context of Extrapyramidal disorders, which are listed in the Company's Reference Safety Information for risperidone.

The sponsor reviewed the case reports of abdominal pain and vomiting and reports that there is no evidence to suggest additional cases of (undiagnosed) acute pancreatitis.

The sponsor further reports that in the cumulative postmarketing dataset through 28 February 2006, a total of 15 cases of pancreatitis or blood amylase or lipase elevation in pediatric patients were received. Three (3) cases (US-JNJFOC-20031102009, US-JNJFOC-20031102076, NSADSS2003009984) reported isolated blood amylase increase, and 2 cases reported isolated lipase increase (EMADSS2001006754, NSADSS2001031768), without abdominal complaints. The remaining 10 cases reported pancreatitis. According to the sponsor, no disproportionality was seen for the events of Nausea, Vomiting, and Abdominal pain, and no disproportionality for acute or chronic pancreatitis, amylase or lipase increase for pediatric group. The two serious AEs in pediatric patients coded as "Pancreatitis acute" and "Pancreatitis" reported during this period are summarized below:

- Subject US-JNJFOC-20051101696 is a 12-year-old boy born with infantile pancreatic duct (not otherwise specified). Reportedly, he received "risperidone 1 mg, once a month for several years for the treatment of mood swings" as well as unspecified doses of valproate semisodium and sertraline hydrochloride for unclear duration. The patient developed pancreatitis and was hospitalized for 1 week. No relevant symptoms or laboratory data were reported. Risperidone (dose unknown) was continued, but action taken with other medications was not reported. The patient recovered (date unknown) from pancreatitis.

- Subject US-JNJFOC-20051103146 is a male child of unknown age with no reported relevant medical history. He received unknown doses (and formulations) of risperidone and olanzapine, sometime in 2002 to July 2004, as well as quetiapine fumarate for unknown duration. A diagnosis of pancreatitis was made on an unspecified date. Like the above case, no relevant laboratory findings were reported. Risperidone was discontinued.

Action taken with other treatment was not reported. The outcome is unknown.

Reviewers' Comment: Both of the pancreatic cases in pediatric group presented above lack of detailed history and laboratory information and are confounded by other concomitant medications (b) (5) .

Of the 13 serious cases of Metabolism and Nutritional Disorders listed in Table 8, the sponsor reports 10 serious cases of glucose metabolism within this 6-month period. The sponsor states that 8 of these 10 cases are newly diagnosed diabetes mellitius and the remaining 2 are hypoglycemia or blood glucose increased only. The sponsor considers 5 of these 10 cases lack of sufficient information such as history, dosage, treatment indication, and duration, and among others; 3 of these 5 cases are confounded with olanzapine. The rest of the 5 cases of diabetes mellitus are summaries below by the sponsor:

- "AU-JNJFOC-20050902626 (Report was received from a physician.) A 14-year-old girl (weight 130 lbs, height63 inches), who reportedly had no history of obesity and no family history of diabetes, received oral risperidone 2 mg daily for 3 months for hallucinations when she presented with insulin-dependent diabetes mellitus. Concomitant medications included citalopram hydrobromide. The patient's initial blood glucose of 11.7 mmol/L was discovered on screening, and was accompanied by weight loss and nocturia. Prolactin level was 2100 mM/L. Risperidone was discontinued and citalopram hydrobromide continued. The patient's blood sugar decreased to "normal," and insulin requirements ceased initially when risperidone was discontinued, but later her blood sugar increased, and insulin therapy was resumed. The patient continued to receive insulin, and risperidone was not reintroduced."

- "US-JNJFOC-20051103220 A 14-year-old adolescent male, weight of 59.3 kg, height of 163.1 cm, with a medical history of asthma, ADHD, oppositional defiant disorder, and developmental delay, received oral risperidone 2 mg daily (duration was unknown), per office visit of July 1997, for attention deficit disorder. The patient had a family history of adult onset diabetes (a maternal great-grandmother and an aunt who was diagnosed at age 30). Concomitant medications included clonidine, methylphenidate hydrochloride, and paroxetine hydrochloride. (b) (6) the patient was admitted to the hospital with new onset of insulin-dependent diabetes mellitus and diabetic ketoacidosis. Prior to his admission, he reported a 6-day history of nausea and vomiting as well as olydipsia and polyuria and a 5-pound weight loss. During hospitalization the patient responded well to insulin therapy, and he was discharged 5 days later. The patient was seen in the emergency room approximately 1 month after last hospitalization with a diagnosis of hyperglycemia. Both mother and patient reported non-compliance with dietary restrictions at

school. At the time of this report, the action taken for risperidone treatment and outcome were unknown."

- "SE-JNJFOC-20051105514 (Report was received from the Swedish health authority.) An 11-year-old boy, weight unspecified, with a history of autistic syndrome, mental retardation, sleeping disorders and aggressive behavior, was treated with oral risperidone tablets 0.25 mg (frequency unspecified) for an unknown indication. Concomitant medications include: alimemazine tartrate, carbamazepine, and dixyrazine (10 mg in the morning). A couple of weeks after risperidone treatment, the patient was hospitalized due to development of acute diabetes. Laboratory data taken 1 month prior to the treatment with risperidone indicated that the patient's blood sugar was "marginally raised," with a normal HbA1C. "It is thought that the raised blood sugar was stress induced as the patient was reported to be geared up prior to the taking of specimens." A "mildly raised" prolactin was also seen, and was reported to be "probably due to dixyrazine and alimemazine medication." However, the patient's blood sugar continued to rise above 20 (units unspecified) after the discontinuation of dixyrazine. Risperidone treatment was discontinued 2 months after the initiation, and the patient was treated with insulin. The events were reported to be ongoing at the time of this report."

- "FR-JNJFOC-20051205137 (Report was received from AFSSAPS). A 10-year old boy (29 kg), with a history of behavioral disorder and a family history of father with diabetes, was treated with oral risperidone (formulation unspecified) 1.5 mg daily for behavioral disorder. Cyamemazine was a cosuspect medication. The patient developed polyuria and polydipsia with asthenia, abdominal pain, glycosuria and acetonuria. Cyamemazine was stopped and risperidone was continued. The patient was hospitalized for work-up and treatment of his diabetes, which had worsened. On admission, hyperglycemia was at 10 g/L, and ketonuria was rapidly corrected by insulin. The patient was discharged from the hospital receiving insulin Insulatard 9-0-5 IU and Novorapid 3-04 IU. Risperidone was reduced from 1.5 mg to 1 mg per day and yamezine was resumed at 20 mg a day. At the time of the report, the etiological workup was ongoing. The patient had not yet recovered."

- "FR-JNJFOC-20060300002 (Report was received from a health professional via AFSSAPS.) A 14-year-old boy (weight 40 kg) with a family history of insulin-dependent diabetes mellitus in in his 14-year-old paternal first cousin, was treated with oral risperidone (formulation unspecified) 0.1 mg a day for "hyperactivity disorder." One month after risperidone treatment the patient was hospitalized due to diabetes mellitus. Concomitant medications were not reported. Glycemia was 18 mmol/L. No ketonuria was observed. HbA1c was 8.1%. Kidney function was normal and autoantibodies were negative (antitransglutaminase,

antithyroid peroxidase, antistomach, antisurrenal). Specific antibodies against insulin were positive. Therapy with risperidone was discontinued upon hospitalization. The patient was treated with insulin and stabilized. The patient had not recovered from diabetes mellitus."

Reviewers' Comment: Glucose metabolism data was not obtained or documented well in the clinical trials. The sponsor has agreed to do a Phase IV commitment study for glucose metabolism, though a longer duration than the sponsor proposed so far will be needed.

Finally, the sponsor reports that through special search, no disproportionality with respect to suicide, suicidal ideation, or attempt was observed in children or adolescents on risperidone during this review period. There were 8 serious AEs involving suicidality in children or adolescents during this reporting period: Three resulted in deaths and are summarized in the subsection of Death. The remaining 5 cases are summarized by the sponsor and are presented below:

- "DE-JNJFOC-20051102757 describes a 16-year-old boy, weight 60 kg, with an unknown history, who attempted suicide by taking 100 mL risperidone oral solution (total 100 mg) and another unspecified drug (total amount unknown). No significant clinical symptoms were observed. Outcome was unknown."

- "DE-JNJFOC-20060105012 describes a 16-year-old girl, weight 64 kg, with an unknown history, received oral risperidone solution for an unknown indication. The patient attempted suicide by ingesting 50 ml of risperidone solution (total 50 mg). Three and a half hours later the patient developed tiredness and tachycardia with a heart rate of 110-120/min. No concomitant medications were reported. The actions taken and the outcome were unknown."

- "DE-JNJFOC-20060105716 describes a 16-year-old boy (weight and history unknown) received risperidone tablets (dose and duration unspecified) for an unknown indication. No concomitant medications were reported. One day the patient attempted suicide by ingesting 30 tablets of risperidone in 24 hours. Seven days after this ingestion the patient suffered from a headache and gastric complaints. The actions taken and outcome were unknown."

- "DE-JNJFOC-20051102757 describes a 16-year-old boy, weight 60 kg, with an unknown history, who attempted suicide by taking 100 mL risperidone oral solution (total 100 mg) and another unspecified drug (total amount unknown). No significant clinical symptoms were observed. Outcome was unknown."

- "DE-JNJFOC-20060105012 describes a 16-year-old girl, weight 64 kg, with an unknown history, received oral risperidone solution for an unknown indication. The patient attempted suicide by ingesting 50 ml of risperidone solution (total 50 mg). Three and a half hours later the patient developed tiredness and tachycardia with a heart rate of 110-120/min. No concomitant medications were reported. The actions taken and the outcome were unknown."

During this period, one additional case was considered and reported as tardive dyskinesia and is considered as one of the serious cases by the sponsor: "JP-JNJFOC-20051000314 An 8-year-old girl (weight and history unspecified) received oral risperidone 1 mg daily for 3 months for an unknown indication. No concomitant medications were reported. The patient experienced "teeth chattering." The physician concluded that the event was not an adverse reaction to risperidone and thus increased the dose of risperidone to 1.5 mg daily. The pharmacist suspected that the "teeth chattering" might be a symptom of tardive dyskinesia. Risperidone therapy is ongoing. The outcome of the event is unknown."

There were 6 cases involving a serious AE within the Cardiac Disorders MedDRA SOC; they included the following PTs: Tachycardia (4 cases), Cardiac arrest (1 case) which led to death, and Palpitations (1 case). The sponsor does not describe all these cases in detail but below is of these cases that also involve prolonged QT and is summarized by the sponsor here: "JP-JNJFOC-20051205339 A 13-year-old girl with a history of schizophrenia received oral risperidone, 2 mg daily, for the treatment of schizophrenia. Concomitant medications included biperiden. One week after risperidone initiation, QTc prolonged of 474 milliseconds was observed on admission to the hospital for the treatment of schizophrenia. The reason for ECG on admission was unknown. There were no baseline QTc data available for comparison. The patient's hallucinations did not resolve with risperidone treatment and risperidone 2 mg daily continued. Five days after hospitalization, QTc was 483 msec. It was reported that patient's QTc was 469 msec afterwards and the patient was recovering. Risperidone was increased to 4 mg daily (date unspecified). The outcome of QTc prolonged was reported as improving. No information is available on correction formula used and heart rate changes."

Reviewer's Comment: These events will need to be noted in the postmarketing section of the labeling.

5. Regulatory Status Update

The sponsor reports that since January 16, 2006, the "autism indication" has been approved in Sweden and Switzerland (b) (4)

The Swedish labeling is submitted in English. The specific indication is written as "severe behavioral disturbances in children and adolescents with autism."

In the Indications/Application possibilities section, the Swiss labeling reads, "For symptomatic treatment of Autistic disturbances with symptoms which extend above all on hyperactivity and irritability (including aggression, self-injurious behaviour, anxiety and repetitive behaviour), in the case of children and juveniles up to 5 years. Initiation of therapy and regular control of treatment should be carried out by an experienced Physician. The medicinal therapy should be carried out in the scope of an integrated concept with social- and psychotherapy therapeutic treatment."

(b) (4)

(b) (4)

6. Proposed US labeling, with acceptance of the Agency requested changes in the most recent AE letter.

   The following summarizes my review of the drafted labeling submitted by the sponsor:

(b) (4)

III. Conclusion and Recommendations

Overall, as I recommended in the previous review, considering risperidone is effective for irritablility associated with autistic disorder and there is no drug on the market that can help this patient population, as well as the relative safety presented by the sponsor, I recommend an approval action for this application.

However, also as I recommended before, the following need to be pursued to ensure the postmarketing safety despite the approval decision:

1) Long term Phase 4 Commitment Studies for glucose metabolism and metabolic syndrome in this patient population and for risperidone impact on sexual maturation (see Safety Team Reviewer, Dr. Villalba's review).

2) OSE search for brain edema events as well as cardiac deaths in pediatric patients treated with risperidone.

June Cai, M.D.
October 4, 2006

Cc: NDA 20-272/036
NDA 21-444/008
NDA 20-588/024
HFD-130 Div. Files
HFD-130/JCai
/NKhin
/MMathis
/TLaughren

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/s/

June Cai
10/4/2006 02:18:12 PM
MEDICAL OFFICER

Ni Aye Khin
10/5/2006 12:26:08 PM
MEDICAL OFFICER
See also memo to file.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research

Date: September 29, 2006

From: Russell G. Katz, M.D.
Division Director

Subject: NDA 20272 (SLR-041); Risperidone; Johnson & Johnson

To: Director
Division of Psychiatry Products (HFD-130)
Center for Drug Evaluation and Research

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20272 (SLR-041)**
Sponsor:	**Johnson & Johnson**
Drug:	**Risperidone**
Approved Indication:	**Schizophrenia/Bipolar Mania**
Material Submitted:	**Supplemental NDA/Consult**
Correspondence Date:	**2/23/05**
Date Received By Reviewer:	**9/25/06**
Date Review Completed	**9/29/06**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Introduction

This submission has been received as a consultation from the Division of Psychiatry Products (HFD-130). The submission consists of a "Changes Being Effected" Supplemental New Drug Application (labeling supplement) for risperidone.

The proposed changes to the product labeling for risperidone that this Division has been asked to address in this consultation describe a possibly increased (b) (4) "sensitivity" to antipsychotic medication in patients with Parkinson's Disease and Dementia with Lewy Bodies who are administered risperidone.

Other unrelated changes to the product labeling are also proposed in this submission, which this Division has not been asked to address.

This Division has been asked to provide comments on specific items pertaining to this application, as outlined further below.

Risperidone (Risperdal®) is approved for the treatment of schizophrenia, as well as bipolar mania ("short-term term treatment of acute manic or mixed episodes associated with Bipolar I disorder") in tablet, oral solution, and orally disintegrating tablet formulations, under NDAs 20272, 20588, and 21444, respectively.

The current submission has been cross-referenced to the following additional supplemental applications by the Division of Psychiatry Products.

NDA	Supplement
20588	SLR-028
20588	SLR-029
21346	SLR-009
21444	SLR-015

2. Contents Of Submission

This submission consists of the following items

- Cover letter
- Proposed labeling changes
- A report authored by the sponsor entitled "Risperidone Use In Patients With Lewy Body Dementia"
- A report entitled "The Risk Of Neuroleptic Malignant Syndrome Associated With Risperidone In Parkinson's Disease And Dementia With Lewy Bodies" authored by (b) (4)

3. Contents Of Review

The contents of this submission will be addressed under the following main headings and in the same order as below:

- Proposed labeling changes that are relevant to this consultation
- Comments in cover letter to submission
- Comments/special instructions from Division of Psychiatry Products
- "Sensitivity" (to neuroleptics) in patients with Parkinson's Disease and Dementia with Lewy Bodies
- Summary comments (including recommended revised labeling text)

The focus of this restricted review is to "provide a brief clinical description of the term 'sensitivity' as it is used by neurologists with respect to patients with Parkinson's Disease or Dementia with Lewy Bodies and their response to antipsychotic medication," as requested by the Division of Psychiatry Products. This review will not otherwise address whether the proposed labeling changes are adequately supported by available data, or whether changes to the labeling for antipsychotic drugs as a class are warranted; the review will not, in particular, form an assessment as to whether the clinical syndromes that have been considered manifestations of neuroleptic "sensitivity" are indeed caused by the neuroleptics to which they have been attributed.

4. Proposed Labeling Changes That Are Relevant To This Consultation

The following changes (highlighted) have been proposed to a subsection entitled "Use In Patients With Concomitant Illness" contained in the PRECAUTIONS section of the product label.

Use in Patients With Concomitant Illness

(b) (4)

Note that a description of neuroleptic malignant syndrome is provided in the current approved labeling for risperidone in the WARNINGS section.

A few other changes to the product labeling have been proposed in this submission. These include a minor clarification and a description of the concomitant use of risperidone and furosemide (both in the PRECAUTIONS section of the label). I have not reviewed these proposed changes.

5. Comments In Cover Letter To Submission

In the cover letter to this submission, the sponsor describes the main proposed changes to labeling (i.e., a description of a possibly increased (b) (4) "sensitivity" to antipsychotic medication in patients with Parkinson's Disease and Dementia with Lewy Bodies who are administered risperidone)

The following is also stated:

- (b) (4)
- (b) (4)

(b) (4)

(b) (4)

- (b) (4)

6. Comments/Special Instructions From Division Of Psychiatry Products

These are copied verbatim below, from the consultation request.

COMMENTS/SPECIAL INSTRUCTIONS:

Per discussion 5-22-06 and attached background information [hard copy only], please provide a brief clinical description of the term 'sensitivity' as it is used by neurologists with respect to patients with Parkinson's Disease or Dementia with Lewy Bodies and their response to antipsychotic medication. If labeling changes are recommended, either as class labeling or to the applicant's own CBE revisions, please indicate how the applicant's proposed language [see attachments] might best be revised to reflect the understanding of practicing neurologists. Please link the consult response to the supplements referenced above.

7. "Sensitivity" (To Neuroleptics) In Patients With Parkinson's Disease And Dementia With Lewy Bodies

The term "neuroleptic sensitivity" as it applies to a patient with Parkinson's Disease or any other condition whose manifestations include parkinsonism (e.g., Dementia with Lewy Bodies) is generally used by neurologists to describe a clinical worsening, most often in mental or motor function, that appears attributable to the neuroleptic itself (note that this assertion is based on an impression derived from personal observation, and not on an analysis of data).

There does not appear to be a widely-accepted definition and do not appear to be any formal widely-used consensus criteria, for "neuroleptic sensitivity," although that term is widely used in the medical literature, and is, indeed, listed as a suggestive diagnostic feature among the most recently proposed diagnostic criteria for Dementia with Lewy Bodies (McKeith IG, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863-72).

In a recently-published study, authored by a number of individuals considered to be experts in the subject (Aarsland D, Perry R, Larsen JP, McKeith IG, O'Brien JT, Perry EK, Burn D, Ballard CG. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry 2005;66:633-7), the following rather broad spectrum of symptoms was considered, apparently on an arbitrary basis, to be indicative of "sensitivity" to neuroleptics, provided those symptoms emerged or worsened after the administration of an antipsychotic agent, and provided no other adequate cause was apparent:

- Cognitive worsening
- Impairment of consciousness/drowsiness
- Agitation
- Worsening of parkinsonism (tremor, akinesia, loss of balance and rigidity)
- Orthostatic hypotension
- Falls
- Dizziness
- Impairment of activities of daily living
- Other physical symptoms

As regards the relationship between "sensitivity" to neuroleptics and neuroleptic malignant syndrome, the following may be pertinent:

- In the medical literature, neuroleptic malignant syndrome (some of whose symptoms overlap with those listed immediately above) appears to have been considered part of the spectrum of "sensitivity" seen in some patients with Dementia with Lewy Bodies who are administered neuroleptic drugs.

- (It is unclear if there are any published reports, at all, of instances of neuroleptic malignant syndrome that have occurred in patients with Parkinson's Disease who have been administered neuroleptics, or whether unpublished similar reports exist in the safety database for risperidone or other marketed antipsychotic drugs [neuroleptic malignant syndrome has been described in patients in whom dopaminergic drugs have been withdrawn, in a number of published reports]).

- Moreover, the core pathophysiological mechanisms that underlie both neuroleptic malignant syndrome and at least some of the other symptoms (e.g., worsening of parkinsonism) that are considered manifestations of "sensitivity" are believed to be similar in that they both involve dopaminergic blockade.

- Finally, it appears likely that clinical neurologists would consider neuroleptic malignant syndrome occurring in patients with Parkinson's Disease or Dementia with Lewy Bodies who are administered antipsychotic medication to be a manifestation of "neuroleptic sensitivity."

Note that in the current submission (in the report entitled "Risperidone Use In Patients With Lewy Body Dementia") the sponsor has stated the following (emphasis mine)

"As the behavioral disturbances associated with Lewy body dementia are similar to those observed in patients with Alzheimer's disease, symptomatic treatment with an antipsychotic medication may be considered.

Frequently, however, there is an unusual sensitivity to antipsychotic medications and benzodiazepines, with exaggerated adverse responses to standard doses. This neuroleptic sensitivity may include sedation, sudden rigidity, postural instability, falls, rapid deterioration with increased confusion, immobility, rigidity, fixed-flexion posture, and decreased oral intake, with some reactions similar to the well-known neuroleptic malignant syndrome."

[As also cited by the sponsor, the text of the second paragraph above has been derived from the following publication, which I have read: Rojas-Fernandez CH, MacKnight C. Dementia with Lewy bodies: review and pharmacotherapeutic implications. Pharmacotherapy 1999;19:795-803. The same publication describes constellations of clinical symptoms that are entirely consistent with neuroleptic malignant syndrome as being manifestations of "sensitivity" to neuroleptics].

8. Summary Comments

- This submission consists of a "Changes Being Effected" Supplemental New Drug Application for risperidone. The submission has been received as a consultation from the Division of Psychiatry Products.

- The proposed changes to the product labeling that this Division has been asked to address in this consultation describe a possible increased (b) (4) "sensitivity" to antipsychotic medication in patients with Parkinson's Disease and Dementia with Lewy Bodies who are administered risperidone. In the current consultation, this Division has only been asked to provide a clinical description of the term "sensitivity" as it is used by neurologists in regard to patients with Parkinson's Disease or Dementia with Lewy Bodies and their response to antipsychotic medication (and to recommend changes to the product labeling, if indicated).

- There does not appear to be a consensus definition or widely-accepted, precise set of diagnostic criteria for "sensitivity" as it applies to neuroleptic-treated patients with underlying Parkinson's Disease and other clinical conditions in which parkinsonism is a prominent manifestation (such as Dementia with Lewy Bodies). However, when used in both the medical literature and in clinical practice, it does apparently refer to a clinical deterioration that is attributable to the neuroleptic drug; among the clinical symptoms claimed to be subsumed under the rubric of "neuroleptic sensitivity" are sedation, cognitive deterioration, and worsening parkinsonism, as well as features consistent with the neuroleptic

malignant syndrome, and less-specific manifestations such as impairment of activities of daily living and reduced intake of food and fluids.

- **It is important to again emphasize that this review is primarily descriptive and directed at outlining what the term "sensitivity" (in relation to neuroleptics when they are administered to patients with underlying Parkinson's Disease and other clinical conditions in which parkinsonism is a prominent manifestation [such as Dementia with Lewy Bodies]) appears to imply when it is used in the medical literature and by clinical neurologists at large. In keeping with what has been stated in the request for this consultation, I have <u>not</u> attempted to determine from an analysis of the medical literature or other data, whether the various clinical symptoms considered to be manifestations of "sensitivity" to neuroleptics, including risperidone, constitute a homogenous clinical entity or are caused by such drugs.**

- The proposed new labeling text under the heading "Use in Patients with Concomitant Illness" (PRECAUTIONS section) is satisfactory, except in two respects

  - (b) (4)

  - (b) (4)

Revised labeling text has been proposed below.

8.1 Recommended Revised Labeling Text

(The highlighted text below is newly proposed).

Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses. 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.

Ranjit B. Mani, M.D.

Medical Reviewer

rbm 9/29/06
cc:
HFD-120
NDA 20272 (SLR-041)

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/s/

Ranjit Mani
9/29/2006 11:19:24 AM
MEDICAL OFFICER

Russell Katz
9/29/2006 03:53:14 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

INDs:

NDA 20-272 RISPERDAL® Tablets
NDA 20-588 RISPERDAL® Oral Solution
NDA 21-444 RISPERDAL® M-Tab Orally Disintegrating Tablets

(b) (4)

SPONSOR:	Johnson and Johnson
DRUG:	Risperdal
MATERIAL SUBMITTED:	CBE precautionary text with use of furosemide in elderly patients with dementia
CORRESPONDENCE DATE:	2/20/2005
DATE RECEIVED:	2/23/2005

I. REVIEW:

The sponsor sent in a CBE which I believe is wording we had agreed on in the past regarding the use of furosemide with Risperdal. I believe we can accept this wording as indicated below.

Earl Hearst
HFD-130

1 page immediately following withheld b(4) - Draft Labeling

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

/s/

Earl Hearst
9/20/2006 02:16:09 PM
MEDICAL OFFICER

Ni Aye Khin
9/21/2006 09:39:28 AM
MEDICAL OFFICER
I agree with Dr. Hearst that this labeling supplement be approved.

Review and Evaluation of Clinical Data

NDA #20272/S-036
(Cross References 20588/024 and 21444/008)

Sponsor:	Johnson & Johnson
Drug:	Risperidone
Indication:	Irritability associated with Autistic Disorder in Children and Adolescents
Material Submitted	Response to May 19, 2005 Non-approvable Letter
Corresponding Date	January 16, 2006
Date Received	July 17, 2006

I. Background

The sponsor submitted NDA#20272/S-036 for the approval of risperidone in the treatment of children with autistic disorder on December 19, 2003. The division issued an approvable letter on June 18, 2004 after reviewing the application. The sponsor's response to the Agency approvable letter was not satisfactory, mainly due to lack of identification of minimal effective dose and high risk of adverse events at lowest dose tested, as well as the long-term safety. This led to a non-approvable letter that was issued on May 19, 2005. Upon the sponsor's request for a meeting to discuss the deficiencies and issues, the Division as well as Dr. Temple met the sponsor on December 7, 2005. It was decided that the sponsor would need to make a resubmission to amend the deficiencies and issues identified in the first and second action letters and to provide new information discussed at the meeting.

In addition to Juvenile Rat Toxicity Study Report, this submission essentially includes the following aspects for clinical review:

1. Efficacy: Dose analyses, including mean dose by week, Sheiner analyses, and dosing recommendations

2. Safety:
1) Responses to safety concerns cited in the non-approvable (NA) letter including clarification of evaluable EKG data and a re-analyses of dyskinesia events

2) New safety information including glucose-related data, prolactin and leptin data from studies RIS-USA-150 and RIS-INT-84

3) A safety update including a pharmacovigilance report (April 2005) and serious adverse events from ongoing pediatric studies (November 2005)

4) Worldwide literature search and appropriate references (November 2005)

3. Labeling:
1) Regulatory status update with a worldwide registration status and foreign labeling with English translations where the indication to treat Autism has been approved

2) US labeling history, proposed labeling text (MS Word and SPL format), annotated labeling, last approved labeling, and currently used labeling

3) Proposed indication for (b) (4)

These issues are reviewed in order in the following section, Evaluation of Clinical Data. The issue of effective dosing is also reviewed by the Agency Biopharmaceuticals Science Reviewer, Andrew Jackson, PhD (see separate review by Dr. Jackson).

II. Evaluation of Clinical Data

1. Efficacy: Dose analyses, including mean dose by week, Sheiner analyses, and dosing recommendations

   Sponsor's Response:
   Based on the two short term studies, Study RIS-USA150 and RIS-CAN-23 (autistic disorder subset), the sponsor summarizes the dose over time data in the following table (Table 1).

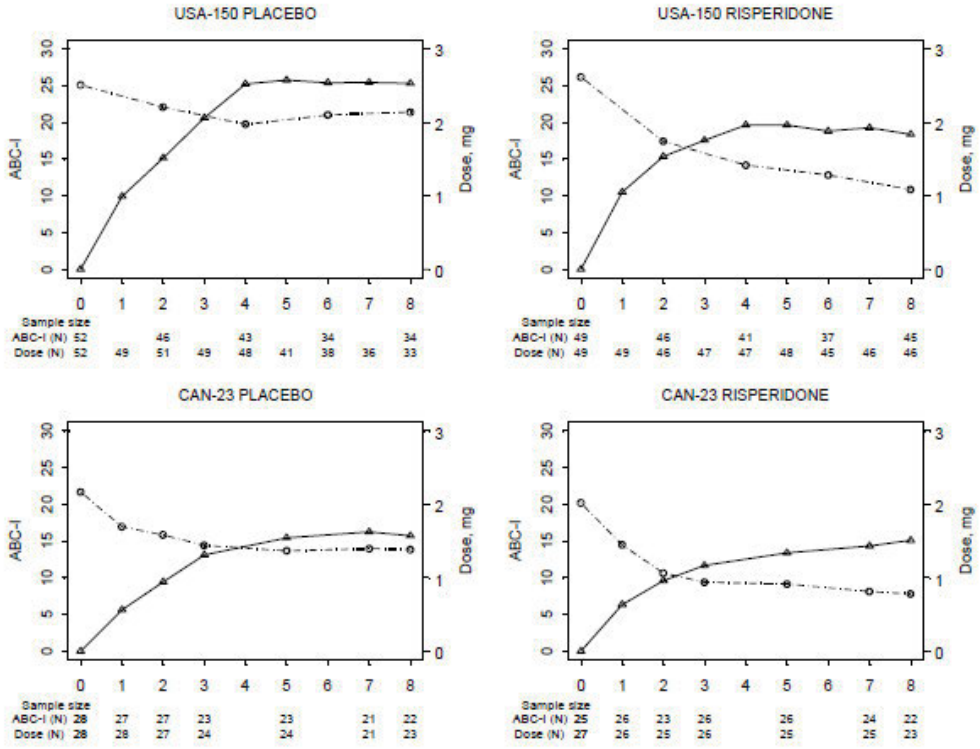
Table 1: Dose by Week – RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)

Study Time point	Placeboa			Risperidone		
	N	Mean (SD)	Med (Min, Max)	N	Mean (SD)	Med (Min, Max)
RIS-USA-150						
Week 1	49	0.99 (0.22)	1 (0.5, 1.5)	49	1.05 (0.19)	1 (0.5, 1.5)
Week 2	51	1.51 (0.34)	1.5 (0.5, 2.5)	46	1.53 (0.32)	1.5 (1, 2.5)
Week 3	49	2.06 (0.44)	2 (1, 3)	47	1.76 (0.54)	2 (0.5, 3)
Week 4	48	2.52 (0.50)	2.5 (1, 3.5)	47	1.96 (0.63)	2 (0.5, 3.5)
Week 5	41	2.57 (0.44)	2.5 (1.5, 3.5)	48	1.96 (0.62)	2 (0.5, 3.5)
Week 6	38	2.54 (0.54)	2.5 (1, 3.5)	45	1.88 (0.75)	2 (0, 3.5)
Week 7	36	2.54 (0.54)	2.5 (1, 3.5)	46	1.92 (0.65)	2 (0.5, 3.5)
Week 8	33	2.53 (0.53)	2.5 (1, 3.5)	46	1.84 (0.71)	2 (0, 3.5)
RIS-CAN-23						
Week 1	28	0.56 (0.19)	0.5 (0.4, 1.1)	26	0.63 (0.25)	0.6 (0.3, 1.4)
Week 2	27	0.94 (0.32)	0.8 (0.5, 1.7)	25	0.96 (0.36)	0.9 (0.4, 2.1)
Week 3	24	1.31 (0.41)	1.2 (0.8, 2.4)	26	1.17 (0.54)	1 (0.4, 2.8)
Week 5	24	1.54 (0.49)	1.4 (0.8, 2.9)	25	1.34 (0.72)	1.2 (0.5, 4.2)
Week 7	21	1.62 (0.60)	1.4 (0, 3.4)	25	1.43 (0.71)	1.2 (0.5, 4.2)
Week 8	23	1.57 (0.69)	1.4 (0, 3.4)	23	1.51 (0.70)	1.3 (0.7, 4.2)

The daily doses were shown by week. They are from the day before a subject's visit for the given week, except CAN-23 had no Week 4 or 6 visits. For placebo subjects, the risperidone-equivalent dose is summarized based on the number of tablets or volume of solution that were administered.

Mean dose by week is plotted superimposing on the mean available ABC Irritability subscale scores (ABC-I) in the following figure (Figure 1).

Figure 1: Mean Dose (Triangles) and Mean ABC-I Score (Circles) by Week - RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)



In Study USA-150, mean dose of both treatment groups increased through Week 4 and then reached to a plateau pattern correlating with significantly improved mean ABC-I score during the same period (through Week 4); mean ABC-I score from Week 4 to 8 in risperidone treatment group continued to improved while no improvement was seen in placebo.

In both treatment groups of Study CAN-23, mean dose increased throughout the study, and at a greater rate from Baseline to Week 3. It correlates with the improvement of mean ABC-I score over time.

The distribution of maximum daily dose of risperidone in both studies by response at end point is summarized in the table below (Table 2). Response is defined as a 25% or more improvement on ABC-I and CGI-C rating of much or very much improved at

end point. Overall, about 90% of the responders received a maximum daily dose of ≤ 2.5mg.

Table 2: Distribution of Maximum Daily Dose by Response Status at End Point
(Risperidone Subjects with Autism in RIS-USA-150 and RIS-CAN-23)

Maximum Daily	Nonresponder			Responder		Total		
Dose (mg)	n	%	Cum.%	n	% Cum.%	n	%	Cum.%
>0.5, <=1.0	2	7.4	7.4	2	4.2 4.2	4	5.3	5.3
>1.0, <=1.5	7	25.9	33.3	13	27.1 31.3	20	26.7	32.0
>1.5, <=2.0	8	29.6	63.0	12	25.0 56.3	20	26.7	58.7
>2.0, <=2.5	10	37.0	100.0	16	33.3 89.6	26	34.7	93.3
>2.5, <=3.0	0	0.0	100.0	2	4.2 93.8	2	2.7	96.0
>3.0, <=3.5	0	0.0	100.0	2	4.2 97.9	2	2.7	98.7
>3.5	0	0.0	100.0	1	2.1 100.0	1	1.3	100.0
Total	27			48		75		

Response: >=25% improvement on ABC Irritability subscale and CGI-C rating of much or very much improved at end point

The sponsor utilized Sheiner analysis for dose response analysis. However, the result of analysis showed a negative ED50[1] (-0.06) for Study USA-150 and a very small ED50 (0.08) for Study CAN-23. This is mainly due to the difference in study design between the sponsor's trials and the one used in Sheiner's method. Thus, the minimum effective dose cannot be fully determined, as agreed by Dr. Jackson.

The following are the key components of dosing recommendation by the sponsor:

a) The underlying clinical principle is to "start low, and go slow."

b) After initiating risperidone treatment at 0.25 mg/day and 0.5 mg/day for patients <20 kg and >20 kg, respectively, it is proposed that dose increments to the recommended dose of 0.5 mg/day and 1 mg/day for <20 kg and >20 kg patients may be done from Day 4 onwards.

c) The recommended dose should be tried for at least 14 days, if tolerable.

d) Further dose increments of 0.25 mg/day and 0.5 mg/day for <20 kg and >20 kg patients should be based on efficacy and tolerability assessments and should also be given a trial of not less than 14 days at each dose.

e) Analyses demonstrated that 90% of patients who showed a response (>25% response on the primary endpoint, ABC-I subscale) received doses of risperidone between 0.5 mg and 2.5 mg per day.

f) In one of the pivotal trials (RIS-CAN-23), at Week 3, when the therapeutic effect

[1] ED50: Dose at which half of maximal effect is observed.

reached a plateau, the maximum daily dose of risperidone was 1.0 mg in patients <20 kg, 2.5 mg in patients >20 kg, and 3.0 mg in patients >45 kg.

g) Gradual lowering of doses should be attempted after efficacy has been achieved and maintained, to ensure adequate balance of efficacy and safety.

h) Patients experiencing persistent somnolence may benefit from risperidone being administered once daily at bedtime or half the daily dose twice daily

The Agency Biopharmaceutical Science Review is conducted by Andrew Jackson, PhD. Dr. Jackson points out the following issues:

1) The sponsor's study design showed that it is difficult to understand their rationale for increasing or decreasing doses.
2) Due to the study design that is different from the design in Sheiner's method, the result is not interpretable, from which the minimal effective dose is still hard to determine.
3) (b) (4)
4) (b) (4)
5) (b) (4)

Concerning above mentioned issues, Dr. Jackson (b) (4) recommends a fixed dose placebo-parallel controlled trial as a Phase IV study.

Clinical Reviewer's Comments: I basically agree with the FDA Biopharmaceutical Science Reviewer, Andrew Jackson's opinions on study design (b) (4) *issues in this submission.* (b) (4) *The best way to solve these issues is by having a fixed dose study in this patient group.*

(b) (4)

However, as the sponsor states in this submission that the psychiatric treatment community has been prescribing this medication for children with autistic disorder, frequently with much higher dosages than studied that lead to more adverse effects,

and the fact that there is no medication available for the irritable behavioral problem in patients with this disorder which can make the patients' caretakers devastated and even put a patient in danger. Given that risperidone does show efficacy in treating these patients' irritability and the above mentioned risks, it seems acceptable that an approval action could be taken though it would be ideal to establish the starting dose and the titration intervals for the clinicians.

The sponsor does seem to be reasonable in dosing recommendation. The approach "start low and go slow" is often used in Psychiatry for special populations.

(b) (4)

Finally, a fixed dose study needs to be conducted as a Phase 4 commitment.

2. Safety:

1) Responses to safety concerns cited in the Not Approvable letter including clarification of evaluable EKG data and a re-analyses of dyskinesia events

The NA letter expressed our concerns regarding some of the common adverse events as well as those more specifically related to the use of antipsychotics such as extrapyramidal symptoms (EPS), their relationship with dosage and coding issues.

Sponsor's Response:

According to the original submission, the sponsor defined four EPS-related adverse event terms, each of which encompasses certain WHO preferred terms:

- Tremor (WHO preferred term tremor)
- Akathisia (WHO preferred term hyperkinesia)
- Parkinsonism (WHO preferred terms extrapyramidal disorder, hypokinesia, and bradykinesia)
- Dystonia (WHO preferred terms dystonia, hypertonia, oculogyric crisis, involuntary muscle contractions, tetany, and tongue paralysis).

Summarized below are the new analyses the sponsor provided in this submission.

The sponsor reports that of the 41 EPS adverse events occurred in 20 subjects of the risperidone group, 31 (76%) occurred at a dose above 1 mg. However, no evidence of a relationship of EPS-related AEs to mode dose group (29% for ≤1 mg/day, 30% for >1 to <2 mg/day, and 21% for ≥2 mg/day) was observed. The sponsor summarizes the distribution of severity of selected AEs in Table 3 below and reports that no consistent pattern exists across mode dose groups in the occurrence or severity of EPS events.

Nevertheless, the sponsor asserts that "very few patients had moderate or severe adverse events, and very few patients had remained on a mode dose of 1 mg or lower at the end of the trials."

Table 3. Severity Distribution of Selected AEs (by the Sponsor)

Autism Subset – RIS-USA-150 Part 1, RIS-CAN-23

	Placebo (N=80)				Risperidone (N=76)			
Adverse event	Total[a]	Mild n (%)[b]	Mod n (%)	Sev n (%)	Total	Mild n (%)	Mod n (%)	Sev n (%)
Somnolence	18	16 (89)	2 (11)	0	51	31 (61)	18 (35)	2 (4)
Fatigue	10	10 (83)	0	0	32	24 (75)	8 (25)	0
Confusion	0	--	--	--	4	2 (50)	2 (50)	0
EPS AEs (grouped terms)								
Dystonia	5	5 (100)	0	0	9	8 (89)	1 (11)	0
Tremor	1	1 (100)	0	0	9	6 (67)	3 (33)	0
Parkinsonism	0	--	--	--	6	1 (17)	4 (67)	1 (17)
Dyskinesia	0	--	--	--	5	4 (80)	1 (20)	0
Akathisia	1	1 (100)	0	0	1	0	0	1 (100)
Dyskinesia tardive	1	1 (100)	0	0	0	--	--	--

All Double-Blind Placebo-Controlled Studies

	Placebo (N=237)				Risperidone (N=222)			
Adverse event	Total[a]	Mild n (%)[b]	Mod n (%)	Sev n (%)	Total	Mild n (%)	Mod n (%)	Sev n (%)
Somnolence	32	29 (91)	3 (9)	0	110	63 (57)	43 (39)	4 (4)
Fatigue	12	10 (83)	2 (17)	0	51	31 (61)	20 (40)	0
Confusion	0	--	--	--	4	2 (50)	2 (50)	0
EPS AEs (grouped terms)								
Dystonia	8	7 (88)	0	1 (13)	15	14 (93)	1 (7)	0
Tremor	2	2 (100)	0	0	15	10 (67)	5 (33)	0
Parkinsonism	0	--	--	--	8	3 (38)	4 (50)	1 (13)
Dyskinesia	2	1 (50)	1 (50)	0	5	4 (80)	1 (20)	0
Akathisia	3	2 (67)	1 (33)	0	3	2 (67)	0	1 (33)
Dyskinesia tardive	1	1 (100)	0	0	0	--	--	--

a Number of subjects with event.

b n = number of subjects with given level of severity based on the subject's most severe event.
% = Percent of total number of subjects with event who had this level of severity as their most severe event.

The sponsor further presents that the incidence of parkinsonism was 8% (6/76) in the risperidone group and 0% in the placebo group. It was highest in the ≤1 mg/day mode dose group (4/17 [24%] vs. 1/30 [3%] in the >1 to <2 mg/day mode dose group and 1/29 [3%] in the ≥2 mg/day mode dose group. The dose at onset for these events was ~0.5 mg for 2 subjects, 1 mg for 1 subject, and ~2 mg for 3 subjects.

Clinical Reviewers Comments: As in the original analysis, tremor, parkinsonism, and dyskinesia are associated with risperidone use; dystonia is also associated when all double-blind placebo-controlled studies were pooled, but not when only two autism studies were pooled (see Tables 3 and 4).

Table 4: Incidence of EPS Events, Nervousness, Anxiety, and Agitation

Pooled Autism Population-RIS USA 150 and RIS CAN 23[a]

Grouped term	Placebo (N=80) n (%)	Risperidone (N=76) n (%)
Total No. Subjects With Selected AEs EPS + Nervousness + Anxiety + Agitation	21 (26.3)	31 (40.8)
Total No. Subjects With EPS AEs *(original SCS)*	8 (10.0)	21 (27.6)
Anxiety	12 (15.0)	12 (15.8)
Dystonia	5 (6.3)	9 (11.8)
Tremor	**1 (1.3)**	**9 (11.8)**
Parkinsonism	**0**	**6 (7.9)**
Agitation	7 (8.8)	3 (3.9)
Dyskinesia	**0**	**5 (6.6)**
Nervousness	4 (5.0)	3 (3.9)
Akathisia	1 (1.3)	1 (1.3)
Dyskinesia tardive	1 (1.3)	0

All Double-Blind Placebo-Controlled Studies[b]

Grouped term	Placebo (N=237) n (%)	Risperidone (N=222) n (%)
Total No. Subjects With Selected AEs EPS + Nervousness + Anxiety + Agitation	34 (14.3)	48 (21.6)
Total No. Subjects With EPS AEs *(original SCS)*	14 (5.9)	36 (16.2)
Anxiety	13 (5.5)	16 (7.2)
Dystonia	**8 (3.4)**	**15 (6.8)**
Tremor	**2 (0.8)**	**15 (6.8)**
Parkinsonism	**0**	**8 (3.6)**
Agitation	11 (4.6)	5 (2.3)
Dyskinesia	**2 (0.8)**	**5 (2.3)**
Nervousness	8 (3.4)	4 (1.8)
Akathisia	3 (1.3)	3 (1.4)
Dyskinesia tardive	1 (0.4)	0

Note: Adverse events reported during treatment or within 4 days of end of treatment are included. Incidence is based on the number of subjects, not the number of events. [a]Data from the following studies were pooled: RIS-CAN-23, RIS-USA-150 b Data from the following studies were pooled: RIS-CAN-23, RIS-USA-150, RIS-CAN-19, RIS-NED-9, RIS-USA-150

With regard to akathisia, the sponsor conducted further analyses on the data from the autism trials to rule out the possibility of miscoding of akathisia according to our request. Events of treatment-emergent agitation, nervousness and anxiety were assumed to represent possible akathisia and were thereby re-coded as EPS. The re-analysis results are shown in Table 4 above.

The sponsor reports that most of the additional patients with agitation, nervousness, and anxiety were in the placebo group rather than in the risperidone group (13 vs. 10). Thus, when anxiety and nervousness and agitation combined with subjects with subjects with EPS, the incidence of 'EPS' increases more in the placebo group than in the risperidone group. Overall, 21 (26.3%) of 80 patients in the placebo group and 31 (40.8%) of 76 patients in the risperidone group had "EPS" with the inclusion of these terms (see Table 4 above).

As for other events that might be akathisia such as those coded as unable to sit still and restlessness, the sponsor concluded from the analysis of akathisia items of the ESRS in the double-blind, placebo-controlled studies that these items are more of the nature of the underlying disease than treatment-emergent adverse events (see Table 5).

Table 5. Descriptive Statistics of Akathisia Items of the ESRS
Double-Blind Placebo-Controlled Studies

	Placebo						Risperidone					
Parameter					Change						Change	
Timepoint	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
All Studies (RIS-NED-9, RIS-CAN-19, RIS-USA-93, RIS-CAN-23)												
Akathisia (range: 0 to 6)												
Baseline	168	0.3	1.05				151	0.3	0.98			
End point	174	0.3	1.00	168	0.0	1.13	163	0.1	0.55	151	-0.2	0.89
Restless, nervous, unable to keep still (range: 0 to 3)												
Baseline	168	0.5	0.92				151	0.5	0.90			
End point	174	0.5	0.91	168	-0.1	0.84	163	0.3	0.61	151	-0.3	0.76
RIS-CAN-23 Autistic Disorder subjects												
Akathisia (range: 0 to 6)												
Baseline	28	0.3	0.97				27	0.3	0.98			
End point	28	0.1	0.26	28	-0.2	0.77	27	0.0	0.00	27	-0.3	0.98
Restless, nervous, unable to keep still (range: 0 to 3)												
Baseline	28	0.4	0.84				27	0.4	0.69			
End point	28	0.4	0.78	28	-0.1	0.26	27	0.1	0.32	27	-0.3	0.53

Clinical Reviewers Comments: These results provide some reassurance. However, in this analysis, Study US-150, a major autism study is not included because ESRS was not applied in this trial. An analysis with all terms of possible akathisia are combined would probably be more helpful here.

Tardive dyskinesia

In response to our concerns, the sponsor reports that a close review of events of dyskinesia as well as dystonia was conducted. The sponsor states that further clinical follow-up and relevant medical history were also obtained with particular attention to verbatim description of the adverse events, severity, duration and outcome of the adverse event (recovered or not recovered), associated adverse events, neurological examination, and AIMS score. The sponsor asserts that though all five subjects who had dyskinesia in the double-blind studies were treated with risperidone, the onset and length of these events do not meet criteria of tardive dyskinesia. In addition, all other cases searched had "recovered" outcome except 2 placebo patients, and duration ranged from 2 to16 days for the recovered events. Thus, the sponsor concluded that it does not appear that there were

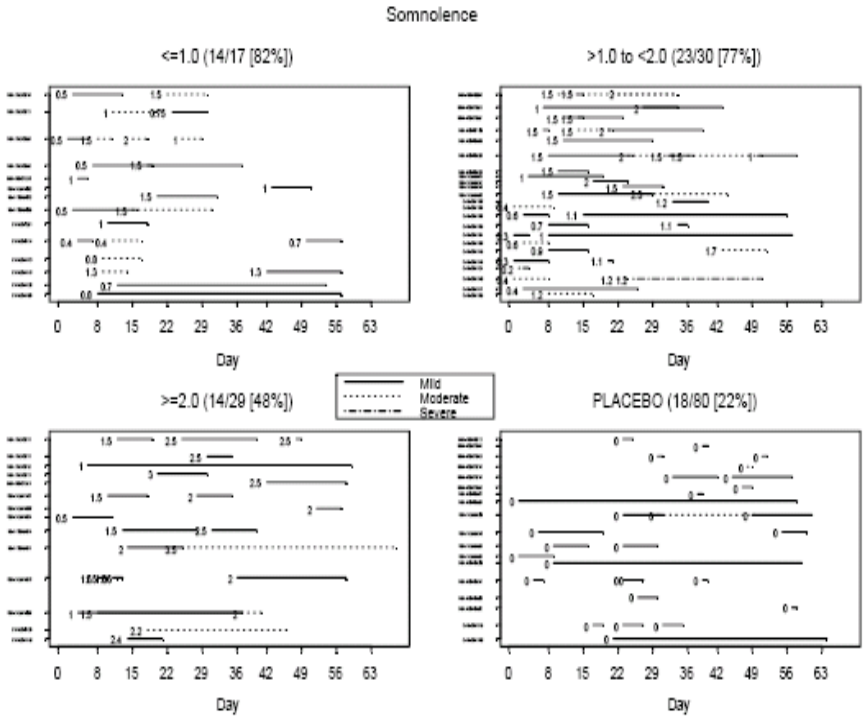
any events of tardive dyskinesia/dystonia among risperidone-treated patients with the adverse event of dystonia.

Clinical Reviewers Comments: Incidence of tardive dyskinesia should be searched in long term trials as opposed to short term trials where no event would meet the criteria of this diagnosis.

Somnolence and Fatigue

Despite somnolence is the most frequent treatment emergent AE and fatigue is among the common treatment emergent adverse events, the coding for these terms was not very clear in original submission. The sponsor's response was mostly satisfactory in the second submission in response to our AE letter except a few confusing ones that didn't seem to affect the overall statistic result. In this submission, the sponsor presents AE mode - dose relationships of selected AEs. The figures below (Figures 2 and 3) summarized by the sponsor illustrate these two AEs by mode dose group:

Figure 2: Somnolence by Mode Dose Group
-- Autism Subset (RIS-USA-150, RIS-CAN-23)



Each event for each subject is plotted from the event's start day (relative to first dose) to the stop day; the number indicates the dose (mg) at onset; the line style indicates the severity of the event. Percents in the panel titles are calculated based on the number of subjects, not the number of events.

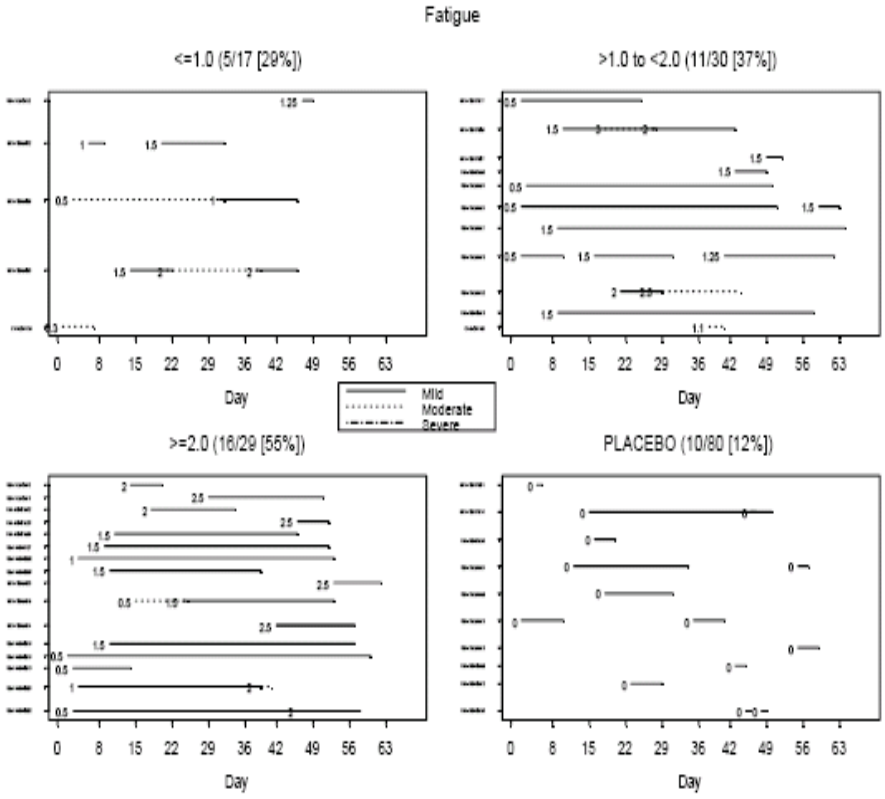
As the sponsor illustrated in the above figure, somnolence is more frequent in patients in the ≤1 mg and >1 mg to <2 mg mode dose groups than in the ≥2 mg mode dose group (77-82% vs. 48%). Onset of somnolence was most frequently during Weeks 1 to 2, and then mostly decreasing over time. The number of events with onset after Day 15

increases with increasing mode dose group, from 29% (7/24) in the ≤1 mg mode dose group, to 37% (15/41) in the >1 to <2 mg mode dose group, and 50% (12/24) in the ≥2 mg mode dose group.

The median duration of somnolence is 16 days for risperidone and 8.5 days for placebo. As Table 6 (on page 13) shows, in the risperidone group, 61% of somnolence were reported as mild, 35% were moderate and 4% were severe; the corresponding numbers for the placebo group were: 89% (mild) and 11% (moderate).

Figure 3 depicts the distribution of fatigue and dose mode group.

Figure 3: Fatigue by Mode Dose Group
– Autism Subset (RIS-USA-150, RIS-CAN-23)



Each event for each subject is plotted from the event's start day (relative to first dose) to the stop day; the number indicates the dose (mg) at onset; the line style indicates the severity of the event. Percents in the panel titles are calculated based on the number of subjects, not the number of events.

As in the case of somnolence, onset of fatigue was most frequently during Weeks 1 to 2. Events of fatigue tended to have longer duration than somnolence; median duration of this event was 32 days for risperidone and 5 days for placebo. Fatigue is more frequent in the ≥2 mg mode dose group (16/29, 55%) than in the lower dose groups (5/17, 29% for the ≤1 mg/day mode dose group and 11/30, 37% for the >1 to <2 mg/day mode dose group). As Table 6 (on page 13) shows, the majority of this adverse event was rated as

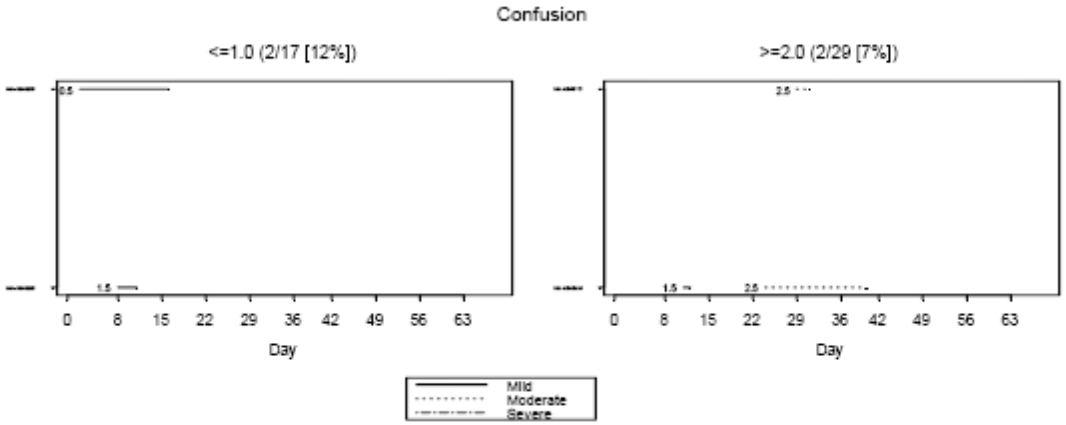
mild in severity, with a few cases rated as moderate. The sponsor reports that none of fatigue cases resulted in discontinuation.

Clinical Reviewer's Comment: The sponsor's analysis for these two events is reasonable. It is possible that the high prevalence of somnolence was related to treatment naivety of this patient population in the trials; however, one can't rule out the differences in brain function and brain sensitivity to this drug in these patients that we still don't understand clearly. Additionally, although most events of somnolence and fatigue are mild and a few moderate, this effect can probably further slow down the patients' activities and further increase their weight gain.

Confusion

Sponsor's response: The sponsor depicted the severity of confusion by mode dose group in the following figure:

Figure 4: Confusion by Mode Dose Group – Autism Subset (RIS-USA-150, RIS-CAN-23)



*Each event for each subject is plotted from the event's start day (relative to first dose) to the stop day; the number indicates the dose (mg) at onset; the line style indicates the severity of the event. Percents in the panel titles are calculated based on the number of subjects, not the number of events.

This adverse event is relatively infrequent. The above figure shows that confusion is reported in the ≤1 mg and ≥2 mg mode dose groups (2/17, 12% and 2/29, 7%), respectively. The duration varies from 1 to 16 days (median duration 8.5 days).

Overall Adverse Events Analysis

For all AEs by mode-dose group analysis, the sponsor provided the following table with two-pooled autism trials (US150 and CAN-23).

Clinical Reviewers Comments: Except those mentioned above, most other AEs do not seem to have a clear mode-dose relationship pattern from this analysis. Higher dose of risperidone does not seem to be associated with higher incidence of AE in many cases,

but tachycardia and automatism seem to be related to higher doses of risperidone. Again, without a fixed dose study, such estimation of dose-response of AEs is far from accurate.

Table 6: Adverse Events by Mode-Dose Group (Pooled Autism Population-RIS USA 150 and RIS CAN 23[a])

Adverse Event **System Organ Class** WHO-preferred term	Placebo (N=80) n (%)	RIS ≤1 mg (N=17) n (%)	RIS >1 mg ~ < 2 mg (N=30) n (%)	RIS ≥2 mg (N=29) n (%)
Psychiatric disorders				
Somnolence	18 (23)	14 (82)	23 (77)	14 (48)
Appetite Increased	15 (19)	7 (41)	10 (33)	20 (69)
Confusion	0	2 (12)	0	2 (7)
Body as a whole- general disorders				
Fatigue	10 (13)	5 (29)	11 (37)	16 (55)
Gastro-intestinal system disorders				
Saliva Increased	5 (6)	3 (18)	3 (10)	11 (38)
Constipation	6 (8)	4 (24)	7 (23)	5 (17)
Dry Mouth	5 (6)	2 (12)	5 (17)	3 (10)
Central & peripheral nervous System disorders				
Tremor	1 (1)	1 (6)	5 (17)	3 (10)
Dystonia	5 (6)	2 (12)	3 (10)	4 (14)
Dizziness	2 (3)	1 (6)	1 (3)	5 (17)
Automatism	1 (1)	0	3 (10)	2 (7)
Dyskinesia	0	1 (6)	2 (7)	2 (7)
Parkinsonism	0	4 (24)	1 (3)	1 (3)
Respiratory				
Upper resp. tract infection	12 (15)	6 (35)	12 (40)	8 (28)
Metabolic and Nutritional				
Weight Increase	0	1 (6)	2 (7)	1 (3)
Heart Rate and Rhythm				
Tachycardia	0	0	2 (7)	3 (10)

[a] Adverse events that occurred in the combined risperidone group with an incidence ≥5% and at least twice the incidence in the placebo group.

ECG Data:

Quantitative analysis of ECG data was not analyzed in the original submission. In their resubmission in response to our AE letter, the sponsor replied that such data were not recorded in database or CRF originally per protocol done in Canada. Thus, an assigned cardiologist performed readings of the original tracings from this study. The exceptions are those of 12 subjects from Dr. Shea's site (the sponsor didn't give any reason) and of 1 subject from Dr. Leisher's site due to lack of consent for this subject (Please see page 10 – 11 of my Review of Response dated May 17, 2005.)

Because Dr. Shea's site was one of the main sites of Study CAN-23, we were concerned about lacking of ECG data in this main site. At the meeting of December 7, 2005 and in this submission, the sponsor clarifies that measurements were made for all 77 tracings and these were all used for data summary, 65 were obtained from original tracing and 12 were from "copies."

Clinical Reviewer's Comment: This explanation is accepted. The detailed analysis of these ECG data of CAN-23 is in my previous review (page 10-11): In Study Can-23, QT interval was corrected by Fridericia's analysis and a linear-derived model (LD). Except for heart rate, there were no significant mean changes of ECG parameters from baseline to endpoint in risperidone group compared to those in placebo group. Potentially clinically significant (PCS) increase of heart rate was 22.5% in risperidone group and 10.8% in placebo group. In neither group, patients showed PCS QTcF change at endpoint, but risperidone group showed a slightly higher percentage of PCS QTcLD changes than that placebo group (5% vs 0%). Analysis of categorical changes showed no significant increase in risperidone group in any groups. This is fairly consistent with the results from the pool of other double-blind, placebo-controlled studies (US-150/I, US-93, and CAN-19) in my original clinical review (pages 63- 65) of this application. The sponsor didn't provide a pooled analysis of all double-blind, placebo controlled studies for autism.

2) New safety information including glucose-related data, prolactin and leptin data from studies RIS-USA-150 and RIS-INT-84

Sponsor's Response:
The sponsor states that "adverse events that were potentially related to impaired glucose tolerance or diabetes were analyzed as part of the Safety Update (Section 2.1.5.2) included in the 18 November 2004 Complete Response." "No serum glucose results were available from any autism or DBD study until RIS-INT-79, a DBD trial in children and adolescents. Fasting serum glucose results (taken at baseline, Month 3, Month 6, and Month 9 [end point]) from RIS-INT-79 were discussed in the 18 November 2004 Complete Response (response to Question 8) and in the RIS-INT-79 study report, which was also submitted as part of the 18 November 2004 response."

Again, the sponsor concludes "there were no findings of negative effects on glucose regulation. In RIS-INT-84, a long-term (1-year) open-label follow-up study to RIS-INT-79, laboratory samples, including serum glucose, were taken at Month 6 and Month 12. No glucose-related adverse events were reported and no subject met criteria for diabetes, with changes in insulin levels during the study being in accordance with age-appropriate norms - specifically, increasing levels up to Tanner Stage 3 with a subsequent decline. There was no correlation between insulin levels and glucose values. The combined data on glucose, insulin, and lipids indicate no evidence of an increased risk of metabolic syndrome in these subjects.

Clinical Reviewer's Comments: The sponsor didn't submit new data or data analysis regarding glucose level or its related adverse events. In the submission of November 2004, the sponsor submitted the result of fasting and nonfasting glucose metabolism from study RIS-INT-79, a then completed study in a Disruptive Behavioral Disorders (DBD) in pediatric population. The following was my conclusion for the submitted glucose related data from my previous review: "Over 27% (138/506) of these subjects didn't have fasting glucose value. Based on this data, the sponsor reports the mean change of glucose from

baseline to endpoint was 0.17(+/-0.68)." (For more details, please see page 13-14 of my review of previous response dated May 17, 2005.)

Again, though the sponsor presented fasting insulin levels in the attachment in 2004 submission, there was no proper mathematical transformation of fasting insulin and fasting glucose levels conducted to calculate Insulin Sensitivity. Recent research in the field of glucose regulation has shown fasting insulin level per se is not a good index for prediction of insulin resistance or diabetes mellitus. The sponsor should consider reanalyze insulin level data properly if these data are considered to be used. Furthermore, the diagnosis of metabolic syndrome in adults requires a combination of 2 or 3 components in a set of criteria, regardless the type of criteria[2] commonly used. These include serum triglyceride, high density cholesterol, fasting glucose, blood pressure, abdominal/central obesity measured as waist to hip ratio, waist circumference, or BMI, and in WHO (World Health Organization) criteria, together with insulin resistance (calculated from fasting insulin and fasting glucose, not just fasting insulin or fasting glucose per se). Weight gain or BMI is regarded as a very important predictive factor for metabolic syndrome. Considering the prevalence of diabetes in children and adolescents is rising in recent years and there are concerns about sensitivity of fasting glucose as opposed to glucose tolerance test for diagnosis of diabetes in this population, and moreover, since the exact diagnostic criteria in children and adolescents are not yet established, thus, strictly speaking, it is premature for the sponsor to conclude "no evidence of metabolic syndrome" in children and adolescents. It will be really to the benefit of Autism Society to have a better understanding of the impact of this treatment on patients' glucose metabolism.

Thus, I still consider that another study to demonstrate safety in this area in autistic population is needed.

Leptin Level

Sponsor's Response: The sponsor submits changes in leptin level in the submission and reports that there are no sex-related differences in leptin levels independent of adiposity.

Clinical Reviewer's Comments: As the sponsor states, "There is limited consensus in the literature about the clinical meaningfulness of changes in leptin. Pediatric endocrinology research demonstrates that leptin is a reflection of body fat mass, but the regulation of leptin levels during childhood is poorly understood." "Leptin has been shown to correlate with fasting insulin, but not with insulin sensitivity in healthy children." As discussed above, it is the insulin sensitivity or in another word, insulin resistance that has diagnostic value and clinical importance in metabolic syndrome and cardiovascular disease. Although as the sponsor states that leptin has been implicated as an independent stimulator of the reproductive axis and may have a facilitatory role in human pubertal

[2] Examples of commonly used diagnostic criteria for metabolic syndrome in adults include World Health Organization (1999), ATP-III (The 3rd Report of National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) (2001), and International Diabetes Federation (2003).

development, the clinical significance of this parameter remains unclear. Thus, I will not go into details here.

Prolactin Level

Prolactin data were not available from the placebo controlled autism studies but were available from the studies in patients with DBD and other Pervasive Developmental Disorders. Analysis of prolactin level in other double-blind, placebo-controlled trials in children and adolescents submitted at that time showed significant elevation of prolactin level in risperidone group compared to placebo group, and significantly more subjects in risperidone group had such elevation compared to those in placebo group (please see page 68 of the original clinical review of this application). At the meeting of December 7, 2005, the sponsor agreed to provide prolactin data drawn during Study US-150 as well as additional data from Study INT-84, an open-label extension study of INT-79.

However, the sponsor states that the normal laboratory range is not available. The mean changes of prolactin level from baseline to endpoint in Study US-150 Part 1 are summarized in the table and figure below by the sponsor:

Figure 5. Prolactin Level for Individual Subjects at Baseline and Endpoint of Study US-150 Part 1

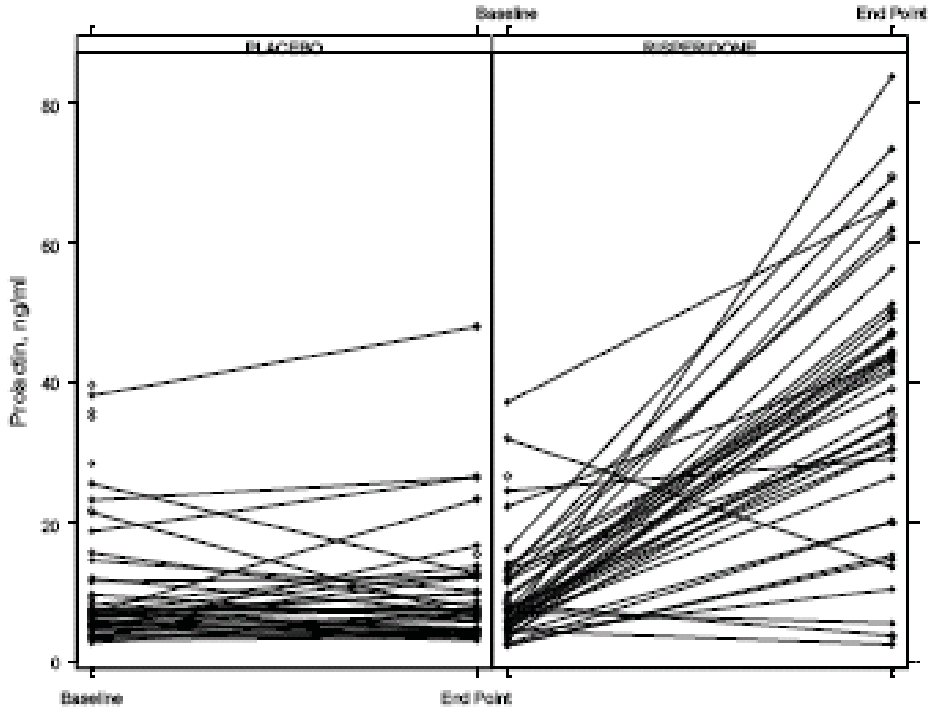


Table 7: Prolactin (ng/mL) - RIS-USA-150 Part 1: All Subjects Analysis Set

	N	Mean (SD)	Mean Change from Baseline (SD)
PLACEBO			
Treatment			
Baseline	48	10.88 (9.943)	
End point	38	10.12 (8.664)	0.79 (6.016)
RISPERIDONE			
Treatment			
Baseline	46	9.39 (7.707)	
End point	45	39.36 (18.718)	29.70 (19.236)

SD = Standard deviation

The sponsor followed up the subjects who continued beyond US-150 Part 1 to US-150 Part 2 (4 months of open-label period) for prolactin level. Table 8 presents the change of prolactin level from baseline to endpoint in both Part 1 and Part 2 of Study US -150.

Table 8: Prolactin (ng/mL) - RIS-USA-150, Parts 1 and 2 (All Subjects Analysis Set)

		N	Mean (SD)	Mean Change from Baseline (SD)
Initially randomized to Placebo				
Part 1	Placebo Treatment (8 weeks)			
	-Baseline	34	11.64 (10.738)	
	-End point (DB)	30	10.91 (9.511)	1.07 (6.708)
Part 2	Risperidone OL (8 weeks)			
	- End point(PNR)	30	33.55 (13.778)	22.87 (14.060)
	Risperiodne OL (4 months)			
	- End point(OL)	25	29.15 (15.222)	16.27 (19.771)
Initially randomized to Risperidone				
Part 1	8 – week DB Treatment			
	- Baseline	31	9.21 (7.769)	
	- End point (DB)	29	44.66 (16.424)	35.84 (16.315)
Part 2	4 - month OL Treatment			
	- End point(OL)	22	36.50 (18.679)	27.46 (17.647)
All Subjects from the 4-month OL				
- End point(OL)		47	32.59 (17.144)	21.61 (19.411)

PLA-DB-RIS Open-Label (OL) section contains those who received placebo in an 8-week double-blind (DB) period of US-150 Part 1. The nonresponders (PNR) went on to receive an 8-week open-label treatment of risperidone (Part 2) before entering another period of 4 months of risperidone treatment; the placebo responders exited the study. (See Fig. A1 in Appendix.)

RIS DB-RIS Open-Label section contains those who received risperidone in an 8-week double-blind period of US150 Part 1. The nonsponders exited the study; the responders

entered a 4-month open-label risperidone treatment (Part 2) directly.

The sponsor reports that no subjects in US-150 had a prolactin value above 100 ng/mL. Most subjects seem to have a relative decreased prolactin level after initial significant increase.

Prolactin level was also measured in another set of study for Disruptive Behavioral Disorder (DBD) patient population: INT-79 (3-month double blind study) and its extension INT-84 (1-year open-label). The sponsor reports that mean value at baseline of INT-79 was ~8 ng/mL; at Month 12 of INT-84 was ~ 15 ng/mL. The mean prolactin level retuned to near baseline levels at Month 6 and Month 9 in subjects who withdrew from Month 3 of Study INT-79, but increased again with the re-administration of risperidone treatment in INT-84. The sponsor further states that the mean prolactin levels are similar in those who were treated for 12 months in INT-84 and those for 21 months continuously in both INT-79 and then INT 84.

It appears that patients with autism had a more significant increase of prolactin level than those of DBD patients'.

Table 9: Potentially Prolactin-Related Treatment-Emergent Adverse Events by Sex and Age

-RIS-INT-84: All Subjects Analysis Set (by the sponsor)

	Prolactin value	**Age: Tanner Stage**	**Sex**
Endocrine disorders			
Gynecomastia			
A30209	61 mU/L Screen	12: 2-INT-79 Screen	M
PLA/RIS	903 mU/L (AA) DB BL		
	112 mU/L OL BL	13: 2 - INT-84 BL	
	47 mU/L M 6	- : 2 - INT-84 EP	
	135 mU/L M 12		
A50389	108 mU/L Screen	12: 1 - INT-79 Screen	M
PLA/RIS	252 mU/L DB BL		
	108 mU/L OL BL	12: 1 - INT-84 BL	
	N/A M 6	- 3 - INT-84 EP	
	N/A M 12		
Reproductive disorders, female			
Dysmenorrhea			
A50392	118 mU/L Screen	13: 3 - INT-79 Screen	F
RIS/RIS	689 mU/L(AA) DB BL		
	545 mU/L OL BL	13: 3 - INT-84 BL	
	554 mU/L M 6	- : 4 - INT-84 EP	
	1144 mU/L (AA) M12		

M=month, OL BL=open-label baseline, Screen=screening RIS-INT-79, DB BL=double-blind baseline RIS-INT-79, EP=open-label end point, N/A=not available

Initial Tanner stage and age were from screening of RIS-INT-79 and thereafter at the time of the measurement.

B= value below reference limit for age group; AA=value above pathological limits

According to the sponsor, no subject discontinued study due to prolactin-related adverse events in these trials. One subject (A30212) with a significant increase of prolactin level (exceeding 2114 mU/L [100 ng/mL]) at open-label baseline reported no potentially prolactin-related adverse events. In Table 9, the sponsor presented the three subjects in Studies INT-79 and INT-84 who had clinically significant prolactin related events. Laboratory normal ranges for prolactin are: 44-374 mU/L for boys and girls ages 5 and 10 years, 42-423 mU/L for boys ages 11 or older, 42-613 mU/L for girls ages 11 or older.

After Dr. Alice Hughes of our Safety Team reviewed the recent report of CATIE trial comparing several newer generation antipsychotics and traditional antipsychotics, she recommended several additions for the PRECAUTIONS section of the risperidone labeling regarding prolactin elevation and its related clinical consequences (see Dr. Hughes' review and Labeling subsection).

3) A safety update including a pharmacovigilance report (April 2005) and serious adverse events from ongoing pediatric studies (November 2005)

Sponsor's Response:

Pharmacovigilance report

The sponsor examined J&JPRD Benefit Risk Management worldwide safety (SCEPTRE) database which was based on spontaneous reports received cumulatively (through 30 April 2005) for postmarketing safety in children receiving risperidone. The worldwide pediatric exposure was approximately (b) (4) person-years. The table below is provided by the sponsor for worldwide annual pediatric exposure to risperidone. Those of age 0-4 year-old and possible intramuscular use are not included. The reason for slight differences (within (b) (4) for Years 2001-2, but about (b) (4) for Year 2003) in the annual exposure of each year compared to what they reported previously is unclear.

(b) (4)

There were 3,571 spontaneous case reports for risperidone involving children and adolescents worldwide (United States 66%, France 7%, Canada 6%, and United Kingdom 6%). Among all of them, 2193 were males, 1138 were females, and 240 cases had no information about patient gender. The distribution by age and diagnosis are presented in the following two tables:

Table 11: Distribution by Age of Spontaneous Case Reports in Pediatric Patients

Age	Total
5	107
6	150
7	157
8	229
9	218
10	246
11	204
12	235
13	268
14	296
15	379
16	355
17	387
Unknown[a]	340
Total	**3571**

[a]: Coded as Child or Adolescent but no specific age provided.

Table 12: Distribution by Diagnosis of Spontaneous Reported Cases in Pediatric Patients

Indication Category	Spontaneous Cases in Patients Aged 5 to 17 Years
Schizophrenia and psychotic disorders[a]	898
Bipolar or mood disorders	308
Autism or pervasive developmental disorder	235
Behavioral disorders[b]	476
Attention deficient disorder (ADD)/hyperactivity disorder (ADHD)	166
Other	456
Unknown	1032
Total	**3571**

Includes serious and nonserious cases received through 30 April 2005.
Cases with more than one indication for risperidone were included only once in the highest category, using the order of categories in the table as a hierarchy.

a: Includes schizophrenia and schizoaffective disorders; also includes psychosis or psychotic symptoms unless noted as associated with a mood disorder.

b: Includes conduct disorder, disruptive behavior disorder, oppositional defiant disorder, disorders of impulse control, intermittent explosive disorder; also includes anger, rage, aggressive behavior, aggressiveness, self-mutilation, self-injury unless noted as associated with one of the other specific categories.

Deaths

A total of 29 pediatric deaths were reported from the sponsor's worldwide search. Compared to the previous year, there are seven more patients.

The following table lists the distribution of reported causes of death in pediatric patients.

Table 13: Distribution by Diagnosis of Deaths in Pediatric Patients in Postmarketing Surveillance

Causes of Death	# of Cases
Completed Suicide	5
(unspecified method)	(2)
(intentional overdose)	(2)
(jumping from a high place)	(1)
Neuroleptic Malignant Syndrome	4
Cardiac Disorders	4
(sudden collapse)	(1)
(myocarditis)	(1)
((left ventricular hypertrophy)	(1)
(fatal arrhythmia)	(1)
Seizure Disorder	3
(asphyxiation from seizure)	(1)
("violent" seizure)	(1)
(epilepsy)	(1)
Infectious Diseases	3
(bronchopneumonia with cardiomegaly)	(1)
(aspiration pneumonia from status epilepticus, possible ARDS)	(1)
(pneumonia, septicemia, ARDS, congestive heart failure)	(1)
Respiratory Disorders	2
(pulmonary embolism)	(1)
(asphyxia due to drowning)	(1)
Gasteroenterologic Disorders (intestinal occlusion)	1
Metabolic Disorders (hypoglycemia from diabetes)	1
Multi-organ Failure	1
Nervous System Disorders (encephalitis)	1
Unknown	4
Total	**29**

[a]ARDS: Acute respiratory distress syndrome

Clinical Reviewer's Comments: The potential association with risperidone or its attribution can not be totally ruled out in many of these cases and they are summarized in Table A1 in Appendix.

There are two additional cases of unknown cause. Cases of unknown cause have very scarce information and some are from second hand information. The previously two

unidentified cases remain to be unknown in this submission. NMS also increased to four (one definite and one probable case in previous submission).

Brain edema or increase intracranial pressure was noticed in two pediatric patients died from NMS. To my knowledge, this phenomenon has not been reported previously. Other two of these NMS appeared to be triggered by overheating (US-JNJFOC-20030707355, JP-JNJFOC-20041106870).

Other newly reported causes are intestinal occlusion, multi-organ failure, as well as myocarditis and fatal arrhythmia. Most of them had diagnosis other than autism and were also on additional concomitant medications.

It is uncertain to me whether these cases of cardiac deaths are related to structural abnormalities or previous heart disease. It would be more helpful if more history and autopsy result of these patients (AU-JNJFOC- 20040305038, JAOCAN2000001168) were provided and more detailed cardiac history from the patient who had childhood arrhythmia was available.

The suicide cases were in ages 16 (n=1) and 17 (n=4). There seemed to be more patients' deaths related to seizure than actually listed, such as a cardiac case (NL-JNJFOC-20040907839) and one of the cases labeled as infectious disease (JAUSA-30419). However, it was hard to rule in or rule out risperidone as the cause of these seizures. A history of epilepsy seems common in these cases.

In conclusion, cerebral edema is not listed as a side effect in existing labeling. Together with two other cases from postmarketing surveillance in which patients died (see Deaths subsection), this is the third case that a patient developed intracranial problem (cerebral edema, one of those who died was said having increased intracranial pressure) while on risperidone. Despite NMS was the major condition in those two death cases, intracranial problem or brain edema has not been part of the symptomatology of NMS. This adverse event is of concern. More detailed information of these cases as well as that of cardiac death cases is needed. A further search of these events is recommended. (I communicated with the Division Direction, Dr. Laughren who recommends a consult for both brain edema and cardiac deaths to be sent to Office of Epidemiology and Surveillance.)

Serious Adverse Events

The sponsor reports that compared to the cases reported for all other age groups, the pediatric group had fewer SAEs among all the spontaneous case reports (19.2% of the 3,571 pediatric cases as opposed to 34.1% of the 24,912 cases for all other age groups). A comparison of the pediatric group and all other age groups for SAE rates by system organ class is presented in Table 14 (see next page).

A few of SAEs have higher incidences in pediatric patient group according to this list. These include: Immune system disorders, eye disorder, congenital, family and genetic disorders, and disorders of reproductive system & breast. The following also happened slightly more in pediatric group: Renal and urinary disorder, nervous system disorders,

injury, poisoning and procedural complications, skin and subcutaneous tissue disorder, gastrointestinal disorder, endocrine disorder, and blood, lymphatic system disorder and "investigations." (*It's unclear to me what the definition for "Investigations" event means in the submission and what the detailed events about the category "Congenital, Familial & Genetic Disorder.*")

A total of eight immune system disorders were reported: Two had an anaphylactic reaction but both recovered.

Table 14: Serious Adverse Events by System Organ Class in Pediatric Group and All Other Age Groups

System Organ Class	Number of Spontaneous Serious Cases		Percentage of Spontaneous Serious Cases		Proportional Ratio of Serious Cases[b]
	5 to 17 Years	All Other Ages[a]	5 to 17 Years	All Other Ages[a]	
Blood & Lymphatic System Disorders	51	569	7.2	6.7	1.08
Cardiac Disorder	48	931	6.8	11.0	0.62
Congenital, Familial & Genetic Disorder	4	30	0.6	0.4	1.61
Ear and Labyrinth Disorder	2	29	0.3	0.3	0.83
Endocrine Disorder	15	152	2.1	1.8	1.19
Eye Disorder	32	202	4.5	2.4	1.91
Gastrointestinal Disorder	76	749	10.8	8.8	1.22
General Disorders & Administration Site Conditions	131	2129	18.6	25.1	0.74
Hepatobiliary Disorders	15	233	2.1	2.7	0.78
Immune System Disorders	8	37	1.1	0.4	2.61
Infections and Infestations	32	490	4.5	5.8	0.79
Injury, Poisoning & Procedural Complications	58	623	8.2	7.3	1.12
Investigations	140	1318	19.9	15.5	1.28
Metabolism & Nutrition Disorders	51	728	7.2	8.6	0.84
Musculoskeletal & Connective Tissue Disorders	33	485	4.7	5.7	0.82
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	9	168	1.3	2.0	0.65
Nervous System Disorders	352	3763	50.0	44.3	1.12
Pregnancy, Puerperium and Perinatal Conditions	0	38	0	0.4	
Psychiatric Disorders	140	1799	19.9	21.2	0.94
Renal & Urinary Disorders	42	412	6.0	4.9	1.23
Reproductive System & Breast	38	324	5.4	3.8	1.41
Respiratory, Thoracic & Mediastinal Disorders	47	669	6.7	7.9	0.85
Skin & Subcutaneous Tissue Disorder	33	339	4.7	4.0	1.17
Social Circumstances	2	65	0.3	0.8	0.37
Surgical and Medical Procedures	4	58	0.6	0.7	0.83
Vascular Disorders	29	512	4.1	6.0	0.68
Total Number of Cases	**704**	**8488**			

Serious cases can include both serious and nonserious events.

a: Does not include serious cases for which age was unknown.

b: % of spontaneous serious cases in ages 5-17 years divided by the % of spontaneous serious cases in all other ages.

Additionally, the sponsor also conducted a search for pre-defined areas of clinical interest (including suicidality, self-injurious behavior or ideation, overdose, glucose metabolism disorders, lipid metabolism disorders, weight gain, metabolic disorders, potentially prolactin-related events, EPS-related events, and sedation). Table 15 (below) reveals some events with relatively higher reporting rates in children and adolescents compared with all other age groups: Self-injurious behavior or ideation, overdose/intentional misuse, weight gain, sedation, gynecomastia, galactorrhea, hyperprolactinemia.

Here, the sponsor argues that self-injurious behavior or ideation and gynecomstia are related to a pattern of events consistent with the underlying disease being treated and normal developmental changes in pubertal males, respectively. Despite higher incidences of intentional misuse/overdoes, the sponsor also reports that cumulative reviews of overdose or reports with fatal outcome in children and adolescents did not suggest a new safety concern for risperidone.

Table 15: Proportional Reporting Ratios by Age Group for Predefined Areas of Clinical Interest

	Number of Spontaneous Cases		% of Spontaneous Cases		Proportional Ratio of Cases[b]
	5 to 17 Years	All Other Ages[a]	5 to 17 Years	All Other Ages[a]	
Completed suicide	5	202	0.1	0.8	0.17
Suicidal ideation, Suicide attempt	34	438	1.0	1.8	0.54
Self-injurious behaviour or ideation	10	21	0.3	<0.1	3.32
Overdose, Intentional misuse	26	149	0.7	0.6	1.22
Glucose metabolism disorders	61	468	1.7	1.9	0.91
Lipid disorders	20	173	0.6	0.7	0.81
Weight gain	482	1282	13.5	5.1	2.62
Metabolic disorders	30	253	0.8	1.0	0.83
Potentially prolactin-related events					
Hyperprolactinaemia	253	1358	7.1	5.5	1.30
Galactorrhea	240	986	6.7	4.0	1.70
Gynaecomastia	118	159	3.3	0.6	5.18
Amenorrhea	66	978	1.8	3.9	0.47
EPS-related adverse events	527	3837	14.8	15.4	0.96
Sedation	331	1945	9.3	7.8	1.19
Total Number of Cases	**3571**	**24912**			

a: Does not include cases for which the age was unknown.
b: % of spontaneous cases in ages 5-17 years divided by the % of spontaneous cases in all other ages.

As of November 30, 2005, there were four ongoing clinical trials conducted in children and adolescent subjects (for bipolar disorder or schizophrenia): RIS-BIM-301, RIS-USA-231, RIS-SCH-302, and RIS-USA-234. Three of these studies (301, 302, and 231) are double-blind studies and Study 234 is open-label extension of Study 231. These studies enrolled 921 children and adolescents, among them 775 subjects had completed or discontinued and the rest 146 subjects were still in studies as of November 30, 2005.

The sponsor obtained SAE cases that occurred either during treatment or within 30 days of discontinuing treatment from the company's Benefit Risk Management worldwide safety database (SCEPTRE). The report discloses a total of 65 cases with a total of 85 SAEs during the ongoing pediatric studies from July 2004 to November 2005. Overall, the sponsor reports that the most common SAEs are (in decreasing order) schizophrenia, suicidal ideation, bipolar disorder, suicidal attempt, and psychotic disorder, NOS, and no new clinically significant information from these reports.

The following tables (Tables 16-18) are submitted by the sponsor for treatment-emergent SAEs in each of the three ongoing double-blind studies. The sponsor indicates the numbers are numbers of subjects instead of numbers of events, but apparently, there are overlaps of the subcategories, such as within the psychiatric disorder category. (The sponsor confirms that the numbers would not add up to the total, since the same subject could have had more than one of the SAEs listed.) Additionally, the sponsor did not integrate the three studies for dose group information probably due to slight different dose groups/categories were used in each of these studies.

The incidence of serious adverse events during treatment period of Study US-231 or within 30 days of last medication is shown in Table 16.

Table 16: Incidence of Serious Adverse Events in Study RIS-USA-231 During Treatment or Within 30 Days of Last Medication
(JNJPRD--TRIAL RIS-USA-231: Intent-to-Treat Analysis Set)

AE System Organ Class Adverse Event Preferred Term	RIS LOW DOSE	RIS HIGH DOSE
	(N=141)	(N=138)
	n (%)	n (%)
Total no. subjects with serious AEs	4 (2.8)	7 (5.1)
Psychiatric disorders	4 (2.8)	7 (5.1)
Psychosis	4 (2.8)	7 (5.1)
Suicide attempt	1 (0.7)	0
Centr & periph nervous system disorders	1 (0.7)	0
Cerebral edema (“Oedema cerebral”)	1 (0.7)	0

The only unusual case in this study so far is cerebral edema: Subject RO-JNJFOC-20050700284 of RIS-USA-231 is a 17-year-old girl diagnosed with schizophrenia and a history of 4 previous psychiatric hospitalizations, as well as multiple trauma and suspected cerebral concussion from an accident (timing unknown). She was treated with risperidone 0.45 mg (lower dose group) daily for 9 days. Starting Day 6, the subject had increased delusional thoughts, confusion and disorientation. On Day 10, the subject stated that she was going to kill herself, but there was no report of actual suicide attempt. The following day, the subject was withdrawn from the study and treated with lorazepam and alprazolam. She was reported to have clouded mental state with confusion. The subject was taken to the emergency room where a CT scan confirmed cerebral edema. Potential infectious causes were excluded. The subject remained being aggravated, with hallucinations, persecutory delusions and feeling of guilt, but no more suicidal ideations. The sponsor did not report any further consequence of this patient.

In Study 301 (see Table 17), psychosis/manic-depressive are more in risperidone 3-6 mg group; suicidal attempt are more significant in both risperidone 0.5-2.5mg group and risperidone group overall. Other SAEs, such as allergic reaction (in doses 3-6mg), asthma, and bronchospams (in doses up to 2.5mg) are seen only risperidone groups from this report.

Table 17: Incidence of Serious Adverse Events in Study RIS-BIM-301 During Treatment or Within 30 Days of Last Medication
(JNJPRD--TRIAL RIS-BIM-301: Intent-to-Treat Analysis Set)

AE System Organ Class AE Preferred Term	**PLACEBO**	**RIS 0.5-2.5 MG**	**RIS 3-6 MG**	**ALL RIS**
	(N=58)	(N=50)	(N=61)	(N=111)
	n (%)	n (%)	n (%)	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)

In Study 302 (see Table 18), only psychosis seems to be more in both risperidone groups. All other listed SAEs are from placebo group.

Table 18: Incidence of Serious Adverse Events in Study RIS-SCH-302 During Treatment or Within 30 Days of Last Medication
(JNJPRD--TRIAL RIS-SCH-302: Intent-to-Treat Analysis Set)

AE System Organ Class AE Preferred Term	**PLACEBO**	**RIS 1-3 MG**	**RIS 4-6 MG**	**ALL RIS**
	(N=54)	(N=55)	(N=51)	(N=106)
	n (%)	n (%)	n (%)	n (%)
Total no. subjects with serious AEs	2 (3.7)	1 (1.8)	1 (2.0)	2 (1.9)
Psychiatric disorders	1 (1.9)	1 (1.8)	1 (2.0)	2 (1.9)
Psychosis	0	1 (1.8)	1 (2.0)	2 (1.9)
Depression	1 (1.9)	0	0	0
Gastrointestinal system disorders	1 (1.9)	0	0	0
Appendicitis	1 (1.9)	0	0	0
Bowel motility disorder	1 (1.9)	0	0	0
Peritonitis	1 (1.9)	0	0	0
Secondary terms	1 (1.9)	0	0	0
Post-operative pain	1 (1.9)	0	0	0

Study 234 is a long term open-label safety study. Upon request, the sponsor submits the following SAE listing in the initial period of this study (Table 19, for the purpose of presentation, some columns contain unnecessary information are deleted to make the table fit the document). One subject died from suicide in this trial. Most of other patients were listed as "recovered," except for 3 unresolved and 1 unknown. The patient with hepatic lesion (A35111) was recovered but "with sequalae."

Table 19: Serious Adverse Events during *Initial* Study RIS-USA-234
Jul-01-2004 to Nov-30-2005

Patient Number	Age	Sex	Dose (mg)	AE Preferred Terms	Causality
A35111	18	M	2.0	Hepatic lesion Hyperuricaemia Mixed hyperlipidaemia	Probable
35120	16	M	4.0	Psychotic disorder	Doubtful
A35044	16	M	1.0	Schizophrenia, paranoid type	Doubtful
A36027	16	M	6.0	Schizophrenia	Not Related
A36041	13	M	6.0	Suicidal ideation Bereavement reaction	Not Related
36124	17	F	4.0	Completed suicide	Not Related
A36042	18	M	4.0	Schizophrenia	Not Related
A36009	14	M	3.0	Schizophrenia	Not Related
A36156	16	F	3.0	Intentional overdose Suicide attempt	Probable
A-36369	17	F	6.0	Suicidal ideation	Doubtful
36091	16	M	5.0	Self-injurious ideation Anxiety	Doubtful
A36187	16	M	5.0	Suicide attempt	Doubtful
A36372	17	M	2.0	Vomiting	Possible
A36200	17	M	3.0	Bone sarcoma Metastases to lung	Not Related
7906/A36009	15	M	4.0	Schizophrenia	Not Related
A36200	17	M	3.0	Gastrointestinal haemorrhage	Not Related
A36157	(age not listed)	F	4.5	Abnormal behavior Drug abuser Schizophrenia	Doubtful
A36194	14	F	5.0	Schizophrenia	Doubtful
A36194	14	F	5.0	Schizophrenia	Not Related
A36263	18	F	2.0	Suicide attempt	Not Related
A 36272	18	M	6.0	Schizophrenia	Doubtful

However, in the SAE follow-up listing, the sponsor reports that all subjects recovered from SAE.

Cases of death and discontinuations from ongoing trials are not submitted. (Still waiting for the sponsor's response.)

Clinical Reviewer's Comments: From postmarketing surveillance, there appears no disproportionality for events involving suicide or suicidal ideation, and extrapyramidal syndromes in children or adolescents. Glucose metabolism disorder in pediatric patients doesn't seem to be more of a concern in this analysis, either, provided glucose and lipids were actually monitored in clinical settings.

Detailed descriptions of cases of "Congential, Familial & Genetic Disorders" will need to be obtained from the sponsor, so is the explanation of cases of "Investigations."

For subjects in ongoing trials, any cases of deaths and discontinuations need to be submitted. For the patient with hepatic lesion resolved with sequalae in Study 234, the sponsor didn't provide CRF or summary. Since the patient recovered but with consequence, it is of concern. Thus, the patient's more detailed history should be obtained.

4) Worldwide literature search and appropriate references (November 2005)

Sponsor's Response:
The sponsor's previous safety update for this application provided literature search from May 1, 1993 to June 30, 2004. In this submission, the sponsor provides an updated literature search for the period of July 1, 2004 to November 30, 2005. The Sponsor searched company's literature repository (b) (4) for articles relating to the use of risperidone in children and adolescents (≤ 17 years of age) as well as Medline. The reviews and articles on a mixed population of children and adults or young adults only were excluded from assessment, so were those containing original data summarized as part of the original application for approval (e.g., J&J-PRD-sponsored trials of disruptive behavior disorders, RIS-CAN-23 and RIS-USA-150).

About 90 articles were published on risperidone use in the pediatric population, among these, 5 were conducted in children with autism and 38 were in non-autistic pediatric populations containing original clinical data. The majority of these are case reports and relatively short term open-label studies. There was one double-blind placebo-controlled study and one comparative reference-controlled study.

The following is a summary of the above mentioned double-blind, placebo-controlled study provided by the sponsor: "Troost et al (2005) reported a replication of the RIS-USA-150 trial. This was a 3-phase, 32-week study of risperidone in children (aged 5 to 17 years) with autism, Asperger's, or PDD-NOS with severe behavioral disturbance. Responders to 8 weeks of open risperidone treatment (responder criteria identical to RIS-USA-150) continued open treatment with risperidone for an additional 18 weeks then received either placebo discontinuation or risperidone treatment for 8 weeks. Of the 36 patients initially enrolled, 24 (67%) completed the 24 weeks of open treatment (mean dose at 24-week endpoint = 1.81 mg/day). During double-blind discontinuation, 67% of placebo-treated patients relapsed versus 25% on risperidone (p=0.049). The most common adverse effects were increased appetite, anxiety, fatigue, and increased thirst (average weight gain = 5.7 ± 2.8 kg in 24 weeks; p<0.0001), though all reported adverse

events were mild to moderate in severity. Objective and subjective measures found a low incidence of movement disorders, consistent with RIS-USA-150. The authors concluded that risperidone was effective and safe in reducing tantrums, aggression, and self injurious behavior in autistic children over several months, but weight gain may limit its use."

Exposure is reported for 142 patients in this search (2,476 from previous summary). Though dose and treatment duration were not provided in all studies, reported risperidone doses ranged from 0.25 to 6 mg/day, and the duration of treatment was up to 2 years. Safety results were reported in 28 articles (141 in the previous summary) with large variability in the reporting of adverse events, including clinical trials and case reports.

In the published literatures, no death was reported. Serious adverse events were reported for 3 patients (11 in the previous summary): NMS was noted in 1 patient (5 in previous summaries), tardive dyskinesia in 1 patient (3 in the previous summary), and pancreatitis in 1 patient, none was autistic patient.

Discontinuation of risperidone due to adverse events was reported in 4 articles. The most frequently reported treatment-limiting adverse events for children with autism are increased appetite (n=21), anxiety (n=13), and fatigue/tiredness (n=10). Table 20 shows the common AEs reported in the newly searched literature provided by the sponsor (see next page).

The most frequent adverse events reported are weight gain, sedation, and EPS. For children with other/mixed diagnoses, the most commonly reported adverse effects were hyperprolactinemia (n=17), weight increase (n=8), and sexual dysfunctions (n=8).

Clinical Reviewer's Comment:
Though not of critical importance, the total number of article provided by the sponsor is inconsistent in the summary (92) and in the detailed report in Appendix 3 (86).

3. Regulatory Issues and Labeling:
The sponsor was asked to provide the following information listed in items 1), 2), and 3).

1) Regulatory status update with a worldwide registration status and foreign labeling with English translations where the indication to treat Autism has been approved

Sponsor's Response:

(b) (4)

(b) (4)

Table 20: Adverse Events Reported for Risperidone-Treated Children (ages 5 to 17 years) in Prospective Studies of Children with Autism and Other Psychiatric or Developmental Disorders from Articles Containing Original Clinical Data

Adverse Event	Autism N of children reporting an AE*	Other N of children reporting an AE*
Acute confusional state	--	1
Adverse events related to increased prolactin	--	5
Anxiety	10	--
Ataxia	--	1
Blurred vision	--	1
Breast pain	--	1
Breast swelling	--	1
Decreased diastolic blood pressure	--	1
Diabetes mellitus	--	1
Drooling	3	--
Dystonic reaction	--	1
Enuresis	5	1
Excessive sedation	1	--
Extrapyramidal disorder/EPS	--	2
Facial twitching	--	1
Fatigue/tiredness	9	--
Galactorrhea	--	4
Headache	3	--
Hyperprolactinemia	--	17
Impaired fasting glucose	--	1
Impaired glucose tolerance	--	3
Increased appetite	16	--
Increased thirst	7	--
Insomnia	4	--
Muscle rigidity	2	--
Nausea	3	1
Neurological side effects	--	3
Neuroleptic malignant syndrome	--	1
OCD symptom exacerbation	--	1
Pancreatitis	--	1
Parkinsonism	--	1
Polydipsia	--	1
Polyuria	--	1
Priaprism	1	--
Psychosis	--	2
Rash	--	1
Restlessness/agitation	2	--
Rhinitis	3	--
Sedation	--	4
Separation Anxiety	--	1
Sexual dysfunctions	--	8
Stomach/Abdominal pain	3	--
Tardive dyskinesia	--	1
Tremor	1	1
Vomiting	--	2
Weight increase	2	8

*Note: as the total number of children treated with risperidone was not reported in all publications, an accurate percentage of patients cannot be calculated; it can be determined that *at least* 142 patients from these published studies were treated with risperidone

(b) (4)

A total of 12 countries have approved the use of risperidone for this population; however, among them only 7 approved for the indication of autism and 5 approved its use for treatment of behavioral symptoms or disruptive behaviors associated with autistic disorder (see Table 21).

Table 21: The Approved Indications In Foreign Countries

Countries	Approved Indication
Argentina	Treatment of patients having autism as from 5 years old
Australia	Treatment of behavioral disorders associated with autism in children and adolescents
Finland	Treatment of autistic disorder related irritability, social withdrawal and hyperactivity in children (5 years of age and over) and adolescents. Risperdal is recommended for the treatment of autistic disorder only with prescription by Child Neurologists, Child and Adolescent Psychiatrists or physicians conversant with treatment of autistic disorders in children and adolescents.
France	Children aged 5 to 11 years: Treatment of behavioral disorders (such as hetero-aggression, self-mutilation, major impulsiveness and severe stereotypy) observed in autistic syndromes, in monotherapy.
Ireland	Treatment of severe disruptive behavioral symptoms in children and adolescents with autism and pervasive developmental disorders.
Latvia	Treatment of autism in children and adolescents
New Zealand	Treatment of autism in children and adolescents
Philippines	Treatment of autism in children and adolescents
Poland	Short-term treatment of autism in children and adolescents
Portugal	Treatment of autism in children and adolescents
Singapore	Treatment of behavioral disorders associated with autism (e.g. irritability, social withdrawal, stereotypic behavior, hyperactivity and inappropriate speech) in children and adolescents.
Thailand	Treatment of autism in children and adolescents

2) US Labeling history, proposed labeling text (MS Word and SPL format), annotated labeling, last approved labeling, and currently used labeling

The last approved labeling for RISPERDAL® was approved on August 25, 2005. Safety information regarding mortality in elderly patients with dementia-related psychosis was included as a BOXED WARNING and an update to the WARNINGS section of the label.

Afterwards, the sponsor submitted labeling (CBE) supplements containing new safety information, including the addition of (b) (4) pituitary adenomas to the ADVERSE REACTIONS section, Postintroduction subsection and reversible extrapyramidal symptoms in the neonate to the PRECAUTION section, and Pregnancy subsection.

In addition to last approved and current labeling, the sponsor provides a list of changes in the proposed labeling in this submission - see review of Item 3) for proposed changes.

3) Proposed indication and changes for risperidone (b) (4)

The following review is based on revisions to Risperdal® labeling proposed by the sponsor and submitted to the Agency in this submission (1-16-2006).

(b) (4)

(b) (4)

(b) (4)

1 Page immediately following withheld b(4) - Draft Labeling

(b) (4)

III. Conclusion and Recommendation:

From clinical perspective, there is no approved treatment available for autism or its associated symptoms at present. The sponsor has conducted two trials that show efficacy in treating irritability associated with this disease. However, the lowest effective dosage has yet to be established; this has been felt to be an important clinical issue since knowledge of the lowest effective dose may assist prescribers in avoiding excessive occurrence of adverse events. On the other hand, the practice of starting at a low dose and slowly titrating upward is not unreasonable. Thus, I do not feel that lack of a minimum effective dose precludes approval of this application.

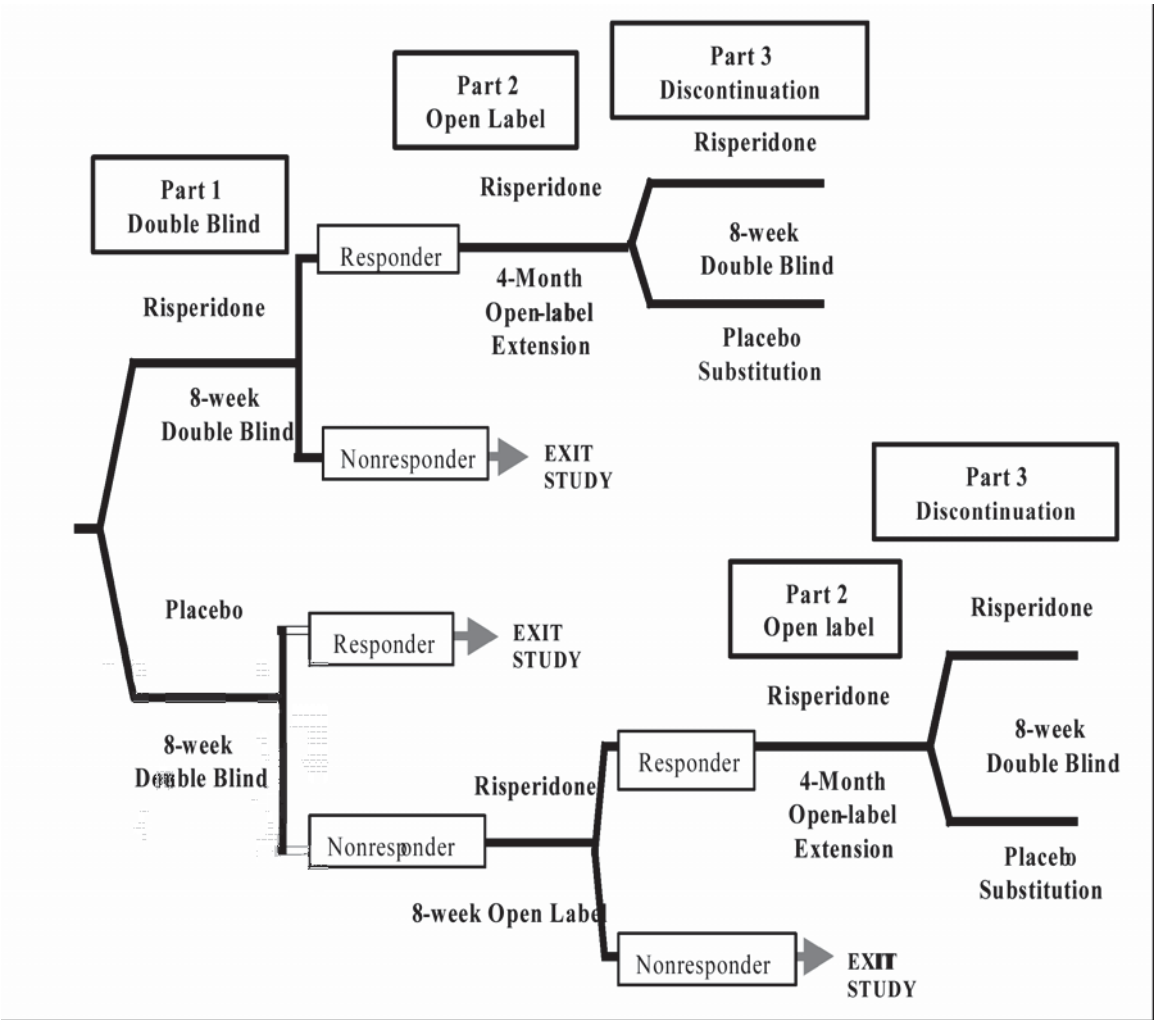
I recommend that the Division take an approvable action on this application along with the following recommendations:

1. *Phase 4 commitment studies for fixed dose and serum glucose metabolism (including insulin sensitivity)*
2. *Clarification in the labeling about the facts of the clinical trials and newer safety information as well as dosage issues*
3. *A specific safety search by Office of Epidemiology and Surveillance on serious adverse event of brain edema and cardiac deaths in pediatric patients reported in postmarketing surveillance*

4. *Clarifications on several issues that are from the Postmarketing Surveillance and ongoing trials:*
    - *Cases of death and discontinuations in ongoing trials, if any.*
    - *The outcome of a patient who had hepatic lesion but resolved with sequalae in an ongoing study*
    - *The definitions for "Investigations" as SAE and the cases included in the SAE category of "Congential, Familial & Genetic Disorders" from the surveillance*

Appendix:

I. Figure A1. Study Schedule of US-150:



II. Table A1. Deaths with Potential Association/Attribution of Risperidone:

Case No.	Description	Diagnosis	Dosage	Other Meds
EMADSS-2001007063	A 17-year-old male died from **suicide** several days after told to double the dose.	"concentration problems"	Unknown (told to double it)	No information
NSADSS-2002032601 (Literature report)	A 15-year-old patient (sex not specified) died from **overdosing** 15g of risperidone and desipramine	unknown	(Treating dose unknown)	unknown amount of desipramine
US-JNJ-FOC-20030904721 (Literature report)	A 17-year-old male was found seizing after an **intentional ingestion** of a combination of drugs and died from "acute intoxication."	unknown	(Treating dose unknown) Autopsy risperidone blood level: 174 ng/mL,.	Autopsy bupropion blood level: 19,500ng/mL; Sertraline level: 100ng/mL
US-JNJFOC-20040505340.	A 15-year-old male experienced a "**violent seizure", collapsed**, and died.	"A history of violent behavior"	risperidone (0.25 mg twice daily, dates unknown) Toxicology reports obtained a day after the child's death revealed "normal blood" with no detectable medications noted	lorazepam, trazodone, and paroxetine hydrochloride.
JASAF-42624	A 14-year-old male had not had a seizure for 2 years at the last clinic visit. Found deceased by his family, incontinent of urine, in the prone position, head buried in a pillow, and some blood at the nose ("**asphyxiation secondary to a seizure**"). It was also questioned whether the death could have been related to QT prolongation with torsades.	conduct disorder, mental retardation, a history of generalized tonic-clonic epilepsy	risperidone (3 mg daily) for 8 months	Carbamazepine (level 35 [units not provided]) and valproate (level 171 [units not provided]), with addition of thioridazine, methylphenidate, and imipramine

Case No.	Description	Diagnosis	Dosage	Other Meds
GB-JNJFOC-20040801640	A 14-year-old male was hospitalized twice during that course for "possible fits" during treatment for agitation Died from **sudden death in an epileptic episode**.	developmental delay with agitation; mebendazole poisoning, neonatal respiratory arrest, tachy-arrhythmias, epilepsy in infancy	risperidone up to 1 mg daily for 7.5 months	paracetamol diprobase cream
NSADSS-2001009791	A 13-year-old male expired from renal failure due to **NMS** 7 days after initiating therapy with risperidone.	schizophrenia	risperidone (2mg daily) for two days (stopped after development of NMS)	chlorpromazine biperiden
US-JNJFOC-20040908713	An 8-year-old female had clinical symptoms and signs of **NMS**, also with increased intracranial pressure and died. Bronchopneumonia and multi-organ failure were also mentioned.	Unspecified (appears depression and then acute psychosis)	unspecified doses of risperidone	haloperidol, chlorpromazine, diphenhydramine, and lorazepam,
JP-JNJFOC-20041106870	A 16 year-old male died from **NMS** which happened after running under the sun during soccer practice and developed dehydration and heat attack. He also had brain edema,	OCD	risperidone 1 mg dialy for two years	clomipramine 225mg daily with unspecified lenghth
US-JNJFOC-20030707355	A 16-year-old male was found unconscious at home with a temperature of 110°F, unstable vital signs, creatine kinase 4747, myoglobin 9954, troponin levels 33.8 (units not provided) and died probably **NMS**).	mental retardation, behavioral disorder, and developmental delay (Patient's home may have been without electricity for days.)	risperidone 0.5 mg twice daily (duration unknown),	topiramate 100 mg twice daily, valproic acid 125 mg ("7 or 8 times a day") – (No level provided)

Case No.	Description	Diagnosis	Dosage	Other Meds
AU-JNJFOC-20040305038	A 10 year-old male suddenly collapsed three months following the initiation of risperidone therapy (14 hours after the last dose of risperidone). Autopsy was preformed but no result was provided. (Possibility of "congenital heart problems" or a family history of "coronary artery disease" was considered by the reporter.)	Conduct disorder An ECG done about 1 month prior to the child's death was "normal."	risperidone (0.5 mg daily)	n/a
ES-JNJFOC-20040706670	An 11-year-old female was diagnosed with m**yocarditis** and developed arrhythmia after hospitalization with a fever, four days after starting biperiden and fluphenzaine. Died 24 hours after onset of the event.	obsessive compulsive disorder unknown medical history	risperidone 2 mg daily for 35 days.	oxcarbazepine 600 mg daily for 35 days; biperiden 2.5 mg daily; 1 dose of fluphenazine decanoate 12 mg
NL-JNJFOC-20040907839	A 14-year-old, 48 kg female died from a **fatal arrhythmia** while lying in bed. She underwent repair of a VSD 1 month after commencing risperidone. Autopsy revealed scarring at the site of ventricular septal defect (VSD) repair, calcification and foreign body giant cells in the vicinity of the AV node with thickening of the tricuspid valve chordae tendinae, There was also evidence of **epileptic insults.**	abnormal behavior, suicide attempts, insomnia. a history of an unspecified cardiac arrhythmia requiring a cardiac assistance device around the age of 2 years	risperidone 1-2 mg daily for 4 months	citalopram, naproxen, paracetamol, lactulose

Case No.	Description	Diagnosis	Dosage	Other Meds
JAOCAN2000001168	A 16-year-old male died. (He had two syncopal episodes, one about 18 months and another about 3-4 months prior to death.) Initially thought to be due to **left ventricular hypertrophy**. Possible drug-drug interaction was being investigated.	autism spectrum disorder	risperidone 4 mg daily for unspecified period.	sertraline 100 mg daily (discontinued on the same day that the patient died.) Was on on methylphenidate prior to the initiation of risperidone therapy.
FR-JNJFOC-20040909788	A 17-year-old female presented with a diagnosis of septic shock related to **small intestinal occlusion** (Ogilvie Syndrome), resulting in death after emergency total colectomy	autism a history of epilepsy and unspecified abdominal pain	risperidone 1 mg twice daily for 9 and one-half weeks	cyamemazine
JACFRA-2000000231	A 17-year-old female hospitalized for "delirium of poisoning" was treated with risperidone. One week later, the patient had a **pulmonary embolism** and died (confirmed by autopsy).	Iron deficiency anemia, a prothrombin time of 50%, and decreased factor V	risperidone (up to 8 mg/ day)	cyamemazine
JAUSA-24527	An 11-year-old female was found collapsed on her bedroom floor and died. Primary cause of death was **bronchopneumonia**, with **cardiomegaly** as a contributing cause of death. Also, focal left ventricular hypertrophy, hepato-splenomegaly, and bridging necrosis of the liver and spleen.	depression and hallucinations mental retardation obesity enuresis. (a maternal second cousin also died suddenly as a teenager but no detailed description for cause or history)	risperidone (2 mg daily) for about 1 year	Imipramine (unknown dosage but also possibly for 1 year according to the summary)

Case No.	Description	Diagnosis	Dosage	Other Meds
JAUSA-30419	A 15-year-old female expired secondary to **aspiration pneumonia** from **status epilepticus** while on risperidone	a history of tuberous sclerosis and epilepsy	risperidone (1mg daily) for unclear period	n/a

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/s/

June Cai
7/6/2006 11:25:43 AM
MEDICAL OFFICER

Ni Aye Khin
7/6/2006 01:04:33 PM
MEDICAL OFFICER
I agree with Dr. Cai that this set of supplements is approvable; see memo to file for more detailed comments.

REVIEW AND EVALUATION OF CLINICAL DATA

NDAs:

21-444	015	CBE	Risperdal (Risperidone) (b) (4) Distingrating Tablets	Updates Precautions section to further strengthen and include (b) (4) Dementia with Lewy body or Parkinson's Disease. Requests CLASS LABELING for all anti-psychotics.
20-588	028	CBE	Risperdol Soln. (Risperidone)	Updates Precautions section to strengthen information on use in patients with Dementia with Lewy body or Parkinson's Disease.
20-588	029	CBE	Risperdol Soln. (Risperidone)	Updates Precautions section to further strengthen and include (b) (4) Dementia with Lewy body or Parkinson's Disease. Requests CLASS LABELING for all anti-psychotics.
21-346	009	CBE	Risperdol Consta (Risperidone) LA Injection	Updates Precautions section to further strengthen and include (b) (4) Dementia with Lewy body or Parkinson's Disease. Requests CLASS LABELING for all anti-psychotics.
20-272	041	CBE	Risperdol Tablets (Risperidone)	Updates Precautions section to further strengthen and include (b) (4) Dementia with Lewy body or Parkinson's Disease. Requests CLASS LABELING for all anti-psychotics.

DRUG: see above

SPONSOR: Johnson and Johnson

MATERIAL RECEIVED: Labeling change and request for class labeling

DATE OF SUBMISSION: 8/25/05

DATE RECEIVED: 8/25/05

I. REVIEW:

The sponsor has submitted labeling changes across the Risperdol products.

Please see Sponsor's conclusion below in italics.

DISCUSSION AND CONCLUSIONS

Although no conclusive double-blind controlled studies are available that indicate an increased risk for neuroleptic sensitivity in patients with Lewy body dementia treated with risperidone, the clinicopathologic similarity of Lewy body dementia with Parkinson's disease, including the presence of Lewy bodies, motor impairments, visual hallucinations, and neuroleptic sensitivity in both,[1] and the results from the J&JPRD literature and postmarketing searches support the inclusion of Lewy body dementia in the (b) (4) *Precautions section of the RISPERDAL company core data sheet.*

The results from the literature and postmarketing searches on risperidone use in patients with Lewy body dementia yielded mixed reports. Risperidone provided efficacy without neuroleptic sensitivity, as well as efficacy with neuroleptic sensitivity, which included extrapyramidal side effects and was severe in some cases.

Some overall observations that can be made from the literature and postmarketing searches on risperidone use in patients with Lewy body dementia include the following:

- *Neuroleptic sensitivity did not appear to be dose related, though there was some evidence that low doses were better tolerated.*
- *In most cases, neuroleptic sensitivity occurred after a short duration of treatment.*
- *The use of concomitant antidepressants, the diagnosis of Parkinson's disease or Lewy body dementia, or the presence of side effects with previous antipsychotic treatment were important indicators of potential neuroleptic sensitivity.*
- *There was a lack of controlled studies to evaluate the efficacy and safety of atypical antipsychotic agents in the treatment of psychotic and behavioral disturbances in Lewy body dementia sufferers.*

In conclusion, as for Parkinson's disease, caution is also recommended when prescribing RISPERDAL to patients with known or suspected Lewy body dementia because these patients may be at an increased risk for neuroleptic sensitivity, including neuroleptic malignant syndrome or parkinsonian symptoms. This increased risk seems to be present with all antipsychotic agents.

They have requested we consider class labeling across all antipsychotic and have added this labeling.

(b) (4)

II. Recommendations:

I recommend we accept these labeling changes as proposed.

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120

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

/s/

Earl Hearst
4/3/2006 11:36:58 AM
MEDICAL OFFICER

Paul Andreason
4/6/2006 10:25:42 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA #20272/S-036
(Cross References 20588/024 and 21444/008)

Sponsor:	Johnson & Johnson
Drug:	Risperidone
Indication:	Autistic Disorder in Children
Material Submitted	Response to June 18, 2004 Approvable Letter
Corresponding Date	November 18, 2004
Date Received	November 29, 2004

I. Background

The sponsor submitted NDA#20272/S-036 for the approval of risperidone in the treatment of children with autistic disorder on December 19, 2003. The division issued an approvable letter on June 18, 2004. In addition to the issues of juvenile toxicity studies as phase 4 commitment (**Question #1** in our approvable letter) and the pop PK data from one of the pivotal trials (**Question #7** in our approvable letter), RIS-USA-150, our letter indicated that the sponsor needs to address the following clinical issues related to both efficacy and safety analyses of this NDA supplement.

Question #2. Re-analyze part III of study USA-150 using a Kaplan-Meier survival analysis and the definition of relapse based only on the 25% worsening of ABC Irritability subscale change.

Question #3. Interpret height and weight increases within the context of percentile rankings based on age and gender (i.e., z-scores).

Question #4. Explain the discrepancies regarding four investigators from study USA-150 who are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose.

Question #5. Provide a reanalysis of the effect of demographic variables on adverse event reporting rates.

Question #6. Provide an analysis of quantitative ECG data from study CAN-23

Question #8. Perform an adequate assessment of 1) cognitive function in Autistic patients and 2) glucose metabolism in a cohort of children that includes substantial numbers of Autistic patients. Depending on whether it is determined that a fixed dose

controlled trial will be required prior to approval or not, these measures may be assessed at that time or be performed in Phase 4.

Question #9. Re-analyze the verbatim terms coded as "somnolence" and "fatigue," verbatim terms subsumed under the various preferred terms that represent abnormal movements and extrapyramidal symptoms, and events coded as “nervousness", “agitation”, and "anxiety" or “akathisia” to determine if these terms represent a similar clinical phenomenon.

Question #10. Evaluate the time course of the important adverse events, including the time of onset and the duration of their persistence fully.

Additionally, the sponsor needs to submit the Safety Update according to the following instructions:

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Most of these questions concern safety issues in this population. This submission contains the sponsor's response to the above concerns. Before I start the review from the second question in our approvable letter, I will discuss the issue of minimum effective dose briefly in the following section.

II. Clinical Data

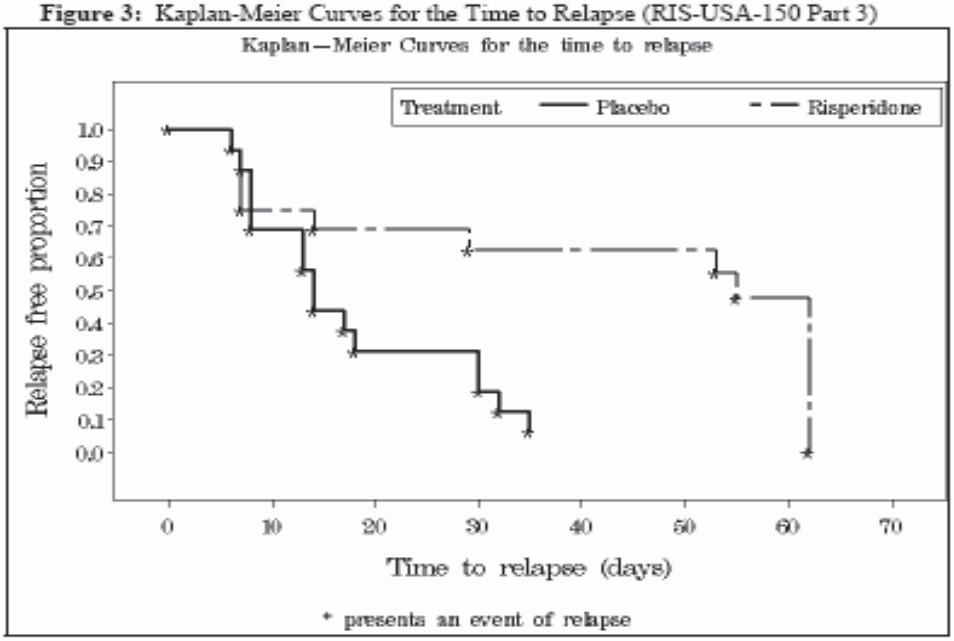
We have had a question regarding the Minimum Effective Dose for this patient population with the aim of minimizing the safety risk to pediatric patients with autism. In this submission, the sponsor submitted the Pop PK data and the FDA Biopharmacology Reviewer, John Duan, Ph.D. reviewed this part of the submission (See Dr. Duan's review for details). I agree with Dr. Duan that there are still uncertainties pertaining to the dose recommendation. There is no clear rationale for the 0.5mg starting dose.

Question #2. We had question regarding the (b) (4) analysis of Part II of Study US-150. The analyses of this long term relapse prevention study was problematic because different relapse criteria are described in different parts of the protocol (the results of one analysis are significant and the results of the other are not).

In this resubmission, the sponsor uses the definition of *relapse* as we suggested that was based only on the 25% worsening of ABC Irritability subscale change. *Time of relapse* is defined as the number of days from the date of randomization in Part 3 to the date of the first visit when the change from baseline on the ABC Irritability subscale is a worsening of ≥25%. A total of 32 subjects were included in the final interim analysis, which was the primary analysis set for efficacy of the relapse-prevention section of the Study US-150 (Part 3).

The sponsor provides the following figure of Kaplan-Meier curves for survival analysis. (Please see next page for the figure.)

Figure 3: Kaplan-Meier Curves for the Time to Relapse (RIS-USA-150 Part 3)



The following table shows statistical significance (p=0.008) between treatment groups by log rank test (Chi-square [1df] = 6.94). The mean time to relapse was 14 days for the placebo group and 55 days for risperidone group.

Table 1. Time to Relapse between Treatment Groups by Log Rank Test

Randomization Treatment Group	Point Estimate	Confidence Limit		P-value
	Days	Lower 95%	Upper 95%	
Placebo	30	14	35	
	14	8	30	
	8	7	14	
Risperidone	62	55	62	
	55	14	62	0.008
	10	7	55	

Question #3 We asked to interpret height and weight increases within the context of percentile rankings based on age and gender (i.e., z-scores). We requested the sponsor to compute the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time (e.g. at least three months).

In response, the sponsor calculated the z-scores from a) the pools the data from the following controlled studies for conduct disorder or other disruptive behavior disorders:

- RIS-CAN-20 and RIS-USA-97 (one-year open-label risperidone studies followed six-week controlled studies, RIS-CAN-19 and RIS-USA-93, respectively)

- RIS-INT-41 (one-year open-label risperidone study)
- RIS-INT-70 (one-year open-label extension from INT-41)
- RIS-HUN-4 (two-year open-label extension from INT-41)
- RIS-INT-79 (a relapse-prevention study for conduct disorder with three-month open-label followed by a randomized placebo-controlled six-month period)

Data from relapse-prevention study on autistic disorder (US-150 Part 2/3) was analyzed separately. This study is essentially a relapse-preventions study that followed an eight-week double-blind risperidone treatment, US-150- Part 1.

In cases of those studies with extensions, "baseline" was considered from the drug-free state that is before the first dose of risperidone of the first part of the study; Endpoints were considered from the extension periods. For the relapse prevention studies, it could be from the point that the subjects were last on open label treatment of risperidone if they were randomized to placebo subsequently or during the double blind period if they were randomized to risperidone subsequently.

The following table displays the change of z-scores for weight, height, and body mass index (BMI) from baseline to endpoint in all subjects treated with risperidone for at least three months, including autistic patients and patients with disruptive behavioral disorders (DBD).

Table 2. Baseline and End Point Z-Scores for Weight, Height, and Body Mass Index (BMI): All Risperidone-Treated Subjects

Exposure Days	Change in Z-Scores					
	Autistic Patients			DBD Patients		
	N	Mean	SD	N	Mean	SD
≥ 90 Days						
Weight (kg)	57	0.44	0.66	846	0.41	0.48
Height (cm)	55	0.16	0.34	646	0.15	0.43
BMI (kg/m^2)	54	0.45	0.73	669	0.40	0.63
≥ 180 Days						
Weight (kg)	28	0.55	0.49	676	0.43	0.50
Height (cm)	26	0.19	0.28	501	0.16	0.45
BMI (kg/m^2)	26	0.55	0.61	523	0.42	0.67
≥ 270 Days						
Weight (kg)	-	-	-	330	0.48	0.53
Height (cm)	-	-	-	238	0.17	0.51
BMI (kg/m^2)	-	-	-	250	0.48	0.72
≥ 360 Days						
Weight (kg)	-	-	-	62	0.41	0.59
Height (cm)	-	-	-	62	0.12	0.67
BMI (kg/m^2)	-	-	-	62	0.48	0.81

Changes of z-scores in autistic subjects who were treated with risperidone for 180 days were larger than the changes of z-scores in those who were treated for 90 days compared to changes in DBD patients. According to the data submitted, at baseline, autistic patients also showed higher z-scores for weight, height, and BMI than those of DBDs. There can be several possibilities, including history of previous treatment, or a reflection that the body development and metabolism are different from that of DBD patients. No negative mean z-score changes in either group observed.

Question #4. Additionally, we requested explanation of the discrepancies regarding the four investigators from study USA-150 listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose (namely, (b) (6)).

The sponsor provides the follow clarifications:

(b) (6) from Site (b) (6) was incorrectly listed as having financial disclosure. Despite due diligence was exercised in retrieving her financial disclosure information, complete information was not received. Thus, she should have been listed as not having financial disclosure certification.

Both (b) (6) and (b) (6) from Site (b) (6) were listed incorrectly for not having financial disclosure certifications. They both should have been listed as having had the certifications.

(b) (6) from Site (b) (6) was a pharmacist but didn't function as a subinvestigator. His name was incorrectly included in the lists and now is removed from the lists.

Question #5 We have requested the sponsor to provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of drug : placebo odds of each common, drug-related (occurring in at least 5% of drug-treated patients and at least twice as frequent than the placebo rate) adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

The sponsor pooled double blind, placebo-controlled studies on Autistic Disorder, namely, RIS-USA-150 Part I and RIS-CAN-23.

<u>Age Effect:</u>
Since most subjects were 12year-old or younger and only 6 of 156 subjects with Autistic Disorder were over 12 year-old Thus, the age group analysis is of limited usefulness.

<u>Gender Effect:</u>

Analysis of gender effect on adverse events is presented in the table below by the sponsor.

Table 3. Summary of Rates of Common, Drug-Related Adverse Events by Gender:
Pooled Double-Blind, Placebo-Controlled Data in Autistic Patients

Body System Preferred Term	**Gender**	Placebo n/N (%)	Risperidone n/N (%)	Odds Ratio (95% CI)	Breslow-Day *P*-value
Psychiatric					
Somnolence	Female	1/13 (8)	15/18 (83)	60 (5.5, 652.9)	0.03
	Male	17/67 (25)	36/58 (62)	4.8 (2.2, 10.3)	
Appetite increased	Female	1/13 (8)	9/18 (50)	12 (1.3, 112.7)	0.30
	Male	14/67 (21)	28/58 (48)	3.5 (1.6, 7.7)	
Confusion	Female	0/13 (0)	1/18 (6)	N/A	N/A
	Male	0/67 (0)	3/58 (5)	N/A	
Gastrointestinal					
	Female	0/13 (0)	3/18 (17)	N/A	0.42
Saliva increased	Male	5/67 (7)	14/58 (24)	3.9 (1.3, 11.8)	
Constipation	Female	0/13 (0)	4/18 (22)	N/A	0.26
	Male	6/67 (9)	12/58 (21)	2.7 (0.9, 7.6)	
Dry Mouth	Female	1/13 (8)	2/18 (11)	1.5 (0.1, 18.5)	0.72
	Male	4/67 (6)	8/58 (14)	2.5 (0.7, 8.9)	
Fatigue	Female	1/13 (8)	6/18 (33)	6 (0.6, 57.7)	0.91
	Male	9/67 (13)	26/58 (45)	5.2 (2.2, 12.5)	
Central & peripheral nervous system					
Tremor	Female	1/13 (8)	3/18 (17)	2.4 (0.2, 26.1)	0.14
	Male	0/67 (0)	6/58 (10)	N/A	
Dystonia	Female	1/13 (8)	0/18 (0)	N/A	0.07
	Male	4/67 (6)	9/58 (16)	2.9 (0.8, 10.0)	
Dizziness	Female	1/13 (8)	4/18 (22)	3.4 (0.3, 35.0)	0.96
	Male	1/67 (1)	3/58 (5)	3.6 (0.4, 35.6)	
Automatism	Female	0/13 (0)	0/18 (0)	N/A	N/A
	Male	1/67 (1)	5/58 (9)	6.2 (0.7, 54.9)	
Dyskinesia	Female	0/13 (0)	1/18 (6)	N/A	N/A

	Male	0/67 (0)	4/58 (7)	N/A	
Parkinsonism	Female	0/13 (0)	0/18 (0)	N/A	N/A
	Male	0/67 (0)	6/58 (10)	N/A	
Respiratory					
Upper respiratory tract infection	Female	2/13 (15)	6/18 (33)	2.8 (0.5, 16.6)	0.93
	Male	10/67 (15)	20/58 (34)	3 (1.3, 7.1)	
Metabolic and nutritional					
Weight increase	Female	0/13 (0)	3/18 (17)	N/A	N/A
	Male	0/67 (0)	1/58 (2)	N/A	
Heart rate and rhythm					
Tachycardia	Female	0/13 (0)	0/18 (0)	N/A	N/A
	Male	0/67 (0)	5/58 (9)	N/A	

Except for somnolence, gender effect didn't impact the incidence of adverse events listed in the above table. Based on Breslow-Day *p*-value (0.03), there was gender effect on incidence of somnolence: Female subjects were significantly more predisposed to somnolence than males in risperidone treated group. The sponsor reports that same pool of all double blind, placebo-controlled studies also showed

Race Effect:

In the table below, the sponsor provided analysis of race effect on adverse events. Odds ratio of risperidone versus placebo was calculated at 95% confidence interval. Breslow-Day *p*-values of racial group analysis of each adverse event showed homogeneity among racial groups.

Table 4. Summary of Rates of Common, Drug-Related Adverse Events by Race: Pooled Double-Blind, Placebo-Controlled Data in Subjects with Autistic Disorder

Body System Preferred Term	**Race**	Placebo n/N (%)	Risperidone n/N (%)	Odds Ratio (95% CI)	Breslow-Day *P*-value
Psychiatric					
Somnolence	Black	3/12 (25)	6/8 (75)	9 (1.1, 71)	0.93
	Caucasian	11/51 (22)	32/50 (64)	6.5 (2.7, 15.6)	
	Other	4/17 (24)	13/18 (72)	8.5 (1.8, 38.8)	
Appetite increased	Black	1/12 (8)	3/8 (38)	6.6 (0.5, 80.2)	0.48
	Caucasian	9/51 (18)	26/50 (52)	5.1 (2, 12.5)	
	Other	5/17 (29)	8/18 (44)	1.9 (0.5, 7.8)	
Confusion	Black	0/12 (0)	1/8 (13)	N/A	N/A
	Caucasian	0/51 (0)	3/50 (6)	N/A	
Gastrointestinal					
Saliva increased	Black	1/12 (8)	2/8 (25)	3.7 (0.3, 49.3)	0.94
	Caucasian	3/51 (6)	12/50 (24)	5.1 (1.3, 19.2)	
	Other	1/17 (6)	3/18 (17)	3.2 (0.3, 34.2)	

Constipation	Caucasian	5/51 (10)	12/50 (24)	2.9 (0.9, 9)	0.73
	Other	1/17 (6)	4/18 (22)	4.6 (0.5, 45.9)	
Dry Mouth	Black	1/12 (8)	2/8 (25)	3.7 (0.3, 49.3)	0.93
	Caucasian	2/51 (4)	4/50 (8)	2.1 (0.4, 12.2)	
	Other	2/17 (12)	4/18 (22)	2.1 (0.3, 13.6)	
Body as a whole – general					
Fatigue	Black	2/12 (17)	2/8 (25)	1.7 (0.2, 15.1)	0.34
	Caucasian	4/51 (8)	21/50 (42)	8.5 (2.7, 27.3)	
	Other	4/17 (24)	9/18 (50)	3.3 (0.8, 13.9)	
Central & peripheral nervous system					
Tremor	Caucasian	1/51 (2)	7/50 (14)	8.1 (1, 68.8)	0.61
	Other	0/17 (0)	2/18 (11)	N/A	
Dystonia	Black	1/12 (8)	0/8 (0)	N/A	0.27
	Caucasian	2/51 (4)	7/50 (14)	4 (0.8, 20.2)	
	Other	2/17 (12)	2/18 (11)	0.9 (0.1, 7.5)	
Dizziness	Black	1/12 (8)	0/8 (0)	N/A	0.20
	Caucasian	1/51 (2)	5/50 (10)	5.6 (0.6, 49.4)	
	Other	0/17 (0)	2/18 (11)	N/A	
Automatism	Caucasian	1/51 (2)	4/50 (8)	4.3 (0.5, 40.3)	0.64
	Other	0/17 (0)	1/18 (6)	N/A	
Dyskinesia	Caucasian	0/51 (0)	4/50 (8)	N/A	N/A
	Other	0/17 (0)	1/18 (6)	N/A	
Parkinsonism	Black	0/12 (0)	1/8 (13)	N/A	N/A
	Caucasian	0/51 (0)	3/50 (6)	N/A	
	Other	0/17 (0)	2/18 (11)	N/A	
Respiratory					
Upper respiratory tract infection	Black	1/12 (8)	3/8 (38)	6.6 (0.5, 80.2)	0.11
	Caucasian	7/51 (14)	20/50 (40)	4.2 (1.6, 11.1)	
	Other	4/17 (24)	3/18 (17)	0.7 (0.1, 3.5)	
Metabolic and nutritional					
Weight increase	Caucasian	0/51 (0)	4/50 (8)	N/A	N/A
Heart rate and rhythm					
Tachycardia	Black	0/12 (0)	1/8 (13)	N/A	N/A
	Caucasian	0/51 (0)	3/50 (6)	N/A	
	Other	0/17 (0)	1/18 (6)	N/A	

Question #6 We also requested an analysis of quantitative ECG data from study RIS-CAN-23.

The sponsor replies that such data were not recorded in database or CRF originally per protocol done in Canada. Thus, an assigned cardiologist performed readings of the original tracings from this study. The exceptions are those of 12 subjects from Dr. Shea's site (the sponsor didn't give any reason) and of 1 subject from Dr. Leisher's site (due to lack of consent for this subject).

The tables below are based on the results of sponsor's analyses of change from baseline to endpoint in ECG parameters in study RIS-CAN-23.

Table 5. Mean Change from Baseline to Endpoint in ECG Parameters (Study CAN-23) (ITT)

ECG Parameter	Placebo N	Placebo Mean Change	Risperidone N	Risperidone Mean Change
HR (bpm)	37	-2.8	40	+4.9
PR (msec)	37	+1.9	40	-1.3
QRS (msec)	37	0.0	40	+0.8
QT (msec)	37	+7.8	40	-2.5
QTcF (msec)	37	+7.4	40	+3.2
QTcLD (msec)	37	+6.4	40	+3.5

Table 6a. PCS CRITERIA FOR ECG CHANGES

ECG Parameter	Low (shortened)	High (prolonged)
HR (bpm)	65	120
PR (msec)	--	210
QRS (msec)	50	120
QT (msec)	200	500
QTc (males)	--	>450
QTc (females)		>470

Table 6b. Proportions of Patients Meeting PCS ECG Criteria at Endpoint (Study CAN-23)

Parameter	Placebo N tot	Placebo N pcs	Placebo %pcs	Risperidone N tot	Risperidone N pcs	Risperidone %pcs
HR (low)	37	2	5.4	40	0	0.0
HR (high)	37	4	10.8	40	9	22.5
PR (high)	37	0	0.0	40	0	0.0
QRS (low)	37	0	0.0	40	0	0.0
QRS (high)	37	0	0.0	40	0	0.0
QT (low)	37	0	0.0	40	0	0.0
QT (high)	37	0	0.0	40	0	0.0
QTcF (high)	37	0	0.0	40	0	0.0
QTcLD (high)	37	0	0.0	40	2	5.0

Table 7. Proportions of Patients by Categorical Change in QTc (CAN-23)

Parameter		Placebo N tot	Placebo N cat	Placebo % cat	Risperidone N tot	Risperidone N cat	Risperidone % cat
QTcF	**<30 msec**	37	34	91.9	40	37	92.5
	=30-60 msec	37	2	5.4	40	3	7.5
	>60 msec	37	1	2.7	40	0	0.0

QTcLD	**<30 msec**	37	35	94.6	40	38	95.0
	=30-60 msec	37	2	5.4	40	2	5.0
	>60 msec	37	0	0.0	40	0	0.0

However, the total number of subjects of this study was 79 (40 in risperidone group and 39 in placebo group) in the original submission. Based on the statements regarding copies of original ECG tracings obtained, as mentioned above, the total number of subjects should be 66 (79-12-1) and so it is inconsistent. Therefore, clarification and reanalysis will be required. In addition, Dr. Shea's site did involve 12 subjects which was the 3rd largest site in this study. If copies of ECG tracings can't be obtained and analyzed, explanation must be provided.

Question #8 Further safety concerns we had were inadequate assessments of cognitive function and glucose metabolism in a cohort of children that includes substantial numbers of autistic patients.

Cognitive function

In this response, the sponsor provides the results of analysis for the cognitive assessment batteries that were collected, but were not analyzed, in the previously submitted trials on autism. In study RIS-USA-150, the following five batteries were measured at baseline, Week 4, Week 8 of Part 1 and Part 3 of the study:

- Purdue Pegboard Task: A measure of eye-hand coordination and motor speed;
- Dot Test: Also called Spatial Memory Test: A test of working memory that evaluates the ability of the subject to remember the prior position of dots on subsequent blank pages;
- Verbal Learning Test: A test of verbal learning and memory over brief ("short") and intermediate ("long") periods of time;
- Cancellation Task: A test of attention;
- Analogue Classroom Task: A test of problem solving skills modeled after classroom tests.

The sponsor didn't mention any data from another study on autism, RIS-CAN-23, regarding cognitive function. From a newly finished trial on Disruptive and Behavioral Disorder (RIS-INT-79), the sponsor submitted some cognitive function data; however, this study doesn't include subjects with autism.

The following table is provided by the sponsor that summarizes the findings from cognitive assessment in the Part 1 of RIS-USA-150:

Table 8a. Descriptive Statistics of Five Measures of Cognitive Function

RIS-USA-150

(Analysis Set: Intent-to-Treat; Subjects With End Point Observations Only)

Test	Placebo						Risperidone					
Parameter				Change						Change		
Timepoint	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Perdue Pegboard Task												
Dominant Hand												
Baseline	21	18.9	11.8				24	27.9	17.6			
End point	29	23.5	12.3	21	5.6	9.5	33	25.7	16.0	24	1.3	8.9
Drops Dominant Hand												
Baseline	21	2.0	2.2				24	2.2	2.1			
End point	29	4.1	7.2	21	0.8	3.5	33	3.4	3.9	24	1.4	4.8
Non-Dominant Hand												
Baseline	21	17.0	12.4				24	23.0	17.2			
End point	29	18.4	10.4	21	1.9	9.3	32	22.5	14.6	24	2.0	8.4
Drops Non-Dominant Hand												
Baseline	21	1.9	2.4				24	3.5	4.9			
End point	29	4.2	6.7	21	1.2	3.9	32	3.4	3.3	24	0.2	6.0
Dot Test												
Average No-Delay Distance (cm)												
Baseline	6	3.7	1.4				10	3.5	2.3			
End point	8	5.1	3.4	6	0.6	2.1	17	4.9	2.8	10	0.2	1.1
Average 10-Second Delay Distance (cm)												
Baseline	5	5.5	2.3				9	5.9	2.2			
End point	7	6.1	2.3	5	0.1	1.4	16	5.2	2.0	9	-1.0	2.3
Working Memory Deficit												
Baseline	5	1.9	1.8				9	2.2	3.0			
End point	7	1.1	3.1	5	-0.2	3.2	16	0.7	2.2	9	-1.1	2.3
Verbal Learning Test												
Short Delay Free Recall Total Score												
Baseline	10	20.6	12.2				12	28.5	11.9			
End point	13	20.5	14.7	10	4.4	4.9	18	23.8	15.5	12	3.4	6.7
Long Delay Free Recall Total Score												
Baseline	9	3.1	3.3				10	6.2	4.6			
End point	13	2.9	2.9	9	0.3	1.5	17	4.8	3.9	10	1.2	3.9
Correct Recognitions												
Baseline	7	10.3	4.9				10	11.7	3.5			
End point	10	5.6	5.8	7	-3.6	5.4	16	8.6	5.5	10	0.2	2.2
Correct Rejections												
Baseline	7	8.9	6.5				10	16.3	11.5			
End point	10	5.2	5.6	7	-1.6	3.1	16	13.9	12.8	10	4.3	11.1
Overall Score												
Baseline	7	74.3	35.5				10	100.3	39.7			
End point	10	42.5	38.5	7	-20.7	22.2	16	80.0	56.1	10	10.2	32.9
Cancellation Task												
Correct Detections												
Baseline	8	97.4	64.3				14	120.2	46.3			
End point	11	86.8	57.4	8	-10.4	40.7	19	117.4	49.1	14	12.2	30.9
Errors of Omission												
Baseline	8	17.0	19.7				14	10.6	21.0			
End point	11	23.5	28.6	8	7.3	19.7	19	18.3	33.0	14	-1.1	26.3

Table 8a: Descriptive Statistics of Five Measures of Cognitive Function

(Analysis Set: Intent-to-Treat; Subjects with End Point Observations Only) (Continued)

Test	Placebo						Risperidone					
Parameter				Change						Change		
Timepoint	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Cancellation Task (continued)												
Errors of Comission												
Baseline	7	2.3	4.4				14	5.6	20.5			
End point	11	2.9	7.7	7	1.7	5.5	19	0.4	1.2	14	-5.6	20.6
Classroom Analogue Task												
Problems Attempted												
Baseline	11	31.6	10.2				13	22.3	17.3			
End point	15	28.8	16.9	11	0.6	17.2	20	22.3	13.6	13	3.4	15.9
Number Correct												
Baseline	11	26.2	10.5				13	17.2	11.8			
End point	15	25.1	17.4	11	1.5	17.4	20	20.1	12.3	13	5.5	14.6

It is puzzling that numbers of subjects at endpoint were more than those at baseline for all tests. It is unclear how change from baseline was computed for patients with no baseline score. In addition, from the original submission, a total of 101 subjects were in this study: 49 in risperidone group and 52 in placebo group. Thus, the percentage of subjects who had these assessments was small. It is difficult to make any meaning interpretation of these assessment data.

Glucose metabolism

In the sponsor's reply, it is stated that "information regarding glucose metabolism in a cohort of children was not available for the 19 December 2003 submission of NDA 20-272/S-036. Fasting and nonfasting serum glucose levels were not obtained in RIS-USA-150 Part 1 and 2/3 nor in RIS–CAN-23. Also, the studies that comprised the pooled patient population (DBD and autism) had inconsistent methods of glucose data collection, therefore, glucose was not evaluated for these studies."

Instead, the sponsor submitted the result of fasting and nonfasting glucose metabolism from study RIS-INT-79, a recently completed study in a Disruptive and Behavioral Disorders (DBD) pediatric population. Over 27% (138/506) of these subjects didn't have fasting glucose value. Based on this data, the sponsor reports the mean change of glucose from baseline to endpoint was 0.17(+/-0.68).

The sponsor also presents fasting insulin levels in the attachment but didn't indicate any proper mathematical transformations of fasting insulin and fasting glucose levels conducted. Recent research in the field of glucose regulation has shown fasting insulin level per se is not an excellent index for prediction of insulin resistance or diabetes mellitus. The sponsor should consider reanalyze insulin level data properly should these data are considered to be used.

Moreover, in the submission, the sponsor states, “Since no important safety profiles were observed between DBD patients and autistic patients, a separate study of glucose metabolism doesn't appear to be warranted.” Considering both autism and diabetes mellitus, especially type I diabetes, are autoimmune related diseases and that first degree relatives of autistic patients have higher incidence of type I diabetes, I don’t think one can assume or conclude that glucose metabolism in autism is the same as that in DBD patients based on this preliminary assessment from one study on DBD. Plus, as suggested above, risperidone may be associated with significant increases in body weight and BMI in autistic patients. Thus, I consider the assessment of effect of risperidone on glucose metabolism in autistic patients is critical but still lacking.

In the review by Dr. Khin from FDA DSI last May, it noted that glucose monitoring was one of the issues that were discussed with a Principal Investigator, Dr. Turgay, who recruited the most subjects for Study RIS-CAN-23. Dr. Khin wrote, “We observed the summary of the 1/13/01 investigator meeting; noted there was concern about the effects of risperidone on diabetes. Dr. Turgay stated that he was involved in initiation and implementation of the study. Since they saw no change in blood glucose in the prior two Canadian studies, that might be why they did not include blood glucose level in this study. He stated, though, that they now see in schizophrenia studies that blood glucose is a concern.”

In my opinion, the sponsor must take more serious considerations to address this critical issue among autistic patients, particularly taking into account that compliance is crucial in management of diabetes and can be problematic in autism should the child develops this complication. I strongly recommend that the sponsor consider doing another study to measure glucose metabolism in children with autism.

Question #9 Due to overlap coding of certain clinical symptoms in the original submission, we also asked the sponsor to examine verbatim terms coded as "somnolence" and "fatigue" to determine if these terms represent a similar clinical phenomenon. In addition, the sponsor should perform a re-analysis of verbatim terms subsumed under the various preferred terms that represent abnormal movements and extrapyramidal symptoms to ensure that we have a complete understanding of the incidence of these specific events. We are particularly concerned that events coded as "nervousness", “agitation”, and "anxiety" may represent akathisia.

Fatigue and Somnolence

In this reply, the sponsor notes that “somnolence is generally defined clinically as a sedative effect with reduction in the level of alertness and is often short lived,” while “fatigue is more frequently used clinically to describe a physical or somatic whole body phenomenon of tiredness or weakness and is usually longer in duration.” Based on this report, median duration of fatigue and related verbatim were 30 days compared to that of somnolence and its related verbatim, 16 days. The sponsor thus concludes that conditions coded under fatigue and somnolence were different clinical presentations.

According to the sponsor, both fatigue and somnolence have similar times of onset from the beginning of the treatment. The sponsor reports the relative risk was similar for both somnolence (3.0) and fatigue (3.4) with regard to risperidone treatment versus placebo. When combined, the incidence of these two adverse events (fatigue or somnolence) was up to 88% in risperidone group versus 29% in placebo group. Relative risk of the combination was unchanged, 3.1. (See table below presented by the sponsor.)

Table 9. Incidence of Somnolence and Fatigue for Double-Blind Placebo-Controlled Studies by Type of Disorder

(Risperidone Autism Safety Update: All Subjects Analysis Set)

	PLACEBO			RISPERIDONE		
		TYPE OF DISORDER			TYPE OF DISORDER	
Adverse Event Preferred Term	Total (N=237) n (%)	Autistic Disorder (N=80) n (%)	DBD/Other PDD (N=157) n (%)	Total (N=222) n (%)	Autistic Disorder (N=76) n (%)	DBD/Other PDD (N=146) n (%)
Total no. subjects with Somnolence or Fatigue	39 (16.5)	23 (28.8)	16 (10.2)	139 (62.6) RR = 3.8	67 (88.2) RR = 3.1	72 (49.3) RR = 4.8
Somnolence	32 (13.5)	18 (22.5)	14 (8.9)	110 (49.5) RR-= 3.7	51 (67.1) RR = 3.0	59 (40.4) RR = 4.5
Fatigue	12 (5.1)	10 (12.5)	2 (1.3)	51 (23.0) RR = 4.6	32 (42.1) RR = 3.4	19 (13.0) RR = 10.0

Note: Adverse events reported during treatment or within 4 days of end of treatment are included.
Incidence is based on the number of subjects, not the number of events.
RR = relative risk of risperidone (%) versus placebo (%); DBD = Disruptive and Behavioral Disorders; PDD = Pervasive Developmental Disorders
Data from the following studies were pooled for this table: BEL-24, CAN-19, CAN-23, NED-9, USA-150, USA-93

Based on the original coding, the sponsor reports that four verbatim terms for fatigue could have been coded to somnolence because they were closely associated with verbatim terms of somnolence, such as *sedation/fatigue, tired/drowsy, tired/sleepy/taking naps, sleeping in the morning*; On the other hand, the sponsor considers that the three terms that were coded as somnolence, such as *listless/tired/lethargic*, *tired and drowsy*, and *tired/difficulty waking up from nap but was able to arouse*, could have been coded as fatigue due to the fact that these terms contain the verbatim term of "tired." Nevertheless, the sponsor agrees with the original coding for these terms without further reasoning. -- It is interesting that the sponsor considers coding one "tired/drowsy" as "somnolence" while another term, "tired and drowsy" as "fatigue."

Upon closer examination of the verbatim lists the sponsor provided, it seems that in addition to items related to fatigue, the key words for preferred term "fatigue" include words related to tiredness, weariness, and listlessness; The key words for "somnolence" mainly include words related to drowsiness, sleep, lethargy, sedation, napping, slow, grogginess, and items related to "somnolence."

Despite most items of "difficulty waking up" were coded as "somnolence," couple of items such as "problem getting out of bed" or "tired-difficulty waking up" were coded as "fatigue." Moreover, in my opinion, "tired/difficulty waking up" despite "being able to arouse" still seems more a picture of "somnolence" than just fatigue.

It wasn't clear to me why the sponsor also included item "becoming calm" in "somnolence" category, but all these items were only one event of each. Thus, it probably doesn't affect overall statistics for these terms significantly. I agree that overall fatigue symptom is different from somnolence clinically, and most of the terms are coded appropriately overall, but certain codings are still confusing.

Abnormal Movements and EPS

The sponsor lists the following terms as WHO-preferred terms in this category: Bradykinesia, dyskinesia, dyskinesia tardive, dystonia, extrapyramidal disorder, hyperkinesias, hypertonia, hypokinesia, hypotonia, and muscle contractions involuntary, oculogyric crisis, tetany, tongue paralysis, and tremor. --The sponsor presents all adverse event occurrence in the attachment, and states that these terms "were accurately coded to the most appropriate preferred terms and that incidence calculated for each of these EPS-related adverse events is generally accurate." The sponsor didn't present any new information on recalculated incidences of these EPS-related events among this patient population.

Upon more detailed review of all verbatim terms for WHO-preferred terms of EPS-related adverse events re-submitted by the sponsor, I noted the following:

- Akathisia is coded to "hyperkinesias." In addition, all terms related to restlessness were also coded under "hyperkinesias." –Hyperkinesia included terms related to increased activities as well as terms of akathisia and restlessness.
- Akinesia is coded to "hypokinesia."
- Terms related to slowness were coded to either "bradykinesia" or "hypokinesia." –Hypokinesia included akinesia, terms related to decrease movement as well as those related to slowness.
- Most symptoms coded under "dyskinesia" seem to be typical symptoms of "tardive dyskinesia."
- Despite the fact that terms coded under "dystonia" were appropriate, many events that probably should be coded as "dystonia" were coded under other terms. For example, three cases of "stiff tongue" and one case of "tongue stiffness" were coded as "tongue paralysis," which probably should be considered as "dystonia." Another example is "jaw stiffness" which is coded as "tetany" instead of "dystonia." In addition to rigidity of limbs and muscles, "stiffness" and "stiff neck" were also coded as "hypertonia" which in general probably are related to "dystonia." -- These subjects did receive "benzatropine mesilate" for their symptoms of stiffness. (See Attachment 9.8: All Concomitant Medications for Subjects

with AEs of Nervousness or Agitation and Selected Verbatims submitted by the sponsor.)

- Many items in the category of "muscle contractions involuntary," such as grimacing, lip smacking or repeatedly wipes inner lip, facial movement or tics, head tilting or rocking, and eye blinking or winking of eyelid, should be considered as "tardive dyskinesia" as well.
- Parkinsonism is not listed but coded under the term "exptrapyramidal disorder." – The preferred term, "extrapyramidal disorder" is not used as a general term to include other symptoms in this category as it should be.
- Most terms were appropriately coded as "tremor" except for "lip tremor."

In our original review finished in May 2004, we noticed the problem of these same verbatim terms coded to different preferred terms (page 66 of our original clinical review). This problem has not been changed or corrected in this response. The sponsor needs to re-analyze these terms and provide the true incidence of each category of these events.

Akathisia

In response to our concern regarding the symptom of akathisia coded to other preferred terms, such as **agitation, nervousness, and anxiety**, the sponsor pooled the safety database of all risperidone-treated subjects (from both double-blind and open-label trials) to review the events that were coded under these terms and the concomitant EPS-related medications used in these events. The sponsor also reports that "other adverse events" and psychometric scales for extrapyramidal symptoms were reviewed to determine the possibility of akathisia.

Upon reviewing these results, I find several problems in the methodology applied.

First, the sponsor didn't provide the detailed list of "EPS-related medications." They seem to imply that the use of these medications indicated the presence of EPS and vice-versa. It is not clear to me what medications for treatment of akathisia were examined. Without knowing the specific medications, the validiity of this method cannot be assessed. Potential problems with this method are illustrated by the following two cases: The sponsor reports that "only one subject (RIS-USA-150/N5127) was administered anti-EPS medication in conjunction with the suspect verbatim event (motor restlessness) and had no other adverse events suggesting a likelihood of akathisia." This patient received benzatropine mesilate. But in the same list, Attachment 9.8 (All Concomitant Medications for Subjects with AEs of Nervousness or Agitation and Selected Verbatims) submitted by the sponsor, it lists that another subject (INT-41/A03676) with psychomotor agitation received clonazepam which is a benzodiazepine that can also be the treatment for akathisia. But, the sponsor didn't count this second case. Thus, it is unclear that this list actually has included all the subjects who had symptoms that were coded to nervousness, agitation, and anxiety.

Second, it's unclear to me what and how "other adverse events" would help determine whether akathisia existed: The sponsor states that re-examination of the four verbatim terms coded to nervousness (*shaky feeling*, *increased fidgeting of right foot*, *added fidgeting*, *and jittery)* that could have indicated presence of "akathisia" revealed "no reports of other adverse events suggesting a diagnosis of akathisia or EPS-related events, nor did any of these subjects receive EPS-related concomitant medications." The sponsor didn't specify what "other adverse events" were specifically examined and how these helped the final conclusion.

Third, the sponsor didn't explicate the application of proper items of psychometric scales, particularly the "hyperkinetic symptom factor" of Extrapyramdal Symptom Rating Scale (ESRS) that was used to determine akathisia: This factor is not one of the main domains of the scale originally. The sponsor neither specified which items were included in this factor nor described the scoring of this factor.

It is noted that Barnes Akathisia Rating Scale was not used in the two autism trials.

Each the following three scales were applied to one of the two trials on autistic disorder Since both ESRS and SARS have items specifically for "akathisia," these items should be analyzed separately to reflect symptom of akathisia.

1) ESRS (in RIS-CAN-23)
2) Simpson-Angus Rating Scale (SARS) (in RIS-US-150)
3) Abnormal Involuntary Movements (AIMs) (in RIS-US-150)

Another related problem is that the four pages of AIMs scores for four subjects in US-150 selected by the sponsor, first two pages (pages 451 and 452) were identical and the last two pages (pages 453 and 454) were also the same.

Finally, there is still confusion in coding: Among the verbatim terms coded under "**agitation**," terms such as restlessness, motor restlessness, unable to keep still, and psychomotor agitation should be more appropriately coded under "akathisia." Currently, the term "restlessness" is coded as either "hyperkinesias" or "agitation."

My opinion is that in addition to correcting the above mentioned methodology, the sponsor needs to re-analyze this issue by examining the score change of item 10 (akathisia) in the Simpson-Angus Rating Scale or item 6 (akathisia) of Parkinsonism in the Extrapyramdial Symptom Rating Scale (ESRS) of subjects with these verbatim events at the timepoints that correspond to these events.

Question #10. We asked the sponsor to evaluate the time course of the important adverse events, including the time of onset and the duration of their persistence fully.

The Sponsor reports that a review of the adverse events onset and duration for the double blind placebo-controlled data and the all risperidone data was performed. The selected adverse events for this analysis are the following: Somnolence, fatigue, weight increase, increased appetite, any EPS-related adverse event, any potentially prolactin-related adverse event, common adverse events in the gastrointestinal disorder system-organ class with risperidone, tachycardia, convulsions, and suicide attempt. The sponsor states that this selection was based on clinical significance or common presentation with risperidone, but also declares that clinically important adverse events (tardive dyskinesia, convulsions, and suicide attempt) occurred too infrequently to be included in all analyses listed above.

The analysis consists the following: 1) Kaplan-Meier curves of time to onset of the first event; and 2) a summary of the total number of days with the event; and 3) a summary of the percentage of total treatment time during which the event was present. Below is a table the sponsor submitted as part of the response to our question.

Table 10a: Onset and Duration of Adverse Events during Double Blind Studies

Body System Preferred Terms	Onset Day Median (min, max)	Time Point Separation from Placebo	Median Duration Days RIS	Median Duration Days PLA
Psychiatric				
Somnolence	9 (1, 52)	During the 1st week	14	10
Appetite increased	14 (1, 48)	Approximately 2 weeks	30	24
Body as a whole – general				
Fatigue	9 (1, 53)	During the 1st week	25.5	5
Gastrointestinal				
Vomiting	21 (1, 57)	During the 1st week	1	1
Saliva increased	10.5 (1, 45)	Approximately 2 weeks	13	12
Constipation	22 (1, 55)	Approximately 3 weeks	14.5	4.5
Endocrine disorders				
Hyperprolactinemia	43 (42, 49)	Approximately Day 40	1[c]	1[c]
Central and peripheral nervous system				
Dizziness	6.5 (1, 31)	Approximately 2 weeks	13	10.5
Tremor	18 (1, 54)	Approximately 2 weeks	8	13
Tachycardia	17 (1, 57)	Approximately 3 weeks	4.5	No comparison
Metabolic and nutritional				
Weight increased	31.5 (1, 51)	Approximately 2 weeks	22	15
Respiratory				
Upper Respiratory Tract Infection	17.5 (1, 55)	Approximately 2 weeks	10	8

[a] Based on each subject's first event.
[b] Time when Kaplan-Meier curves for placebo and risperidone separate from each other.
[c] Duration of 1 day was due to the laboratory assessment being performed at end point.

The sponsor reports that mean days of onset for "dyskinesia" is 120 days and that of tardive dyskinesia was 218 days among all risperidone treated subjects. Both of these days of onset seem to meet criteria for "drug-induced tardive dykinesia." As I mentioned before that many terms that were coded to dyskinesia seem to be typical symptoms of tardive dyskinesia we see in clinical psychiatry as well. Thus, it is critical to know the duration of these symptoms. However, the sponsor

only provided data on durations of these symptoms from the following double-blind studies lasted from 4 to 8 weeks that are not long enough to examine the emergence of tardive dyskinesia. Still, it is worrisome to see the mean duration of dyskinesia be much longer (43 days) in risperidone group compared to placebo group.

- BEL-24: A *4-wk*, randomized, double-blind, placebo-controlled study on Children and adolescents (12--18 yrs) with mental retardation and behavioral disturbances
- CAN-19: A *6-wk*, randomized, double-blind, placebo-controlled study on Children (5-12 yrs) with borderline intellectual functioning or mild to moderate mental retardation and Conduct or other DBD
- USA-93: *Same as CAN-19*.
- NED-9: A *6-wk*, randomized, double-blind, placebo-controlled study on Adolescents (12-18 yrs) with IQ of 60-90 and diagnosis of Conduct Disorder, ADHD, or ODD
- CAN-23: An 8-wk, randomized, double-blind, placebo-controlled, multicenter study on Children (5-12 yrs) with Autistic Disorder and other PDDs
- USA-150: An *8-wk*, randomized, double-blind, placebo-controlled study on Children/adolescents (5-17 yrs and 2 months) with Autistic Disorder

The table below shows the mean duration of important adverse events with days of range from all the subjects in double-blind studies as mentioned above that extracted from Attachment 10.1 (Duration of selected adverse events for double-blind placebo-controlled studies).

Table 10b: AE Duration in Pooled Double Blind Studies (BEL-24, CAN-19, USA-93, NED-9, CAN-23, USA-150)

Important Adverse Events	**Persistent Duration Days**					
	Risperidone			**Placebo**		
	N	Mean	Range	N	Mean	Range
Aggression reaction	5	25	8-48	10	19	1-56
Agitation	6	24	1-41	11	18	2-46
Ataxia	3	17	2-43	1	8	8-8
Automatism	5	20	7-38	1	13	13-13
Bradykinesia*	1	8	8-8	0	-	-
Convulsion	0	-	-	1	1	1-1
Dyskinesia	4	43	27-57	2	23	2-44
Dyskinesia, Tardive**	0	-	-	1	1	1-1
Dysmenorrhea	1	2	2-2	2	2	1-2
Extrapyramidal disorder*	5	15	1-41	0	-	-
Fatigue	52	27	2-58	12	12	1-45
Gait abnormal	2	8	1-14	1	8	8-8
Gynaecomastia	1	15	15-15	2	11	9-12
Hyperkinesia (includes akathisia)	3	16	5-31	3	13	8-18

Hyperprolactinemia	13	1	1-1	1	1	1-1
Hypertonia	11	13	2-43	6	15	8-28
Hypokinesia	2	11	2-20	0	-	-
Muscle contraction involuntary	3	12	4-24	2	19	15-22
Nervousness	4	31	12-45	8	20	1-53
Somnolence	113	18	1-57	33	16	1-56
Suicide	0	-	-	0	-	-
Tachycardia	8	14	1-44	0	-	-
Tongue paralysis	1	5	5-5	0	-	-
Tremor	15	16	2-61	2	13	4-22
Weight Increase	19	23	1-43	3	19	1-42

*The sponsor includes mainly symptoms of Parkinsonism in this category. It's not clear if it includes all or part of "bradykinesia," because "bradykinesia" is another separated items here.
**Data are from studies that are not long enough to see its emergence or make this diagnosis.

In addition to the issue of tardive dyskinesia, there are several more problems we have here:

1) The above classification was based on the sponsor's response that still contains some confusing coding for certain adverse events as mentioned in the previous sections;

2) Some of these adverse effects had only one or no monitor/measure in the studies, such as serum prolactin in autism studies (see our original clinical review). Thus, the durations for these events presented are meaningless;

3) The sponsor splits the whole group of extrapyramidal symptoms but didn't present every individual symptom here, such as oculogyric crisis, dystonia;

4) Still, we don't know the incidence of these events throughout the time period, such as weekly or monthly. -- A table with number and percentage of subjects who had these events throughout the time period will help illustrate this issue more clearly.

Safety Update:

Additionally, we requested the sponsor to submit the Safety Update according to the following instructions:

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Requests #1-5:

In response to our requests #1-5, the sponsor provided the following:

- Highlights added information in this Safety Update
- Provides the list of Serious Adverse Events (SAEs) and Adverse Events (AEs) leading to dropouts that combine all the completed studies in children and adolescents with autism *and/or* other behavioral disorders, *excluding those ongoing studies (see Clinical Program Update for detail)*.
- The updated lists are compared with the list in the previous submission.
- For indications other than the proposed indication, the sponsor separates the lists for the frequencies of adverse events in autistic disorder and DBD/other PDD as well as those occurring in different treatment groups (See tables in attachment).
- Narratives for both SAEs and dropouts due to AE's are provided.
- The ongoing studies are analyzed separately but no narratives are available.

Report Cut-off Date

After the original submission for this NDA supplement in November, 2003, the sponsor submitted a Four-Month Safety Update with the cut-off date as December 31, 2003. This current Safety Update has finalized results from a newly finished study with the cut-off date as June 30, 2004.

Clinical Program Update

A total of 21 clinical studies on children and adolescents, regardless the indications, were included in the cumulative Update.—According to the sponsor, it includes five studies on autistic disorder. In fact, they are the following:

- RIS-BEL-21: A single-dose PK study
- RIS-BEL-22: A four-week, open-label, phase 2 study
- RIS-CAN-23: An eight-week, double-blind placebo-controlled study

- RIS-US-150: It consists of three parts, two studies—An eight-week double-blind study (Part 1), followed by a randomized withdrawal study (Part 2/3: a four-month, open-label follow-up period and an eight-week double-blind placebo controlled withdrawal trial.)

The *only* study that was completed since last submission was RIS-INT-79: A 6-month, double-blind, placebo-controlled , relapse-prevention study in children and adolescents (5-17 years) with Conduct Disorder or other Disruptive Behavioral Disorder (DBD) who were responders after 12 weeks of treatment with risperidone (6 weeks open-label + 6 weeks single-blind) – Dosage range of risperidone was 0.25mg to 1.5 mg per day. A total of 527 subject received risperidone.

In addition to *one* ongoing study (RIS-INT-84) in children and adolescents with DBD, there are *four* more ongoing Phase 3 studies on children and adolescents with other indications (schizophrenia or bipolar I disorder).

Thus, no new study on autism has been conducted since the last safety update.

Data Collection Update

The sponsor reports that safety data presented here are *separate* for studies on these two categories of indications, but *only serious adverse events, including deaths*, from these studies are included in this submission.

Dose Exposure Update

The total exposure to risperidone increased from 679.6 subject-years to 854.8 subject-years in this Update. Total exposure to placebo is not presented.

Review Strategy

This review is focused on information on death, serious adverse events, and dropouts in the new database.

Death

The sponsor reports that no death has occurred in any completed or ongoing studies on children and adolescents.

Serious Adverse Events (SAE)

I. All completed studies:

The sponsor reports that adding the safety data from the newly completed study INT-79 decreases the overall rate of SAE in subjects (from 9.4% to 7.3%) and the percentage of subjects with DBD/PDD (Pervasive disruptive disorder) who had SAE (from 10.3% in previous submission to 7.7% in this Safety Update). However, the SAE rate is not changed in autism subjects. SAEs among placebo group are not mentioned in this update. An examination of the enumerated incidence of SAE in all risperidone treated patients for all studies shows the following events are with increased rate or new:

Table 11. New Cases and Enumerated Incidence of SAE in All Risperidone Treated Subjects of All Completed Studies

SAEs	New Cases	Cumulative %
Condition aggravated	1	2.4%
Injury	3	1.7%
Aggressive reaction	4	0.3%
Suicide attempt	2	0.4%
Convulsion	1	0.2%
Headache	1	0.2%
Stupor	1	0.1%
Abdominal pain	2	0.4%
Psoriasis	1	0.1%
ECG abnormal	1	0.1%
Lymphadenopathy	1	0.1%
Granulocytopenia	2*	0.1%

*See case descriptions below.

Among the list of SAEs provided, the following five types are considered unexpected and are summarized below:

Abnormal ECG: Subject A30255 was a 12 year-old Caucasian boy in Israel. He was diagnosed as conduct disorder and was given risperidone up to 1.5mg/day. His concomitant medication was methylphenidate which was ongoing prior to study entry. On Day 288, he was noticed having an ECG change of ventricular premature beats on a routine ECG. Study medication was discontinued and he discontinued from the study due to this event. The event did resolve after the medications stopped. It was considered possibly study drug-related.–I agree with this determination for this event.

Granulocytopenia: Subject A30045 was a seven year-old Caucasian boy in Belgium. He carried the diagnosis of oppositional defiant disorder and was on risperidone 0.2-0.75mg/day until Day 84. His WBC was 3.9 giga/L at study baseline but went down to 3.4 giga/L on Day 84; neutrophils became 39.3% and neutrophils ABS was down to 1.34. He then was assigned to placebo group of the study for 17 days but it was discontinued due to granulocytopenia on Day 101. The condition didn't resolve after the study medication was stopped and he dropped out of the trial on Day 120. The concommitent medication was methylphenidate. This subject discontinued from the study due to granuloctytopenia and this was considered possibly drug-related. --I agree that this causal relationship between the drug and this serious adverse event couldn't be excluded.

Another subject A40006 was a nine-year-old Caucasian boy in Poland. He was also diagnosed with oppositional defiant disorder and was on risperidone 0.25 – 0.75mg/day for 85 days till he assigned to placebo group and continued for 167 days. He finished the study on Day 252. Though baseline tests for double blind period were normal, on Day 261, 9 days post-study, the subject was diagnosed with granulocytopenia. Treatment with pyridoxine hydrochloride was started on Day 264 and four days later, hematologic tests went back to normal range (WBC went up to 7.2 giga/L, neutrophils, 50.5%, and lymphocytes was down to 36.7%). The sponsor considers this event is probably not related to the study. –I agree with this conclusion and this subject was on placebo for an extended time period (167 days) and in-between he had a viral infection which is not

uncommon to cause decreased WBC. In addition, the diagnosis of granulopenia was already after the study. Thus, it probably should not be counted.

Lymphadenopathy: Subject A30296 was a seven year-old boy in Israel. He had diagnosis of conduct disorder, coexisting ADHD, and a history of Hodgkin's lymphoma, inguinal hernia, and enlarged adenoids. Physical examination at screening was normal. He received risperidone 0.25-1.2mg/day. He was found having lymph node enlargement on Day 92 while he was on maximum dose of risperidone. The subject's mother confirmed that he was investigated for a suspected malignancy in the upper respiratory tract. No date given for resolution of the lymph node enlargement. Baseline lab tests showed elevated eosinophils and platelet count but no follow-up test results available. Study medication continued until Day 100 because he was determined as a non-sustained responder in Phase 2. This event was considered unlikely drug-related considering his medical history. –I agree with this conclusion.

Syncope: Subject A40199 was an 11 year-old Caucasian boy in Poland who was diagnosed with conduct disorder. His medical history includes allergy, asthmatic bronchitis and bronchial asthma. Physical examination at screening was normal. At study entry, he had bronchial asthma for which he received salmeterol xinafoate (a beta agonist for bronchodialator) and cetirizine dihydrochloride (antihistamines). There was no concomitant medication during the study. He received risperidone 0.25 -0.75mg daily. On Day 5 after his first dose of risperidone 0.75mg/day, he experienced syncope and was hospitalized. Vital signs are unavailable for the time of this event. However, his blood pressure was 125/85mmHg and pulse rate was 78 bpm at screening. No treatment was given and it was considered resolved on Day 7. No description was given between Day 5 to 7. He discontinued from the study on Day 41 due to non-responding. The investigator considers this event is doubtfully related.–Without the vital signs at the time of this event and the length of those anti-asthmatic medication use, it is difficult to determine.

Stupor: Subject A30068 was a 15 year-old black boy in Spain. He was diagnosed with oppositional defiant disorder and had no significant medical history. Physical examination at baseline was unremarkable. At study entry, he was noted to have hypermetropia of the eyes, and spondylolisthesis. There was no concomitant medication taken during the study. He received risperidone 0.5 – 1.3mg/day. His dose was 1.3mg/day on Day 31. On Day 32, he had head trauma from the accident while he was biking. He "lost consciousness for a few seconds resulting in a depressed level of consciousness" that was coded as "stupor." Study medication was held for that day and he was hospitalized for observation for 24 hours. It was resolved on the same day without additional intervention. Study was continued. Though no other adverse events were reported, this subject eventually was lost to follow up on Day 187. The investigator considers this event as unrelated to the study medication. –In my opinion, it is critical to know what happened to the patient eventually and if he was more sedated than usual before he had this accident. Stupor seems unlikely caused by the study medication per se.

Convulsion: Subject A#40013 was a nine year-old boy in Poland with conduct disorder. He had no concomitant medications and no significant medical history. While he was receiving risperidone 0.5mg/day on Day 79, he experienced a convulsion and headache that led hospitalization. He was diagnosed with epilepsy with absence seizures and was treated with valproic acid 300mg po bid. The convulsion and headache resolved on Day 85. He subsequently discontinued from the study on Day 91. It is not clear whether any of his symptoms re-appeared after Day 85. At Week 12. Insulin level was low (14 pmol/L),

ALT and AST mildly elevated (ALT 95U/L and AST 85U/L), and neutrophils was low (14%). No other significant lab tests presented. –My opinion is that this event is probably associated with risperidone use considering the tendency of neuroleptics to lower seizure threshold.

According to the sponsor, additional two subjects in study INT-79 were categorized to WHO-preferred term of suicide attempt, thus the number of subjects who had this SAE increases from four (in the previous submission and had been discussed in the our original review of the sNDA) to six. Neither of these was during the double-blind period of the study. None of these are autistic patients.

II. Ongoing Studies:

The following SAEs in the ongoing studies are considered unexpected and deserve particular attention in my opinion. However, no narrative summaries are available for them. The sponsor needs to provide the narrative summaries for these cases.

Table 12. SAEs in Ongoing Studies

SAEs	Number of Subjects
Adenoidectomy	2*
Aseptic meningitis	1
Operation NOS	1
Papilledema	1
Premature labor	1

*in Studies INT-84 and USA-234

Adverse Events Leading to Drop-out

I. All Completed Studies:

Like the incidence of SAEs, the updated results from adding RIS-INT-79 to the sNDA database decreased the percentage of subjects with DBD/other PDD who had adverse events leading to discontinuation (from 8.5% in the sNDA to 6.6% in the Safety Update), which resulted in a decrease in the overall percentage of subjects with adverse events leading to discontinuations (from 7.8% to 6.3%). The most common reason for discontinuation is insufficient response in both risperidone (4.1%) and placebo groups (20.3%). Adverse events leading to dropout is 1.8% in risperidone group and only 0.8% in placebo group. No change for incidence in autistic subjects as there was no new study among this population. Comparing with the incidences of adverse events leading to the discontinuation for all studies from the updated table presented by the sponsor, the following are the events that are new or with increased incidence leading to discontinuation:

Table 13. New Cases of Adverse Events that Leads to Discontinuation in All Completed Studies

Adverse Events	New or Increased Cases	Cumulative %
Medication Error	1	0.1%
QT Prolonged	1	0.1%
ECG Abnormal	1	0.1%

Respiratory Disorder	1	0.1%
Liver Enzyme Increased	1	0.1%
Skeletal Pain	1	0.1%
Breast Pain	1	0.1%
Lactation Nonpuerperal	1	0.1%
Saliva Increased	1	0.1%
Nausea	1	0.1%
Speech Disorder	1	0.1%
Muscle Contractions Involuntary	1	0.1%
Peripheral Edema	1	0.1%
Hot Flashes	1	0.1%
Crying Abnormal	1	0.1%
Back Pain	1	0.1%
Paranoid Reaction	1	0.1%
Convulsion	1	0.1%
Aggressive Reaction	1	0.1%
Lab Values Abnormal	2	0.1%
Granulocytopenia	1	0.1%
Pain	1	0.2%
Fatigue	2	0.2%
Anxiety	1	0.3%
Suicide Attempt	2	0.3%
Condition Aggravated	1	0.4%
Somnolence	1	0.4%
Headache	1	0.5%
Weight Gain	1	0.9%

Again, the sponsor excluded the ongoing studies on schizophrenia and bipolar in this analysis.

The subject with "Abnormal ECG" was described in the previous section SAE.

The subject with QT prolongation was a 10 year-old Caucasian boy in Germany. He had diagnosis of oppositional defiant disorder and was receiving risperidone 0.75mg/day on Day 84. His ECG changed from baseline HR 64 bpm and QTcB 450ms with a prominent U wave to HR 75bpm and QTcB interval of 530ms with ST-T-U. Electrolytes were not provided. Two weeks after the medication stopped, the QTc interval was still prolonged but became less than 500ms. He discontinued the study eventually due to this AE.—In my opinion, this is probably related to the study medication.

The two subjects with "Lab Value Abnormality" are:

1) Subject #A30083 was an 11 year-old Caucasian boy in Spain with conduct disorder had abnormally high insulin and insulin-like GF-I (growth factor I) levels while taking risperidone 0.5-1.5mg/day. He discontinued the study on

Day 149 due to this adverse effect. The subject also had high prolactin (from baseline 15 went up to 596mU/L) level while on risperidone. Glucose level was not presented.

2) Subject # A30091 was another 13 year-old Caucasian boy in Spain with conduct disorder who discontinued the trial due to high insulin and insulin-like GF-I levels after taking risperidone 0.25 to 1.0 mg/day for 174 days. This subject also had increased prolactin level from 150 mU/L at screening to 505 mU/L while on risperidone. Again, glucose data was not presented.

Subject # A30159 was a 13 year-old Caucasian boy in Germany with oppositional defiant disorder, motor developmental retardation, ADHD. He had mildly elevated ALT at screening (59u/L) and on Day 82, while receiving risperidone 0.6 mg/day, his ALT (reference: 5-45 U/L) was found up to 351 U/L at double blind baseline (Day 84) and 78 U/L when redrawn 8 days after the last dose of risperidone treatment; AST was normal at screening but elevated to 74U/L during the treatment; No bilirubin level is presented; the GGT (reference: 2-49 U/L) was 186 U/L at double blind baseline and was 105 U/L when redrawn 8 days after the last dose of risperidone treatment. He dropped out of the study on Day 90. The investigator considered the increase of SGPT/GGT moderate in severity and very likely related to study medication. –I agree with the sponsor that hepatic enzyme increase has been reported during risperidone treatment and the causal relationship in this case can't be excluded.

II. Ongoing Studies:

Report of dropouts in ongoing studies can not be found in the submission.

Requests #6: We requested the sponsor to provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

In the original submission for this NDA supplement, the sponsor extracted the postmarketed spontaneously reported safety data for the time period of May 1, 1993 through August 30, 2003 for the use of risperidone in children and adolescents 5 through 17 years of age either being treated for or with a history of autism, autistic spectrum disorder, Asperger's syndrome, or Pervasive Developmental Disorder. In the 4-month safety update submitted last year, the reported adverse events covered the time period of 31 August 2003 through 31 December 2003. This update was performed in the Johnson & Johnson Drug Safety and Surveillance worldwide safety database in patients aged 5 through 17 year regardless of indication and for all formulations and dosage forms of the product from 31 May 1993 through 30 June 2004.

According to the sponsor, the estimated U.S. pediatric exposure (children and adolescents) from 1994 to 2004 was (b) (4) person years. The estimate of worldwide pediatric exposure (5 through 17 years of age) during 2001, 2002, and 2003 was (b) (4) , respectively.

Among the total of 3148 cases that were identified, 587 cases were considered as serious. The sponsor provides the following table that includes serious and nonserious cases with different indications received between May 31 1993 through 30 June 2004.

Table 14. Spontaneously Reported Cases in Patients Aged 5 to 17 Years

Indication	Number of Case
Psychosis/Psychoses	399
Schizophrenic Disorder	329
Various Behavioral Disorders	231
ADHD	218
Autistic Disorder	152
Bipolar Disorder	151
Other Diagnoses	1018
Indication Unknown	650
Total	3148

A total of 22 deaths were reported in the postmarketing pediatric surveillance. Based on the sponsor's report, causes of deaths are summarized in the table below:

Table 15. Cases of Deaths in Postmarketing Surveillance and the Reported Causes

Causes of Deaths		Number of Cases
Suicide	Intentional Overdose	2
	Unspecified Method	3
Encephalitis		1
Pulmonary Embolism		1
Bronchopneumonia		1
Drowning		1
Acute Respiratory Distress Syndrome		3
Hypoglycemic Seizure		1
NMS		1
Asphyxiation from Seizure		1
"Violent" Seizure		1
Sudden Death (collapsed)		1
Death after Two Syncopal Episodes		1
Death of Unidentified Case (?)		1
Death probably due to NMS		1
Death of Unidentified Cause		2
Total		22

The suicide cases were in ages 16 (n=1) and 17 (n=4). The case of unidentified case was reported by a health care professional but this 15 year-old girl was not eventually identified, and thus, the sponsor states that the death was not confirmed. The cases of unidentified cause included a patient taking concomitant

imipramine in a group home and died as well as a boy who was administered risperidone at home by his mother and no more information were provided.

The sponsor summarized the serious adverse events in the following table. I didn't find more detailed information on them.

Table 16. Distribution of Adverse Events by System Organ Class in Patients Aged 5 to 17 Years and in Patients of all Other Age (by the Sponsor)

System Organ Class	Number of Spontaneous Serious Cases		% of Spontaneous Serious Cases		Proportional Ratio of Serious Cases[b]
	5 to 17 Years[a]	All Other Ages	5 to 17 Years	All Other Ages	
Blood & Lymphatic System Disorders	48	392	8.5	7.1	1.2
Cardiac Disorder	38	518	6.7	9.4	0.7
Congenital, Familial & Genetic Disorder	4	17	0.7	0.30	2.3
Ear and Labyrinth Disorder	2	17	0.4	0.3	1.3
Endocrine Disorder	11	101	1.9	1.8	1.1
Eye Disorder	20	105	3.5	1.9	1.8
Gastrointestinal Disorder	64	399	11.3	7.2	1.6
General Disorders & Administration Site Conditions	148	1691	26.1	30.6	0.9
Hepatobiliary Disorders	12	142	2.1	2.5	0.8
Immune System Disorders	7	30	1.2	0.5	2.2
Infections and Infestations	22	266	3.9	4.8	0.8
Injury, Poisoning & Procedural Complications	42	328	7.4	5.9	1.3
Investigations	103	712	18.2	12.9	1.4
Metabolism & Nutrition Disorders	41	406	7.2	7.3	<1.0
Musculoskeletal & Connective Tissue Disorders	22	252	3.9	4.6	0.8
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	9	123	1.5	2.2	0.7
Nervous System Disorders	274	1974	48.3	35.7	1.4
Psychiatric Disorders	118	892	20.8	16.2	1.3
Renal & Urinary Disorders	31	218	5.5	3.9	1.4
Reproductive System & Breast	29	195	5.1	3.5	1.5
Respiratory, Thoracic & Mediastinal Disorders	47	343	8.2	6.2	1.3
Skin & Subcutaneous Tissue Disorder	29	205	5.1	3.7	1.4
Social Circumstances	1	37	0.2	0.7	0.3
Surgical and Medical Procedures	2	57	0.4	1.0	0.4
Vascular Disorders	25	285	4.4	5.2	0.8
Total Number of Cases	587	5503			

a: Excludes the 20 cases in which age was indeterminable

b: % of spontaneous serious cases in ages 5-17 years divided by the % of spontaneous serious cases in all other ages

The literature search was conducted by the sponsor in 4 phases. The first search, performed on 25 May 2000, included all clinical published data up to that date. The remaining searches included all available clinical published data from: 26 May 2000 to 31 July 2003 (second search), 31 July 2003 to 31 December 2003 (third search; summarized in the 4-month Safety Update), and 1 January 2004 to 30 June 2004 (fourth search). The sponsor presents the combined results of the 4 searches in this summary. The sponsor's database was searched for articles relating to the use of risperidone in

children and adolescents (≤17 years of age). In addition, the Medline database was searched to check the completeness of the data.

The sponsor reports Literature Survey showed that no death was reported. A total of 11 subjects had SAE. –Among these, 10 of them were in the sNDA. The diagnoses of SAE are listed in the following table:

Table 17. Serious Adverse Events from Postmarketing Surveillance

Serious Adverse Event	No. of Subjects
Neuroleptic malignant syndrome (NMS)	5
Tardive dyskinesia	3*
Acute dystonic reaction	1
Probable viral encephalitis	1
Toxic carbamazepine level and related serious symptoms**	1

*2 subjects in the sNDA.

**After initiation of risperidone treatment. A drug interaction trial was performed, however, it didn't indicate that risperidone would increase carbamazepine level.

The symptoms of the subject with probably viral encephalitis were described as fever, hypertonia, leukocytosis, and elevated CPK. This seems to resemble symptoms of NMS. I am not clear how NMS was ruled out in this case based on this brief description.

According to the sponsor, there were four cases of overdose, but none was fatal.

Discontinuation of risperidone due to adverse events was reported in additional 5 articles. The most common treatment-limiting events were the following:

Table 18. Common Treatment Limiting AEs from Postmarketing Surveillance

Discontinuation AEs	Number of New Cases	Cumulative Cases
Weight gain	3	14
EPS	1	9
Prolactin increase	6	6
Sedation	0	5

Requests #7: We requested the sponsor to provide English translations of current approved foreign labeling not previously submitted.

The sponsor lists labeling for approved pediatric indications, "Conduct Disorder in Mental Retardation/Disruptive Behavior Disorder" from 30 countries and "Autism" from 2 countries. However, *translations of labeling from Brazil, Singapore, and Vietnam are not found*; Instead, there was a page from Janssen-CILAG which was located in UK. No country was indicated on the sample of page 826-831 except "(b) (4), Italy" which is hard to interpret.

Review is focused on contraindications, warnings, and precautions in those translated foreign labeling.

A few countries list conditions other than hypersensitivity to the product (risperidone) as *contraindications*. These include:

- "Severe depression due to alcoholism" or "CNS depressants" (Mexico), or CNS depression due to use of alcohol or CNS-depressing medicines (e.g. Belgium), or situations with overdosage of barbiturates, opiates or alcohol (Iceland and Sweden), as well as "comatose patients" (Mexico)

- Patients with Parkinson's disease (Mexico), dementia patients with Parkinsonian symptoms in the form of rigor, bradykinesia and parkinsonian postural disorders, as well as in dementia patients with a probable diagnosis of Lewy body dementia (in addition to the symptoms of dementia, at least two of the following three symptoms: parkinsonism/visual hallucinations/fluctuating course) (Switzerland)

- Children under 5 years of age (Sweden and South Africa), especially with RISPERDAL film-coated tablets, QUICKLET orodispersible tablets and solution because of insufficient experience (e.g. Germany).

- Patients with phenylketonuria because of the presence of aspartame (e.g. France).

- Existing hyperprolactinemia not caused by drugs (Germany)

- Breast-feeding women (e.g. France and South Africa)

- In combination with quinidine or codeine (Iceland)

Most of the above are listed as part of Warnings (e.g. cerebrovascular adverse events in elderly patients with dementia), Precautions (e.g. potential for cognitive and motor impairment), and Information for Patients (e.g. phenylkentonuria), Postintroduction Reports (e.g. Parkinson's disease aggravated) in the US labeling as well as those of many other countries'. Interaction with quinidine and its risks are acknowledged in the section of "Metabolism" and "Management for Overdosage." In my opinion, the message is clear to clinicians. Codeine is a central nervous system suppressant like alcohol. The risk for such drug interaction is discussed in "Drug Interactions" section of our labeling.

The following *warnings and precautions* are not found in our labeling but mentioned in other countries:

- Premenopausal women who develop secondary amenorrhea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss. (Australia and South Africa)

- Phenothiazines and some beta-blockers may increase the plasma concentrations of risperidone but not those of the antipsychotic fraction. (Australia and Austria)

- Risperdal should be used with particular caution in the presence of prolactindependent tumors, such as prolactinomas of the pituitary gland, and in possibly prolactin-dependent tumors, such as epithelial breast tumors. (Switzerland)

  -- In our labeling, we discussed the increase prolactin release, and pointed out that "the relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown;" We point out that "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." We warn that its antiemetic effect may mask signs and symptoms of brain tumor, intestinal obstruction, Reye's syndrome.

- In patients with dementia of the Lewy body type or Parkinson's disease, physicians should establish the risk/benefit ratio when prescribing antipsychotics, including Risperdal, as there can be an increased risk of neuroleptic malignant syndrome or a deterioration of Parkinson-like symptoms in these patients. (Australia and Austria)

  -- What we emphasized in dementia patients are increased risks of cardiovascular disease, including stroke, dysphagia leading to aspiration pneumonia. Our labeling does not emphasize the risk of worsening of Parkinson-like symptoms or NMS in this population.

- It should be considered in the treatment of patients with lactose intolerance that 0.5 mg tablets contain 91 mg, 1 mg tablets 131 mg, 2 mg tablets 130 mg, 3 mg tablets 195 mg, 4 mg tablets 260 mg lactose as well. (Hungary)

  -- We did have lactose as part of the tablet description at the beginning of the labeling. However, this may not give enough attention to doctors and patients. Thus, we should probably consider mention this in the section of "Information for Patients."

- Risperdal 2 mg tablets should be used with caution in patients with hypersensitivity reactions to azo dyes (E 110), acetylsalicylic acid and other prostaglandin inhibitors… In patients with a particular predisposition (asthma, chronic urticaria or hypersensitivity to nonsteroidal antirheumatics) the azo dye contained in Risperdal 2 mg tablets (E 110, orange yellow) can cause hypersensitivity reactions in skin and respiratory organs. (Switzerland)

-- Hypersensitivity to dye was not mentioned specifically in our labeling, but we point out issue of hypersensitivity in general.

In our current labeling, it is said that "safety and effectiveness in children have not been established. The following are emphasized in the labeling of foreign countries' *for children and adolescents*:

- "Regular clinical monitoring should be arranged, including measurements of height and weight and an examination for neurological adverse effects."

- "Particularly in children near puberty, a regular assessment should be made of endocrine adverse effects."

- "In addition to the monitoring of the tolerability of treatment, a reevaluation of the indication for treatment must be made by the specialist (psychiatrist, pediatric psychiatrist) at each consultation."

- "Data for up to one year indicate there is no effect on growth and puberty. However, the consequences for growth and puberty of exposure for more than one year are unknown."

- "The following adverse events have been reported as very common in children and adolescents with conduct disorders: somnolence, headache, weight increase, hyperprolactinaemia."

- "In short-term studies, sedation was the most common adverse reaction (in 34.6%) and it was more frequent than in adults. Sedation was generally mild and decreased during treatment. Other adverse reactions in short-term studies included headache in 12.3%, hyperprolactinemia in 11.2% and weight increase in 10.2%."

- "Also in long-term studies, somnolence was the most frequent adverse reaction (30.8%), headache 21.1%, weight increase 20% and hyperprolactinemia 15.5%."

- "The combined use of psychostimulants (e.g. methylphenidate) with Risperdal in children and adolescents did not alter the pharmacokinetics and efficacy of Risperdal."

- "The incidence of somnolence was reduced when psychostimulants were used concomitantly."

- "In short-term studies in children and adolescents, weight increase of 2.2 kg with risperidone and 0.6 kg with placebo was observed. In long-term studies, the increase in BMI was double the increase in BMI that is considered normal along with the increase in age."

- "In some children and adolescents, prolactin levels transiently increased to 2- to 4-fold compared to baseline. Prolactin levels approach normal levels with long-term treatment."

- "Adverse reactions potentially related to hyperprolactinemia (gynecomastia in boys, menstruation disturbances, more infrequently galactorrhea or premature puberty) were reported in 3.5% of children and adolescents during long-term studies. Deleterious effects on progress in puberty or on growth in height were not observed during 1 year of treatment."

- "A careful risk-benefit analysis should be done before prescribing Risperdal in children. The need to continue treatment with risperidone should be assessed continuously (*see Undesirable effects).* The indication 'symptomatic treatment of disorders of social behavior, oppositional defiant disorder or other socially disruptive behavior' has been studied in children over 5 years of age. Children under 5 years of age should therefore not be given Risperdal in this indication. There is no experience in children and adolescents under 15 years of age in the other indications."

(b) (4)

III. Conclusions and Recommendations

Based on my review, I do not believe that this drug demonstrate the efficacy of treatment of (b) (4) I am also very concerned of the safety issues of using this drug in children with this disease. This is because the safety data are not sufficient in several aspects (see above review contents) and further studies are needed. Moreover, there is no solid rational for the minimum starting dosage proposed. Thus, I do not recommend the division to take approvable action for this NDA supplement. If necessary, bringing this project to advisory committee in the public forum can be considered.

June Cai, M.D.
May 17, 2005

Cc: NDA XXX
NDA XXX
NDA XXX
HFD-120 Div. Files
HFD-120/JCai
/GDubitsky
/PAndreason
/TLaughren
/CSO

I. Appendix:

Table A1. Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (Provided by the Sponsor)

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
TOTAL NO. SUBJECTS WITH ADVERSE EVENTS	1114 (82.6)	81 (97.6)	1033 (81.7)
PSYCHIATRIC DISORDERS	620 (46.0)	72 (86.7)	548 (43.3)
SOMNOLENCE	386 (28.6)	51 (61.4)	335 (26.5)
APPETITE INCREASED	196 (14.5)	37 (44.6)	159 (12.6)
INSOMNIA	67 (5.0)	14 (16.9)	53 (4.2)
AGGRESSIVE REACTION	66 (4.9)	2 (2.4)	64 (5.1)
AGITATION	49 (3.6)	3 (3.6)	46 (3.6)
ANXIETY	38 (2.8)	12 (14.5)	26 (2.1)
ANOREXIA	34 (2.5)	6 (7.2)	28 (2.2)
EMOTIONAL LABILITY	29 (2.2)	1 (1.2)	28 (2.2)
NERVOUSNESS	28 (2.1)	3 (3.6)	25 (2.0)
DEPRESSION	24 (1.8)	0	24 (1.9)
SLEEP DISORDER	19 (1.4)	0	19 (1.5)
APATHY	18 (1.3)	1 (1.2)	17 (1.3)
CONCENTRATION IMPAIRED	18 (1.3)	3 (3.6)	15 (1.2)
PARONIRIA	13 (1.0)	1 (1.2)	12 (0.9)
CONFUSION	8 (0.6)	4 (4.8)	4 (0.3)
NEUROSIS	8 (0.6)	1 (1.2)	7 (0.6)
SUICIDE ATTEMPT	8 (0.6)	0	8 (0.6)
PERSONALITY DISORDER	6 (0.4)	1 (1.2)	5 (0.4)
THINKING ABNORMAL	5 (0.4)	1 (1.2)	4 (0.3)
AMNESIA	4 (0.3)	0	4 (0.3)
EXCESSIVE MASTURBATION	3 (0.2)	0	3 (0.2)
SOMNAMBULISM	3 (0.2)	0	3 (0.2)
DRUG ABUSE	2 (0.1)	0	2 (0.2)
HALLUCINATION	2 (0.1)	1 (1.2)	1 (0.1)
LIBIDO INCREASED	2 (0.1)	0	2 (0.2)
PARANOID REACTION	2 (0.1)	0	2 (0.2)
DEPRESSION AGGRAVATED	1 (0.1)	0	1 (0.1)
EUPHORIA	1 (0.1)	0	1 (0.1)
MANIC REACTION	1 (0.1)	0	1 (0.1)

Note: Adverse events reported during treatment or within 4 days of end of treatment are included.
Incidence is based on the number of subjects, not the number of events.
Data from the following studies were pooled for this table: BEL-22,BEL-24,CAN-19,CAN-20,CAN-23,HUN-4,INT-41,INT-70,INT-79,NED-9,USA-

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (c

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
BODY AS A WHOLE - GENERAL DISORDERS	553 (41.0)	48 (57.8)	505 (39.9)
FATIGUE	194 (14.4)	33 (39.8)	161 (12.7)
FEVER	141 (10.5)	15 (18.1)	126 (10.0)
INJURY	101 (7.5)	0	101 (8.0)
INFLUENZA-LIKE SYMPTOMS	88 (6.5)	3 (3.6)	85 (6.7)
LAB VALUES ABNORMAL	50 (3.7)	0	50 (4.0)
CONDITION AGGRAVATED	47 (3.5)	0	47 (3.7)
PAIN	25 (1.9)	1 (1.2)	24 (1.9)
LEG PAIN	22 (1.6)	1 (1.2)	21 (1.7)
ASTHENIA	18 (1.3)	0	18 (1.4)
ALLERGIC REACTION	16 (1.2)	0	16 (1.3)
BACK PAIN	15 (1.1)	0	15 (1.2)
CRYING ABNORMAL	13 (1.0)	1 (1.2)	12 (0.9)
ALLERGY	12 (0.9)	0	12 (0.9)
CHEST PAIN	11 (0.8)	1 (1.2)	10 (0.8)
RIGORS	6 (0.4)	0	6 (0.5)
SYNCOPE	6 (0.4)	1 (1.2)	5 (0.4)
ALLERGY AGGRAVATED	5 (0.4)	1 (1.2)	4 (0.3)
MALAISE	5 (0.4)	1 (1.2)	4 (0.3)
OEDEMA	3 (0.2)	1 (1.2)	2 (0.2)
PALLOR	3 (0.2)	0	3 (0.2)
CHEST PAIN SUBSTERNAL	2 (0.1)	0	2 (0.2)
HALITOSIS	2 (0.1)	0	2 (0.2)
HOT FLUSHES	2 (0.1)	0	2 (0.2)
TEMPERATURE CHANGED SENSATION	2 (0.1)	0	2 (0.2)
BREATH ODOUR NOS	1 (0.1)	1 (1.2)	0
CHEST PAIN PRECORDIAL	1 (0.1)	0	1 (0.1)
HYPOTHERMIA	1 (0.1)	0	1 (0.1)
NASAL SEPTUM PERFORATION	1 (0.1)	0	1 (0.1)
OEDEMA GENITAL	1 (0.1)	0	1 (0.1)
OEDEMA MOUTH	1 (0.1)	0	1 (0.1)
OEDEMA PERIPHERAL	1 (0.1)	0	1 (0.1)
SCAR	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continued)

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
RESPIRATORY SYSTEM DISORDERS	547 (40.6)	49 (59.0)	498 (39.4)
RHINITIS	280 (20.8)	28 (33.7)	252 (19.9)
UPPER RESP TRACT INFECTION	189 (14.0)	26 (31.3)	163 (12.9)
COUGHING	140 (10.4)	18 (21.7)	122 (9.6)
PHARYNGITIS	140 (10.4)	2 (2.4)	138 (10.9)
BRONCHITIS	44 (3.3)	0	44 (3.5)
SINUSITIS	38 (2.8)	0	38 (3.0)
ASTHMA	18 (1.3)	2 (2.4)	16 (1.3)
LARYNGITIS	11 (0.8)	0	11 (0.9)
PNEUMONIA	11 (0.8)	0	11 (0.9)
DYSPNOEA	10 (0.7)	0	10 (0.8)
RESPIRATORY DISORDER	6 (0.4)	1 (1.2)	5 (0.4)
BRONCHOSPASM	5 (0.4)	0	5 (0.4)
STRIDOR	2 (0.1)	0	2 (0.2)
TRACHEITIS	2 (0.1)	0	2 (0.2)
HYPERPNOEA	1 (0.1)	0	1 (0.1)
HYPERVENTILATION	1 (0.1)	0	1 (0.1)
PLEURISY	1 (0.1)	0	1 (0.1)
PULMONART CONGESTION	1 (0.1)	0	1 (0.1)
PULMONART OEDEMA	1 (0.1)	0	1 (0.1)
SPUTUM INCREASED	1 (0.1)	0	1 (0.1)
THROAT TIGHTNESS	1 (0.1)	0	1 (0.1)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	490 (36.4)	39 (47.0)	451 (35.7)
HEADACHE	288 (21.4)	11 (13.3)	277 (21.9)
DIZZINESS	70 (5.2)	7 (8.4)	63 (5.0)
HYPERTONIA	48 (3.6)	6 (7.2)	42 (3.3)
TREMOR	46 (3.4)	9 (10.8)	37 (2.9)
EXTRAPYRAMIDAL DISORDER	38 (2.8)	5 (6.0)	33 (2.6)
MUSCLE CONTRACTIONS INVOLUNTARY	30 (2.2)	3 (3.6)	27 (2.1)
SPEECH DISORDER	30 (2.2)	2 (2.4)	28 (2.2)
HYPERKINESIA	28 (2.1)	1 (1.2)	27 (2.1)
HYPOKINESIA	23 (1.7)	1 (1.2)	22 (1.7)
DYSKINESIA	21 (1.6)	5 (6.0)	16 (1.3)
BRADYKINESIA	15 (1.1)	0	15 (1.2)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continued)

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS (continued)			
CRAMPS LEGS	14 (1.0)	0	14 (1.1)
GAIT ABNORMAL	14 (1.0)	0	14 (1.1)
FAECAL INCONTINENCE	13 (1.0)	1 (1.2)	12 (0.9)
DYSTONIA	12 (0.9)	0	12 (0.9)
VERTIGO	10 (0.7)	0	10 (0.8)
AUTOMATISM	7 (0.5)	5 (6.0)	2 (0.2)
MIGRAINE	7 (0.5)	0	7 (0.6)
OCULOGYRIC CRISIS	7 (0.5)	0	7 (0.6)
CONVULSIONS	6 (0.4)	0	6 (0.5)
EEG ABNORMAL	5 (0.4)	0	5 (0.4)
PARAESTHESIA	5 (0.4)	0	5 (0.4)
ABSCENCES	4 (0.3)	2 (2.4)	2 (0.2)
ATAXIA	4 (0.3)	2 (2.4)	2 (0.2)
NEUROPATHY	4 (0.3)	0	4 (0.3)
DYSAESTHESIA	3 (0.2)	0	3 (0.2)
STUPOR	3 (0.2)	1 (1.2)	2 (0.2)
DYSKINESIA TARDIVE	2 (0.1)	0	2 (0.2)
DYSPHONIA	2 (0.1)	0	2 (0.2)
HYPOTONIA	2 (0.1)	1 (1.2)	1 (0.1)
APRAXIA	1 (0.1)	0	1 (0.1)
COORDINATION ABNORMAL	1 (0.1)	0	1 (0.1)
HYPOAESTHESIA	1 (0.1)	0	1 (0.1)
HYPOREFLEXIA	1 (0.1)	0	1 (0.1)
MENINGITIS	1 (0.1)	0	1 (0.1)
NYSTAGMUS	1 (0.1)	0	1 (0.1)
TETANY	1 (0.1)	0	1 (0.1)
TONGUE PARALYSIS	1 (0.1)	0	1 (0.1)
GASTRO-INTESTINAL SYSTEM DISORDERS	467 (34.6)	49 (59.0)	418 (33.0)
VOMITING	148 (11.0)	20 (24.1)	128 (10.1)
ABDOMINAL PAIN	105 (7.8)	2 (2.4)	103 (8.1)
NAUSEA	95 (7.0)	6 (7.2)	89 (7.0)
SALIVA INCREASED	87 (6.5)	18 (21.7)	69 (5.5)
DYSPEPSIA	85 (6.3)	4 (4.8)	81 (6.4)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continued)

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 PDD/OTHER PDD (N=1265)
GASTRO-INTESTINAL SYSTEM DISORDERS (continued)			
DIARRHOEA	79 (5.9)	10 (12.0)	69 (5.5)
CONSTIPATION	43 (3.2)	16 (19.3)	27 (2.1)
GASTROENTERITIS	26 (1.9)	0	26 (2.1)
TOOTH ACHE	18 (1.3)	1 (1.2)	17 (1.3)
MOUTH DRY	17 (1.3)	10 (12.0)	7 (0.6)
TOOTH DISORDER	11 (0.8)	0	11 (0.9)
GASTRITIS	9 (0.7)	0	9 (0.7)
GASTRO-INTESTINAL DISORDER NOS	8 (0.6)	0	8 (0.6)
FLATULENCE	7 (0.5)	2 (2.4)	5 (0.4)
STOMATITIS ULCERATIVE	5 (0.4)	0	5 (0.4)
DYSPHAGIA	3 (0.2)	1 (1.2)	2 (0.2)
GASTROESOPHAGEAL REFLUX	3 (0.2)	0	3 (0.2)
GINGIVITIS	3 (0.2)	0	3 (0.2)
TOOTH CARIES	3 (0.2)	0	3 (0.2)
CHEILITIS	2 (0.1)	0	2 (0.2)
GLOSSITIS	2 (0.1)	0	2 (0.2)
MUCOSITIS NOS	2 (0.1)	0	2 (0.2)
STOMATITIS	2 (0.1)	0	2 (0.2)
STOMATITIS APHTHOUS	2 (0.1)	0	2 (0.2)
TEETH-GRINDING	2 (0.1)	0	2 (0.2)
TONGUE DISORDER	2 (0.1)	0	2 (0.2)
ANUS DISORDER	1 (0.1)	0	1 (0.1)
APPENDICITIS	1 (0.1)	0	1 (0.1)
DIARRHOEA BLOODY	1 (0.1)	0	1 (0.1)
ENTERITIS	1 (0.1)	0	1 (0.1)
HAEMATEMESIS	1 (0.1)	0	1 (0.1)
HAEMORRHAGE RECTUM	1 (0.1)	0	1 (0.1)
HICCUP	1 (0.1)	0	1 (0.1)
LEUKOPLAKIA ORAL	1 (0.1)	0	1 (0.1)
MALABSORPTION	1 (0.1)	0	1 (0.1)
OESOPHAGITIS	1 (0.1)	0	1 (0.1)
ORAL HAEMORRHAGE	1 (0.1)	0	1 (0.1)
PANCREATIC SECRETION DECREASED	1 (0.1)	0	1 (0.1)
PERIODONTAL DESTRUCTION	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continue

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
GASTRO-INTESTINAL SYSTEM DISORDERS (continued)			
TONGUE GEOGRAPHIC	1 (0.1)	0	1 (0.1)
METABOLIC AND NUTRITIONAL DISORDERS	240 (17.8)	12 (14.5)	228 (18.0)
WEIGHT INCREASE	195 (14.5)	6 (7.2)	189 (14.9)
LDH INCREASED	13 (1.0)	0	13 (1.0)
THIRST	12 (0.9)	6 (7.2)	6 (0.5)
PHOSPHATASE ALKALINE INCREASED	8 (0.6)	1 (1.2)	7 (0.6)
OBESITY	5 (0.4)	0	5 (0.4)
CREATININE BLOOD INCREASED	4 (0.3)	0	4 (0.3)
WEIGHT DECREASE	4 (0.3)	0	4 (0.3)
DEHYDRATION	3 (0.2)	0	3 (0.2)
POLYDIPSIA	2 (0.1)	0	2 (0.2)
BUN INCREASED	1 (0.1)	0	1 (0.1)
FLUID OVERLOAD	1 (0.1)	0	1 (0.1)
HYPERKALAEMIA	1 (0.1)	0	1 (0.1)
HYPERNATRAEMIA	1 (0.1)	0	1 (0.1)
HYPERPROTEINAEMIA	1 (0.1)	0	1 (0.1)
HYPERTRIGLYCERIDAEMIA	1 (0.1)	0	1 (0.1)
HYPERURICAEMIA	1 (0.1)	0	1 (0.1)
HYPOCALCAEMIA	1 (0.1)	0	1 (0.1)
HYPOCHOLESTEROLAEMIA	1 (0.1)	0	1 (0.1)
KETOSIS	1 (0.1)	0	1 (0.1)
LACTOSE INTOLERANCE	1 (0.1)	0	1 (0.1)
XEROPHTHALMIA	1 (0.1)	0	1 (0.1)
RESISTANCE MECHANISM DISORDERS	172 (12.8)	2 (2.4)	170 (13.4)
INFECTION VIRAL	59 (4.4)	0	59 (4.7)
INFECTION	45 (3.3)	0	45 (3.6)
INFECTION PARASITIC	33 (2.4)	0	33 (2.6)
OTITIS MEDIA	31 (2.3)	1 (1.2)	30 (2.4)
INFECTION FUNGAL	9 (0.7)	0	9 (0.7)
ABSCESS	7 (0.5)	0	7 (0.6)
HERPES SIMPLEX	7 (0.5)	0	7 (0.6)
INFECTION BACTERIAL	4 (0.3)	0	4 (0.3)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continued)

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 PDD/OTHER PDD (N=1265)
RESISTANCE MECHANISM DISORDERS (continued)			
HERPES ZOSTER	2 (0.1)	0	2 (0.2)
SEPSIS	2 (0.1)	0	2 (0.2)
MONILIASIS	1 (0.1)	1 (1.2)	0
MONILIASIS GENITAL	1 (0.1)	0	1 (0.1)
VACCINATION COMPLICATION	1 (0.1)	0	1 (0.1)
SKIN AND APPENDAGES DISORDERS	169 (12.5)	12 (14.5)	157 (12.4)
RASH	57 (4.2)	8 (9.6)	49 (3.9)
ECZEMA	16 (1.2)	1 (1.2)	15 (1.2)
ACNE	12 (0.9)	2 (2.4)	10 (0.8)
DERMATITIS	12 (0.9)	0	12 (0.9)
PRURITUS	12 (0.9)	1 (1.2)	11 (0.9)
RASH ERYTHEMATOUS	11 (0.8)	0	11 (0.9)
SKIN DISORDER	10 (0.7)	0	10 (0.8)
SKIN DRY	10 (0.7)	1 (1.2)	9 (0.7)
PHOTOSENSITIVITY REACTION	9 (0.7)	0	9 (0.7)
URTICARIA	8 (0.6)	0	8 (0.6)
DERMATITIS FUNGAL	7 (0.5)	0	7 (0.6)
SKIN STRIAE	6 (0.4)	0	6 (0.5)
VERRUCA	6 (0.4)	0	6 (0.5)
RASH MACULO-PAPULAR	5 (0.4)	1 (1.2)	4 (0.3)
SWEATING INCREASED	4 (0.3)	0	4 (0.3)
PARONYCHIA	3 (0.2)	0	3 (0.2)
RASH PUSTULAR	3 (0.2)	0	3 (0.2)
SKIN EXFOLIATION	3 (0.2)	0	3 (0.2)
SKIN ULCERATION	3 (0.2)	0	3 (0.2)
BULLOUS ERUPTION	2 (0.1)	1 (1.2)	1 (0.1)
NAIL DISORDER	2 (0.1)	0	2 (0.2)
ONYCHOMYCOSIS	2 (0.1)	0	2 (0.2)
SEBORRHOEA	2 (0.1)	0	2 (0.2)
ALOPECIA	1 (0.1)	0	1 (0.1)
DERMATITIS CONTACT	1 (0.1)	0	1 (0.1)
HEAT RASH	1 (0.1)	0	1 (0.1)
HYPERKERATOSIS	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continued)

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
SKIN AND APPENDAGES DISORDERS (continued)			
HYPERTRICHOSIS	1 (0.1)	0	1 (0.1)
MELANOSIS	1 (0.1)	0	1 (0.1)
PIGMENTATION ABNORMAL	1 (0.1)	0	1 (0.1)
PITYRIASIS ROSEA	1 (0.1)	0	1 (0.1)
PSORIASIS	1 (0.1)	0	1 (0.1)
SKIN DISCOLOURATION	1 (0.1)	0	1 (0.1)
VESICULAR RASH	1 (0.1)	0	1 (0.1)
URINARY SYSTEM DISORDERS	158 (11.7)	21 (25.3)	137 (10.8)
URINARY INCONTINENCE	100 (7.4)	17 (20.5)	83 (6.6)
HAEMATURIA	22 (1.6)	1 (1.2)	21 (1.7)
URINARY TRACT INFECTION	19 (1.4)	0	19 (1.5)
MICTURITION FREQUENCY	13 (1.0)	2 (2.4)	11 (0.9)
ALBUMINURIA	6 (0.4)	0	6 (0.5)
CYSTITIS	6 (0.4)	0	6 (0.5)
FACE OEDEMA	6 (0.4)	0	6 (0.5)
DYSURIA	5 (0.4)	0	5 (0.4)
GLOMERULONEPHRITIS	2 (0.1)	0	2 (0.2)
POLYURIA	2 (0.1)	0	2 (0.2)
PYURIA	2 (0.1)	0	2 (0.2)
RENAL CALCULUS	1 (0.1)	0	1 (0.1)
RENAL CYST	1 (0.1)	0	1 (0.1)
RENAL PAIN	1 (0.1)	0	1 (0.1)
RENAL TRACT INFLAMMATION	1 (0.1)	0	1 (0.1)
URINARY CRYSTALS	1 (0.1)	0	1 (0.1)
URINE ABNORMAL	1 (0.1)	1 (1.2)	0
ENDOCRINE DISORDERS	131 (9.7)	1 (1.2)	130 (10.3)
HYPERPROLACTINAEMIA	92 (6.8)	0	92 (7.3)
GYNAECOMASTIA	36 (2.7)	1 (1.2)	35 (2.8)
GROWTH HORMONE EXCESS	15 (1.1)	0	15 (1.2)
SIALOADENITIS	1 (0.1)	0	1 (0.1)
THYROID STIM. HORMONE DECREASED	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continue

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 PDD/OTHER PDD (N=1265)
ENDOCRINE DISORDERS (continued)			
THYROIDITIS	1 (0.1)	0	1 (0.1)
WHITE CELL AND RES DISORDERS	104 (7.7)	2 (2.4)	102 (8.1)
EOSINOPHILIA	55 (4.1)	1 (1.2)	54 (4.3)
LEUCOPENIA	22 (1.6)	0	22 (1.7)
LYMPHADENOPATHY	13 (1.0)	1 (1.2)	12 (0.9)
LEUKOCYTOSIS	12 (0.9)	0	12 (0.9)
GRANULOCYTOPENIA	8 (0.6)	0	8 (0.6)
LYMPHOCYTOSIS	4 (0.3)	0	4 (0.3)
LYMPHOPENIA	4 (0.3)	0	4 (0.3)
MONOCYTOSIS	4 (0.3)	0	4 (0.3)
LYMPHADENOPATHY CERVICAL	3 (0.2)	0	3 (0.2)
LYMPHANGITIS	1 (0.1)	0	1 (0.1)
LYMPHOCYTES ATYPICAL	1 (0.1)	0	1 (0.1)
LYMPHOEDEMA	1 (0.1)	0	1 (0.1)
WBC ABNORMAL NOS	1 (0.1)	0	1 (0.1)
PLATELET,BLEEDING & CLOTTING DISORDERS	77 (5.7)	3 (3.6)	74 (5.8)
EPISTAXIS	57 (4.2)	3 (3.6)	54 (4.3)
HAEMATOMA	13 (1.0)	0	13 (1.0)
THROMBOCYTOPENIA	6 (0.4)	0	6 (0.5)
PURPURA	4 (0.3)	0	4 (0.3)
MUSCULO-SKELETAL SYSTEM DISORDERS	74 (5.5)	0	74 (5.8)
MYALGIA	29 (2.2)	0	29 (2.3)
ARTHRALGIA	23 (1.7)	0	23 (1.8)
SKELETAL PAIN	8 (0.6)	0	8 (0.6)
TORTICOLLIS	7 (0.5)	0	7 (0.6)
BONE DISORDER	4 (0.3)	0	4 (0.3)
ARTHRITIS	3 (0.2)	0	3 (0.2)
MYOPATHY	2 (0.1)	0	2 (0.2)
ARTHROPATHY	1 (0.1)	0	1 (0.1)
BURSITIS	1 (0.1)	0	1 (0.1)
COSTOCHONDRITIS	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continue

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
MUSCULO-SKELETAL SYSTEM DISORDERS (continued)			
EPIPHYSIOLYSIS	1 (0.1)	0	1 (0.1)
HAEMARTHROSIS	1 (0.1)	0	1 (0.1)
MUSCLE HYPERTROPHY	1 (0.1)	0	1 (0.1)
MUSCLE WEAKNESS	1 (0.1)	0	1 (0.1)
SECONDARY TERMS	72 (5.3)	2 (2.4)	70 (5.5)
FALL	14 (1.0)	0	14 (1.1)
SURGICAL INTERVENTION	14 (1.0)	0	14 (1.1)
ABRASION NOS	9 (0.7)	1 (1.2)	8 (0.6)
BITE	8 (0.6)	0	8 (0.6)
BURN	7 (0.5)	1 (1.2)	6 (0.5)
MEDICATION ERROR	6 (0.4)	0	6 (0.5)
VARICELLA	6 (0.4)	0	6 (0.5)
MOLLUSCUM CONTAGIOSUM	2 (0.1)	0	2 (0.2)
POST-OPERATIVE PAIN	2 (0.1)	0	2 (0.2)
ALCOHOL PROBLEM	1 (0.1)	0	1 (0.1)
EYE BURNS	1 (0.1)	0	1 (0.1)
FAMILY STRESS	1 (0.1)	0	1 (0.1)
INFLICTED INJURY	1 (0.1)	0	1 (0.1)
JOINT DISLOCATION	1 (0.1)	0	1 (0.1)
SCOLIOSIS	1 (0.1)	0	1 (0.1)
VISION DISORDERS	69 (5.1)	4 (4.8)	65 (5.1)
CONJUNCTIVITIS	32 (2.4)	3 (3.6)	29 (2.3)
EYE ABNORMALITY	13 (1.0)	1 (1.2)	12 (0.9)
VISION ABNORMAL	10 (0.7)	0	10 (0.8)
EYE INFECTION	4 (0.3)	0	4 (0.3)
EYE PAIN	4 (0.3)	0	4 (0.3)
MYDRIASIS	3 (0.2)	0	3 (0.2)
STRABISMUS	2 (0.1)	0	2 (0.2)
DIPLOPIA	1 (0.1)	0	1 (0.1)
GLAUCOMA	1 (0.1)	0	1 (0.1)
PHOTOPHOBIA	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (c

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
VISION DISORDERS (continued)			
PHOTOPSIA	1 (0.1)	0	1 (0.1)
HEART RATE AND RHYTHM DISORDERS	41 (3.0)	7 (8.4)	34 (2.7)
TACHYCARDIA	22 (1.6)	5 (6.0)	17 (1.3)
ARRHYTHMIA	7 (0.5)	1 (1.2)	6 (0.5)
BRADYCARDIA	7 (0.5)	0	7 (0.6)
PALPITATION	4 (0.3)	2 (2.4)	2 (0.2)
BUNDLE BRANCH BLOCK	3 (0.2)	0	3 (0.2)
QT PROLONGED	3 (0.2)	0	3 (0.2)
LIVER AND BILIARY SYSTEM DISORDERS	35 (2.6)	1 (1.2)	34 (2.7)
SGPT INCREASED	14 (1.0)	1 (1.2)	13 (1.0)
SGOT INCREASED	11 (0.8)	0	11 (0.9)
HEPATIC ENZYMES INCREASED	9 (0.7)	0	9 (0.7)
BILIRUBINAEMIA	4 (0.3)	0	4 (0.3)
GAMMA-GT INCREASED	4 (0.3)	0	4 (0.3)
AG RATIO ABNORMAL	1 (0.1)	0	1 (0.1)
HEPATIC FUNCTION ABNORMAL	1 (0.1)	0	1 (0.1)
UREA DECREASED	1 (0.1)	0	1 (0.1)
HEARING AND VESTIBULAR DISORDERS	31 (2.3)	3 (3.6)	28 (2.2)
EAR ACHE	15 (1.1)	1 (1.2)	14 (1.1)
EAR DISORDER NOS	6 (0.4)	0	6 (0.5)
MOTION SICKNESS	4 (0.3)	0	4 (0.3)
HEARING DECREASED	3 (0.2)	0	3 (0.2)
TINNITUS	2 (0.1)	2 (2.4)	0
HYPERACUSIS	1 (0.1)	0	1 (0.1)
VESTIBULAR DISORDER	1 (0.1)	0	1 (0.1)
CARDIOVASCULAR DISORDERS, GENERAL	26 (1.9)	0	26 (2.1)
HYPERTENSION	10 (0.7)	0	10 (0.8)
ECG ABNORMAL	5 (0.4)	0	5 (0.4)
HYPOTENSION	4 (0.3)	0	4 (0.3)
ECG ABNORMAL SPECIFIC	2 (0.1)	0	2 (0.2)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continu

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
CARDIOVASCULAR DISORDERS, GENERAL (continued)			
HEART MURMUR	2 (0.1)	0	2 (0.2)
HYPOTENSION POSTURAL	2 (0.1)	0	2 (0.2)
CIRCULATORY FAILURE	1 (0.1)	0	1 (0.1)
HEART DISORDER	1 (0.1)	0	1 (0.1)
REPRODUCTIVE DISORDERS, FEMALE	23 (1.7)	3 (3.6)	20 (1.6)
AMENORRHOEA	8 (0.6)	1 (1.2)	7 (0.6)
LACTATION NONPUERPERAL	4 (0.3)	0	4 (0.3)
MENORRHAGIA	3 (0.2)	0	3 (0.2)
MENSTRUAL DISORDER	3 (0.2)	1 (1.2)	2 (0.2)
DYSMENORRHOEA	2 (0.1)	0	2 (0.2)
BREAST DISCHARGE	1 (0.1)	0	1 (0.1)
BREAST ENLARGEMENT	1 (0.1)	0	1 (0.1)
BREAST PAIN FEMALE	1 (0.1)	0	1 (0.1)
VAGINAL HAEMORRHAGE	1 (0.1)	0	1 (0.1)
VAGINITIS ATROPHIC	1 (0.1)	0	1 (0.1)
VULVA DISORDER	1 (0.1)	1 (1.2)	0
VULVITIS	1 (0.1)	0	1 (0.1)
RED BLOOD CELL DISORDERS	21 (1.6)	0	21 (1.7)
ANAEMIA	12 (0.9)	0	12 (0.9)
ANAEMIA HYPOCHROMIC	6 (0.4)	0	6 (0.5)
ANAEMIA NORMOCHROMIC	1 (0.1)	0	1 (0.1)
ERITHROCYTES ABNORMAL	1 (0.1)	0	1 (0.1)
PANCYTOPENIA	1 (0.1)	0	1 (0.1)
VASCULAR (EXTRACARDIAC) DISORDERS	9 (0.7)	2 (2.4)	7 (0.6)
FLUSHING	6 (0.4)	2 (2.4)	4 (0.3)
VASODILATATION	2 (0.1)	0	2 (0.2)
VASCULAR DISORDER	1 (0.1)	0	1 (0.1)
NEOPLASM	7 (0.5)	0	7 (0.6)
THROMBOCYTHAEMIA	5 (0.4)	0	5 (0.4)
LIPOMA	1 (0.1)	0	1 (0.1)

See footnotes on the first page of the table.

Risperidone Autism Safety Update

Output DAE04: Incidence of AEs for All Risperidone-Treated Subjects by Type of Disorder (continued)

ANALYSIS SET: ALL SUBJECTS

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	ALL RISPERIDONE Total (N=1348) n (%)	TYPE OF DISORDER, n AUTISTIC DISORDER (N=83)	 DBD/OTHER PDD (N=1265)
NEOPLASM (continued)			
NEOPLASM NOS	1 (0.1)	0	1 (0.1)
REPRODUCTIVE DISORDERS, MALE	7 (0.5)	0	7 (0.6)
PENIS DISORDER	4 (0.3)	0	4 (0.3)
BALANOPOSTHITIS	1 (0.1)	0	1 (0.1)
HERNIA INGUINAL	1 (0.1)	0	1 (0.1)
TESTIS DISORDER	1 (0.1)	0	1 (0.1)
APPLICATION SITE DISORDERS	3 (0.2)	0	3 (0.2)
TYMPANIC MEMBRANE PERFORATION	2 (0.1)	0	2 (0.2)
SKIN NODULE	1 (0.1)	0	1 (0.1)
POISON SPECIFIC TERMS	2 (0.1)	0	2 (0.2)
STING	2 (0.1)	0	2 (0.2)
MYO ENDO PERICARDIAL & VALVE DISORDERS	1 (0.1)	0	1 (0.1)
MITRAL INSUFFICIENCY	1 (0.1)	0	1 (0.1)

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

/s/

June Cai
5/17/05 09:19:31 PM
MEDICAL OFFICER

Paul, Safety Update is included in this.

Paul Andreason
5/19/05 08:07:25 AM
MEDICAL OFFICER
I concur with Dr Cai's recommendation that the Division take a not approvable action on this supplement. Please see my memo to the file dated May 19, 2005.

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#:	20-272/S-036
Related NDA's:	20-588/S-024 21-444/S-008
Sponsor:	Johnson & Johnson
Due Date:	June 19, 2004

Drug Name:

Generic Name:	Risperidone
Trade Name:	Risperdal

Drug Categorization:

Pharmacological Class:	D_2/5-HT_2 Antagonist
Proposed Indication:	Autism
Dosage Forms:	0.25, 0.5, 1, 2, 3, & 4mg Tablets
Route:	Oral

Review Information

Clinical Reviewers:	June Cai, M.D. Gregory M. Dubitsky, M.D.
Completion Date:	May 15, 2004

NDA 20-272/S-036
RISPERDAL FOR AUTISM
TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, it is recommended that this supplemental NDA be granted approvable status.

Prior to final approval, the sponsor should be requested to address the following clinical issues:

1) Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose (b) (6) . These discrepancies should be explained.
2) Relapse data from Part III of study USA-150 should be reanalyzed using a definition for relapse that incorporates only Aberrant Behavior Checklist Irritability subscale criteria since this is the efficacy outcome of interest. This should include a Kaplan-Meier survival analysis of relapse using the interim dataset. Additionally, the sponsor should compute the mean duration of continuous response status for patients randomized into Part III.
3) The sponsor should provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of the drug:placebo odds of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.
4) An analysis of quantitative ECG data from study CAN-23 should be submitted for our review.
5) The sponsor should analyze height data from pediatric patients who have been treated with risperidone continuously for at least 6 months utilizing z-scores to better assess the potential effect of risperidone on growth in the pediatric population.

B. Recommendations for Phase 4 Studies

1) It is recommended that the sponsor conduct a study in children and adolescents which includes a substantial proportion of patients with Autistic Disorder and which assesses fasting serum glucose levels to evaluate the

effect of risperidone on glucose metabolism in the pediatric population.
2) It is further recommended that the sponsor conduct a closely monitored study of cognitive function in patients with Autistic Disorder who are treated with risperidone.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

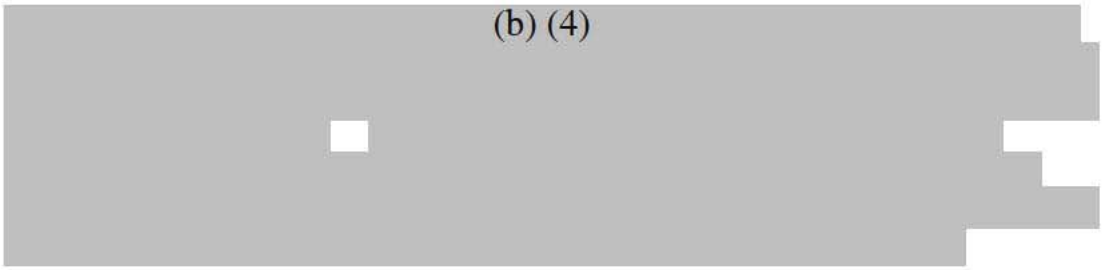
This risperidone clinical program consisted of two Phase 1 pharmacokinetic studies and two Phase 3 studies conducted in the US and Canada from 1999 to end of 2001. The two Phase 3 studies were double blind placebo controlled studies in children and adolescents with autism and other pervasive developmental disorders. A total of 180 patients were studied in these two Phase 3 controlled studies. Among them, 83 autistic patients were exposed to risperidone.

Also, one of the pivotal studies had two continuation phases: a 4 month open-label phase followed by randomized withdrawal with a 4 week follow-up phase.

In addition, supportive safety data was derived from a number of other controlled and uncontrolled trials conducted in pediatric patients with Disruptive Behavioral Disorders (DBD).

B. Efficacy

The acute efficacy of risperidone in reducing irritability-like symptomatology in autistic patients was demonstrated in two 8-week double-blind, placebo-controlled studies, CAN-23 and USA-150/Part I.



C. Safety

The primary safety database consisted of the autistic patients from the two placebo-controlled pivotal studies, CAN-23 and USA-150/Part I, as described above.

To supplement this small sample, safety data was examined from a larger sample of 821 children and adolescents with various forms of Pervasive Developmental Disorder, including the autistic patients, and Disruptive Behavioral Disorders who participated in a number of trials with risperidone.

No previously unrecognized hazards associated with risperidone treatment were discovered. However, a major deficiency in the assessment of safety was lack of serum glucose data in almost all patients.

D. Dosing

The recommended dosing closely parallels the doses utilized in the pivotal trials. (b) (4)

E. Special Populations

The studied group is itself a special population. No other special populations was studied in this submission.

CLINICAL REVIEW

I. Introduction and Background

A. Role in the Treatment Armamentarium

Autistic Disorder (autism) is one of the mental disorders that develops early in childhood and persists throughout life. It occurs in less than 250,000 individuals in the United States (prevalence is reported from 2-20 per 10,000 individuals.). According to DSM-IV-TR (The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision), Autistic Disorder is a type of Pervasive Developmental Disorders with the following core symptoms: 1) Qualitative impairment in social interaction, 2) qualitative impairment in communication, 3) restricted, repetitive, and stereotyped behaviors. Associated behaviors such as hyperactivity, short attention span, impulsivity, aggressiveness, self-injurious behaviors, and temper tantrums may affect the daily life of the individual and the family tremendously.

In addition to the above mentioned mental and behavioral symptoms, autistic patients often have co-morbid medical and neurological disorders. For instances, up to 25-30% of patients have coexisting seizure disorder. Patients with tuberous sclerosis, Downs syndrome, Fragile X syndrome, and other congenital deficits have higher incidences of autism. Less than 5% autistic children also have various metabolic deficits in amino acid, carbohydrate, purine, and peptide metabolism.

There is no definitive treatment for this disorder at present. Physicians have treated autism using traditional antipsychotics and sedatives with little success, and yet these patients often suffer from severe side effects from these medications, such as sedation, extrapyramidal symptoms, and worsening cognitive deficits.

The newer generations of antipsychotics (atypical antipsychotics), such as risperidone, have made remarkable progress in reduction of extrapyramidal symptoms. The sponsor proposed that risperidone has potent effects on serotonin and dopamine neuronal systems, both of which have been implicated in the pathophysiology of autism, and it may have a better safety profile than conventional

antipsychotics. Additionally, the sponsor cautioned that it should be used for the primary benefit of the patient instead of convenience of the caregivers. It must used to foster more adaptive functioning in autistic patients by improving their core and associated deficits rather than sedating patients or decreasing the frequency of any normal behaviors.

This sNDA is intended to support the approval of risperidone for the treatment of irritability-like symptoms associated with autism. (b) (4) (see section VI. for further details). Currently, there are no approved agents to treat either the core symptoms of autism or irritability-like symptoms. Since risperidone would be the first agent approved for symptoms associated with autism, the sNDA has been granted "Priority" review status.

B. Safety Findings with Related Compounds

Atypical agents are listed in **Table I-1** along with the important safety concerns associated with each.

TABLE I-1
MAJOR SAFETY CONCERNS WITH ATYPICAL ANTIPSYCHOTICS

Clozapine	Agranulocytosis Seizures Myocarditis Orthostatic hypotension Hyperglycemia Weight gain
Risperidone	Prolactin elevation Orthostatic hypotension Weight gain
Olanzapine	Orthostatic hypotension Weight gain Hyperglycemia
Quetiapine	Orthostatic hypotension Weight gain ? Cataracts
Ziprasidone	Q-T interval prolongation
Aripiprazole	No known major toxicities
Sertindole (not marketed)	QT interval prolongation Sudden death

C. Administrative History

IND studies included in this supplement were conducted under IND 31,931. Relevant NDA's for risperidone are listed in the table below.

NDA's for Risperidone

NDA	Dosage Form	Date Approved
NDA 20-272	Tablets	29-Dec-1993
NDA 20-588	Oral solution	19 June 1996
NDA 21-444	Orally disintegrating tablets	2 April 2003

On Apr. 1, 2003, the sponsor met FDA for an early consultation meeting regarding using risperidone in treatment of Autistic Disorder, focusing on an efficacy supplement for treating (b) (4) in autistic children (ages 5-12) with risperidone. The key points for this meeting are the following:

- Claim for indication:
  -- Considering the sponsor's claim for this indication would be the first for this disorder, FDA would seek advice from the advisory committee.
  -- A general agreement was that risperidone was not a treatment for the core symptoms of this illness as it might be considered a specific treatment for schizophrenia. The specificity, rational and appropriateness of study measurement was discussed.
  (b) (4)
- Exposure: The sponsor proposed number of subjects (180 of autism for efficacy and additional 700 total for safety) and duration of exposure (616.8 patient-years of exposure) were adequate.
- Statistical Analysis: FDA agreed with the statistical plans submitted for both ISE and ISS, with the

condition that all poolable studies should be coded to use the same adverse event coding scheme.

- Finally, study reports should be submitted prior to sNDA submission and advisory package, with the sNDA.

On July 31, 2003, J&JPRD sponsored-Clinical Advisory Board meeting concluded that the ABC was the most appropriate instrument available for measuring pharmacologic changes in a clinical study of autism.

On Sept. 10, 2003, a pre-NDA meeting this indication was held between the sponsor and FDA Key points from this meeting are the following:

- Claim for indication:
  -- (b) (4) Ethical issue of prescribing and the need of public discussion regarding the appropriateness of instrument used were also highlighted.
  -- The sponsor emphasized that they consider ABC is the most appropriate instrument for measuring (b) (4).
- Statistical plan: FDA agreed that LOCF ANCOVA analysis be considered the primary analysis and dichotomous approach proposed for the CGI-I responder data. The sponsor reported that the analysis of subgroups with or without somnolent effect showed the same effect size in both groups. A representative from OCPB agreed the sponsor proposed plans on analysis of race in the population PK and provided recent FDA guidance.
- Issue of inspection: FDA emphasized the need of inspecting the NIMH sponsored autism study both by the sponsor and FDA.
- Submission: FDA considered the plans for electronic data set and general format for the submission were acceptable. FDA also suggested that the sponsor file the application to the tablet NDA and reference the two related NDA's for oral solution and orally disintegrating tablet of risperidone.

- Issue of priority review: FDA replied to the sponsor's question that it would be decided at the time of filing meeting.

D. Proposed Instructions for Use

For treatment in pediatric (b) (4), risperidone dose should be based on body weight and be administered once or twice daily. Dosing should be started from 0.25 mg/day or 0.5 mg/day, depending upon weight category. From Day 4 of treatment, the dose may be increased up to 0.5 mg/day or 1.0 mg/day. (b) (4)

(b) (4)

E. Foreign Marketing

Risperidone was first registered in the United Kingdom in December 1992 and was first marketed for the treatment of schizophrenia and other psychotic conditions in May 1993. In December 1993, risperidone tablet was approved for the treatment of schizophrenia in the United States and has been widely prescribed since market introduction in 1994. Currently, risperidone is licensed for treatment of schizophrenia in more than 90 countries and adjunctive treatment to mood stabilizers in bipolar disorder patients in over 15 countries. The cumulative exposure to risperidone was estimated to be more than (b) (4) patient-years worldwide as of September 2003.

It is unknown how much of the above exposure was in children and adolescents. Risperidone has not been registered for the treatment of (b) (4) in any country.

II. Clinically Relevant Findings from Other Disciplines and from Consultants

A. Statistical Review and Evaluation

FDA statistician, Kun He, Ph.D., has completed his review. In his review, Dr. He concludes that the sponsor's analysis are mostly valid and the studies CAN-23 and US-150 Part I (b) (4) are positive for efficacy. (Please refer to Dr. He's 5-3-04 review for details.)

I agree with Dr. He's conclusion on studies CAN-23 and Part I of US-150. (b) (4)

B. Biopharmaceutics

The biopharmaceutics review is still in progress. According to FDA biopharmaceutics reviewer, John Duan, Ph.D., the clearance of children and adolescents with autism is 6 times slower than those with DBDs and psychotic disorders. However, this is only based on one small PK study (BEL-21) of children (3-12 year-old) with autism and he feels that these findings may not be reliable. The sponsor has not yet submitted the population PK data from study US-150.

C. Pharmacology/Toxicology

The Pharmacology/Toxicology review is not yet complete. Since this application is for children and adolescents in (b) (4), the sponsor was asked to perform animal studies on juvenile rats for toxicology study after our filing meeting. According to the FDA biopharmaceutics reviewer, Ikram Elayan, Ph.D., the sponsor has proposed doing such studies as a Phase IV commitment.

D. DSI Clinical Site Inspections

The following sites were inspected by the Division of Scientific Investigations (DSI):

- For study RIS-USA-150: Dr. McDougle (Indiana) and Dr. Aman (Ohio).
- For study RIS-CAN-23: Drs. Fleisher (Winnipeg), Shea (Halifax) and Turgay (Scarborough).

According to the DSI inspector, Dr. Ni Khin, the DSI report is still in progress.

III. Human Pharmacokinetics and Pharmacodynamics[1]

A. Pharmacokinetics

The overall pharmacokinetic profile of risperidone obtained from 749 children and adolescents, mostly with psychotic disorder, conduct or other behavioral disorders, is not significantly different from the well established profile of adults.

Absorption: Both risperidone tablets and oral solutions are almost completely absorbed, with or without food, occurring over the full length of the GI tract. Tmax for risperidone is about 1-2 hours in adults and children.

Distribution: Risperidone is extensively bound to plasma protein (albumin and a_1-acid glycoprotein), up to 90%. That of of 9-hydroxy-risperidone is 77%. V_D is 1-2L/kg.

Metabolism: Active antipsychotic components of risperidone include risperidone and 9-hydroxy-risperidone, which together are called “active moiety.” The major metabolic path of risperidone is 9-hydroxylation, which is mainly by CYP2D6 (producing (+) 9-hydroxy-risperidone and inactive 7-hydroxy-risperidone). A minor pathway is by CPY3A4, producing (–) 9-hydroxy-risperidone and inactive nor-risperidone).

[1] Information summarized in this section is based on that presented in the Summary of Clinical Pharmacology Studies contained in the submission as well as discussions with the biopharmaceutics reviewer, Dr. Duan.

Based on the PK study in autism—study RIS-BEL-21, the metabolic rate in pediatric autistic patients (study RIS-BEL-21) is 6 times slower than that in pediatric patients with other behavioral disorders, including psychosis (RIS-USA-160), according to John Duan, Ph.D., the biopharmaceutics reviewer. However, there were only 6 subjects in this PK study and there is no population PK data available yet, so this conclusion needs to be further evaluated.

Elimination: Risperidone is excreted mainly from urine as both active moiety (35-45%) and inactive metabolites (55-65%). $T_{1/2}$ of risperidone is 3-20 hours, and of 9-hydroxy-risperidone is 21-30 hours, depending on the individual's capacity of metabolism. Elimination rate decreases by 60% in patients with moderate to severe renal dysfunction. In liver dysfunction, free plasma fraction can be increased by 35% secondary to decreased albumin and a_1-glycoprotein.

In pediatric patients, clearance is reduced in correlation to lower body weight. Again, in pediatric autistic patients, the elimination is 6 times slower than that in other pediatric patients because of slower metabolism rate.

Gender, ethnicity or age doesn't affect pharmacokinetic parameters.

Drug Interactions:

Psychostimulants such as methylphenidate or atomoxetine didn't appear to affect the pharmacokinetics of risperidone.

Hepatic enzyme inducers, such as carbamezapine, phenytoin and others can decrease the plasma level by 50%.

Risperidone increases Cmax of valproate by 20% based on sponsor's previous study (information from Dr. Duan). Compared with historical data, there was no increase of risperidone level when combined with valproate. There is no data on combination of risperidone and other antiseizure medications, such as lamotrigine, vigabatrin, gabapentin and tiagabine.

Paroxetine or fluoxetine co-administration increased the Cmax and AUC values of active moiety up to 45%. Therefore, caution should be used if risperidone is co-administered

with medications that inhibit the CYP2D6 system. If such medications co-administration is stopped, re-evaluation of the risperidone dosage is needed.

B. Pharmacodynamics

Risperidone is a dopamine receptor-2 (D_2) antagonist. It also antagonizes serotonin-2 receptors ($5\text{-}HT_2$) and D_1, $5\text{-}HT_{1A}$, $5\text{-}HT_{1C}$, and $5\text{-}HT_{1D}$ weakly to moderately.

Moreover, riperidone also has effects on other receptors, including a_1 and a_2 adrenergic and histaminergic-1 receptors, but with low potency. Its alpha blocker effect will potentiate other hypotensive drugs.

It has no affinity for cholinergic muscarinic or alpha-1 or alpha-2 adrenergic receptors.

IV. NDA Data Sources

A. Primary Development Program

Data in support of this application was submitted in two submissions: an original submission dated 12-19-03 and a four-month Safety Update dated 4-5-04.

The original submission contained data from 17 clinical trials with risperidone in children and adolescents. These trials are summarized in **Appendix IV-1**. Two of these trials, **USA-150/Part I** and **CAN-23**, were double-blind, placebo-controlled studies in children and adolescents with autism. These two trials provide support of the sponsor's efficacy claim and are reviewed in detail in section VI. of this review.

The remaining trials provide supportive safety information and are summarized below.

Three other studies were conducted in autistic patients:

- **USA-150/Parts 2/3**, an open-label treatment phase followed by randomized withdrawal.
- **BEL-22**, an open-label, Phase 2 study.
- **BEL-21**, a pharmacokinetic study.

Four double-blind, placebo-controlled trials were conducted in children and adolescents with DBD (Disruptive Behavioral Disorders):

• **CAN-19** and **USA-93** were Phase 3 studies in DBD patients.
• **NED-9** and **BEL-24** were Phase 2 studies in DBD patients.

CAN-20 and **USA-97** were long-term, open-label extensions of CAN-19 and USA-93, respectively.

INT-41 was a one-year, open-label extension study for patients from CAN-19 as well as for de novo patients who met the entry criteria for CAN-19.

Then, there were two open-label extensions for patients from INT-41: **INT-70**, a one-year study, and **HUN-4**, a two-year study.

USA-160 was a pharmacokinetic study in children and adolescents with psychotic and behavioral disorders.

All of the above studies were complete at the time of the original supplement submission. There were also, however, two additional studies that were ongoing at that time:

• **INT-79** was a long-term relapse prevention trial in children and adolescents with Conduct Disorder or other DBD.
• **INT-84** was a one-year extension of INT-79.

Deaths and serious adverse events (SAE's) from these two ongoing studies through 7-31-03 were reported in the original submission.

The four-month Safety Update encompasses the following items:

• clinical trial update for the two studies ongoing at the time of the original submission. As of the cutoff date for the update (12-31-03), INT-79 had been completed and INT-84 was still ongoing.[2]
• update of published literature for the period 7-31-03 through 12-31-03.
• update of postmarketing pharmacovigilance data for the period 8-31-03 through 12-31-03.

[2] The study report for INT-79 was ongoing at the time of the Safety Update submission.

In this review, safety information from the Safety Update is presented separately from information provided in the original submission of this sNDA (see section VII.).

1. Patient Enumeration by Study

Appendix IV-2 enumerates patients by treatment group for the 15 studies which were complete as of the original submission (Parts II and III of USA-150 are counted as one study).

2. Demographic Characteristics

Demographic characteristics of all 156 Autistic patients in the two pivotal studies as well as patients with DBD and other PDD in double-blind, placebo-controlled trials are depicted in **Appendix IV-3**. With respect to the autistic patients, most were male (80.1%), almost all were under the age of 12 years (96.2%), and almost two-thirds were Caucasian (64.7%).

In all, 821 patients received risperidone in completed Phase 2/3 studies: 83 of these patients were autistic and 738 had DBD or other PDD (Pervasive Developmental Disorders). The table below compares the autism and DBD/Other PDD patients in terms of age, weight, and risperidone dosing.

	N	Mean Age (Range)	Mean Weight (Range)	Mean Dose (Range) mg/kg	Mean Dose (Range) mg	Mode Dose (Range) mg/kg	Mode Dose (Range) mg
All subjects who received risperidone in double-blind and open-label studies							
Autistic Disorder	83	7.8 yr (3-16)	31.77 kg (16-104.3)	0.047 (0.01-0.10)	1.432 (0.4-3.19)	0.053 (0.01-0.12)	1.615 (0.5-4.2)
DBD/Other PDD	738	9.4 yr (4-17)	35.83 kg (13.6-113)	0.041 (0-0.09)	1.579 (0.04-4.35)	0.043 (0-0.11)	1.702 (0-4.8)

It should be noted that this Phase 2/3 study pool does not include Parts II and III of USA-150 and the two ongoing studies. Safety data from these latter studies was not integrated into this pool in the Summary of Clinical Safety provided in the original submission. Nonetheless, the safety review of deaths and non-fatal serious adverse events presented below encompasses data from the sponsor's Phase 2/3 pool as well as USA-150 Parts II and III and the ongoing trials.

Demographic features of the 821 risperidone-treated patients in the Phase 2/3 study pool are displayed in **Appendix IV-4**. The majority of these patients were male (81.0%). Most (87.7%) were under the age of 12 years, with a mean age of 9.3 years. Caucasians made up 77.9% of the sample and Blacks constituted 11.0%.

3. Extent of Exposure

The modal dose versus duration of exposure for risperidone for all patient exposure in Phase 2 and Phase 3 studies (except for the two ongoing trials) is displayed in **Appendix IV-5**. A total of 331 patients were exposed for 13 months or longer and 565 were exposed for 7 months or longer. In all, 625 patients received modal doses of 1.0 mg/day or more and 217 received a modal dose of 2.0 mg/day or greater.

B. Other Sources of Clinical Data

1. Other Studies

No other studies were reported in this sNDA.

2. Published Literature

The sponsor's literature survey, as reported in the original submission, was conducted in two phases. The first covered all published data up to and including 5-25-00. The second survey encompassed published articles from 5-26-00 to
7-31-03. Each search was conducted on the sponsor's database for articles pertaining to the use of risperidone in children and adolescents (age 17 years and under). As a check of the completeness of this data, the Medline database was also searched.

The four-month Safety Update included all published data from 7-31-03 to 12-31-03. The search process was identical to that described above.

The results of these literature searches are discussed in section VII. of this review.

3. Postmarketing Experience

The analysis of pharmacovigilance data entailed a search of worldwide, spontaneously reported adverse events associated with the use of risperidone in children and adolescents (ages 5-17) being treated for, or with a history of autism, autistic spectrum disorder, Asperger's syndrome, or other pervasive developmental disorder. These data were extracted from the Johnson & Johnson worldwide safety database for the period 5-1-93 through 8-30-03. These data did not include information from clinical trials in children and adolescents.

The four-month Safety Update of postmarketing data consisted of an identical data survey for the period 8-31-03 through 12-31-03.

The results of these postmarketing adverse event surveys are presented in section VII. of this review.

V. Clinical Review Methods

A. Clinical Review Staff and Responsibilities

The clinical review was a joint effort between two reviewers of Psychiatric Drug Products Group: June Cai, MD and Gregory Dubitsky, MD.

Dr. Cai completed the review of all efficacy data and most of the safety data, except for the sections Cognitive Function and Treatment-Emergent Aggression and the Case Report Form audit, which were completed by Dr. Dubitsky. Dr. Dubitsky also contributed substantially to the following sections: Items Utilized in the Review, Evaluation of Financial Disclosure, Administrative History, Adequacy of Exposure & Safety Assessments, Summary of Important Safety Findings, and Executive Summary.

In addition, as a Senior Medical Reviewer, Dr. Dubitsky served as a mentor to Dr. Cai and oversaw all of Dr. Cai's review work.

B. Items Utilized in the Review

Appendix V-1 lists the items that were utilized in this review.

C. Specific Methods Used to Evaluate Data Quality

The Division of Scientific Investigations (DSI) inspected a total of 5 clinical sites from the 2 pivotal efficacy studies in this submission. Results are pending.

Dr. Dubitsky conducted an audit of 5% (N=7) of the submitted Case Report Forms (CRF's). This audit consisted of a comparison of the adverse event data across the CRF's, Narrative Summaries, and adverse event line listings for consistency.

D. Adherence to Accepted Ethical Standards

The sponsor states that the studies submitted in this sNDA were done in adherence to Good Clinical Practice (GCP) guidelines.

E. Evaluation of Financial Disclosure

There were two covered studies, as defined in 21 CFR 54.2(e), in this sNDA: USA-150 and CAN-23.

With respect to USA-150, the sponsor states that this trial was conducted by NIMH and investigator and subinvestigator financial disclosure information was not systematically collected. The sponsor was able to collect financial information from several investigators for up to one year after study completion. They list 21 investigators as not submitting complete information despite due diligence. They also list 45 investigators who submitted information and had no disclosable financial interests. Curiously, though, four individuals are included on both lists.[3] There was one investigator who had disclosable information:

(b) (6) from site (b) (6), received payments in excess of $25,000 as (b) (6) and for a (b) (6).

For study CAN-23, financial disclosure information was collected from a total of 50 principal investigators and subinvestigators. None of these individuals had disclosable information. However, information was not received from 12 subinvestigators in this trial.

[3] (b) (6)

In conclusion, the sponsor should clarify why 4 investigators from USA-150 are both certified as having no financial interests as well as not having submitted complete information.

The lack of complete financial information for a large fraction (about one-third) of the investigators in USA-150 precludes a definitive determination of whether these individuals had financial interests or arrangements that may have biased the results of that trial. Nonetheless, since investigators in both pivotal studies were blinded to treatment, it seems unlikely that the study results were biased by investigator behavior.

VI. Integrated Review of Efficacy

A. Overview of Studies Relevant to Efficacy

This sNDA contains the results of two 8-week, double-blind, placebo-controlled trials of risperidone in the treatment of irritability-like symptoms in pediatric patients (mostly children 12 years of age and younger):

- CAN-23, conducted mostly in patients with Autistic Disorder but also in patients with other PDD (Pervasive Developmental Disorders).
- USA-150/Part I, conducted in patients with Autistic Disorder.[4]

These two trials are designated as the pivotal studies for this supplement. Both trials included the Irritability subscale of the Aberrant Behavior Checklist (ABC) as a primary variable. This subscale includes 15 items from the ABC, with each item rated on a scale of 0-3 (0 = no problem, 1 = slight problem, 2 =moderate problem, 3 = severe problem) yielding a total maximum score of 45:

[4] This was an NIMH-sponsored study conducted under the Research Units on Pediatric Psychopharmacology [RUPP] Autism Network group Protocol 1.

Injures self on purpose	Cries over minor annoyances and hurts
Aggressive to others (verbal/physical)	Mood changes quickly
Screams inappropriately	Cries and screams inappropriately
Temper tantrums	Stamps feet or bangs objects or slams doors
Irritable and whiny	Deliberately hurts himself/herself
Yells at inappropriate times	Does physical violence to self
Depressed mood	Tantrums when does not get own way
Demands must be met immediately	

In addition, the results of Part II and III of USA-150 were submitted. Part II provided for 4 months of open-label risperidone treatment for responders in Part I of the study. This was followed by Part III, randomization to continued risperidone therapy or placebo for an 8 week follow-up period for patients who maintained a response in Part II. The results of this study were also reviewed for possible description in labeling.

It does not appear than any of the above studies were conducted under IND 31,931.

B. Review of Efficacy Data from Adequate, Well-Controlled Studies

1. Study CAN-23

Investigators/Sites

This is a multicenter study that involves seven different sites in Canada from Aug. 1999 to Dec. 2001. The following table lists the principal investigators from each site and the number of subjects recruited from each of them.

Principal Investigators	Site	Number of Subjects
Shea, Sarah E., M.D.	1	12
Steele, Margaret M., M.D.	2	3
Caroll, Alan M., M.D.	3	15
Turgay, Atilla, M.D.	4	38
Streilein, Karen F., M.D.	5	3
White, Hubert P., M.D.	6	1
Fleisher, William, M.D.	7	9

Objectives:

The sponsor's primary objective of the study was to demonstrate the superiority of risperidone over placebo in the treatment of behavioral symptoms, such as excessive stereotypies and extreme intolerance to change that interfere with daily functioning and social interactions, in children (5 to 12 years-old) with Autistic Disorder or other Pervasive Developmental Disorders (PDD).

Patient Sample

Assuming a 30% discontinuation rate, the sponsor planned to enroll 106 subjects to attain 74 subjects for final evaluation.

In addition to consents obtained and the availability of a responsible person accompanying the child subject, main diagnostic criteria for subject inclusion are:

- Children, male or female, age 5 to 12 years-old.
- Meeting DSM-IV Axis I diagnosis of Pervasive Developmental Disorders (including Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Development Disorder Not Otherwise Specified) with a total score of =30 on the Childhood Autism Rating Scale (CARS) with or without mental retardation.
- Outpatient subject physically healthy based on screening physical examination, medical history, and ECG.

Subjects with the following conditions are excluded:

- Schizophrenia or other psychotic disorders
- History of tardive dyskinesia or Neuroleptic malignant syndrome
- Know hypersensitivity to neuroleptics
- Clinically relevant non-neurological disease
- Recent seizure episode within the past 3 months or the need of more than one anticonvulsant

- Positive HIV or clinically significant laboratory abnormalities
- History or suspicion of alcohol or drug abuse
- Need of disallowed concomitant therapy:
  -antidepressants
  -psychostimulants
  -lithium
  -other antipsychotics
  -naltrexone
  -alpha-2-agonists, clonidine, guanfacine
  -cholinesterase inhibitors
  -anticholinergics (unless necessary for emergent EPS)
  -any sedative/hypnotics (unless being stabilized for 30d)
  -behavioral therapy (unless initiated 30 days prior)

  The dosage of allowed anticonvulsants and other necessary medications for organic disorders were to be kept as constant as possible.
- History of treatment of risperidone in the past 3 months or history of being unresponsive or intolerant to risperidone
- Female patients of childbearing potential engaging in sexual activity

Design

This is an 8-week, randomized, double-blind, parallel-group, multicenter trial. The study medication dosage was flexible (based on weight), ranging from 0.02 to 0.06 mg/kg/day of risperidone oral solution (concentration 1mg/ml) versus placebo.

Dose Schedule:

Dosing was once daily in the morning as an oral solution. If sedation occurred, the dose could be given in the evening or split on a bid schedule. Risperidone was started at 0.01 mg/kg/day, increased to 0.02 mg/kg/day on Day 3, and possibly increased by a maximal increment of 0.02 mg/kg/day (up to 0.04mg/kg/day) on Day 8 depending upon the response. Afterwards, the dosage was raised or lowered at weekly intervals as judged necessary by the clinician. Maximal daily increments is 0.02 mg/kg/day and the maximal permitted dose was 0.06 mg/kg/day. There was no limit for dosage lowering rate. Dosage was calculated based on the weight obtained at each visit.

Assessments:
Efficacy assessments were performed at screening (baseline) and on Days 7, 14, 21, 35, 49 and 56.

- Primary efficacy parameter was the change from baseline to end point on the Irritability subscale of the Aberrant Behavior Checklist (ABC) scored by a parent or care giver.

- Secondary efficacy parameters were the changes at endpoint versus baseline on the four other ABC subscale scores (Hyperactivity/Noncompliance, Inappropriate Speech, Lethargy/Social Withdrawal, and Stereotypic Behavior), the Clinical Global Impression (CGI), the Nisonger Child Behavior Rating Form (N-CBRF) (Parent Version) (see more details in "Analysis" section), and the Visual Analogue Scale (VAS) of the most troublesome symptom as identified by the patient.

Analysis
The null hypothesis was that there would be no difference between the risperidone and placebo groups in the change from baseline to end point on the Irritability scale of the ABC. All statistical tests were interpreted at the 5% significance level, two tailed.

The intent-to-treat (ITT) population comprised all randomized subjects who received at least one dose of study drug. This was the primary analysis sample for efficacy analyses.

The primary efficacy variable was the Irritability subscale of the ABC. The analytic method for this primary variable was analysis of covariance (ANCOVA) with treatment and center as factor and the baseline score as a covariate.

The sponsor included the four other subscales of ABC, CGI, N-CBRF (parent version), and VAS as secondary efficacy variables: CGI contains CGI-S (severity of pervasive development symptoms) and CGI-C (clinical global impression for change), both of which were scored by the clinician on a seven-point scale-- Absent to extremely severe for CGI-S and very much worse to very much improved for CGI-C; N-CBRF includes 66 items (each item scores 0-3), 8 subscales (Adaptive social, Compliant/Calm, Conduct problem, Insecure/Anxious, Overly sensitive, Hyperactivity, Self-injury/Stereotypic, and Self-isolated/ Ritualistic). VAS

was also scored by the parent or caregiver for the most troublesome symptoms of the patient by means of a vertical line across a 100mm line on a 0-100 scale indicating very mild (0) to extremely severe (100).

Baseline Demographics

The majority patients in this study were Caucasian male boys. Average age is 7 years-old (range 5-12 year-old). The risperidone group and placebo group are comparable with respect to age, race, sex, and baseline weight. The following table exhibits the demographics at baseline.

Table. Subject Demographics of Study CAN-23

Demographic Data		**Risperidone**	**Placebo**	**Total**
		(N=40)	(N=39)	(N=79)
Age (years)	Mean (SD)	7.6 (2.3)	7.3 (2.3)	7.5 (2.3)
	Median	7.0	7.0	7.0
	Range	5 - 12	5 - 12	5 - 12
Sex N (%)	Female	11 (27.5)	7 (17.9)	18 (22.8)
	Male	29 (72.5)	32 (82.1)	61 (77.2)
Race N (%)	Black	6 (15.4)	6 (15.0)	12 (15.2)
	Caucasian	27 (67.5)	28 (71.8)	55 (69.6)
	Oriental	0	1 (2.6)	1 (1.3)
	Other	7 (17.5)	4 (10.3)	11 (13.9)
Weight (kg)	Mean (SD)	31.2 (14.5)	27.6 (8.6)	29.4 (12.0)
	Median	27.5	24.0	26.0
	Range	16.0 - 91.3	17.0 - 52.0	16.0 - 91.3

Baseline Severity of Illness

The most common diagnosis is autistic disorder in both risperidone and placebo groups, followed by PDD-NOS in risperidone group and then Asperger’s disorder. The mean total score on the Childhood Autism Rating Scale (CARS) is similar in both risperidone and placebo groups, so is mean IQ, based on the cognitive tests, including Differential Abilities Scale, Leiter International Performances Scales, Ravens Progressive Matrices, Stanford-Binet, McCarthy Scales of Children Abilities, and Wechsler Intelligence Scale for Children, administered to the subjects at baseline. Almost equal number of subjects in each of the treatment group had each of the above tests. The number of subjects that belong to different levels of IQ are comparable in both treatment groups except the above average IQ level where significantly more subjects were assigned to the placebo group (31.4% versus 9.7%). Vineland

adaptive behavioral scores are also comparable in both groups at baseline.

Baseline Illness Characteristics		Risperidone	Placebo
DSM-IV Axis I Diagnosis	Autistic Disorder	27 (67.5%)	28 (71.8%)
	Asperger's disorder	5 (12.5%)	7 (17.9%)
	Childhood disintegrative disorder	1 (2.5%)	0
	PDD-NOS	7 (17.5%)	4 (10.3%)
CARS	Number of Subjects	40	39
	Mean Score	38.9±5.3	39.1± 6.7
	Min-Max Score	31-51	31-53
	Number of Mild-Moderate (scored 31-36)	17 (42.5%)	18 (46.2%)
	Number of Severe (scored 37) (%)	23 (57.5%)	21 (53.8%)
Cognitive Tests --IQ	Number of Subjects	31	35
	Mean	60.4	64.1
	Moderate to Severe Retardation (scored 49 or less) (%)	10 (32.3%)	12 (34.3%)
	Mild Retardation (scored 50 – 70) (%)	12 (38.7%)	8 (22.9%)
	Borderline IQ (scored 71 – 84) (%)	6 (19.4%)	4 (11.4%)
	Average and above > 84 (%)	3 (9.7%)	11 (31.4%)
Irritability Subscale of the ABC	Number of Subjects	37	38
	Mean Score	18.9	21.2

Patient Disposition

The sponsor enrolled a total of 80 subjects and randomized 41 to risperidone group, 39 to placebo group. One of the subjects who was randomized to the risperidone group but didn’t receive any study drug and had no post baseline assessment was excluded from all analyses.

The overall drop-out rate was 8.9% (7/79): Two (5.0%) were from risperidone group and five (12.8%) from placebo group. But, only one from each group (2.5% versus 2.6%) dropped

out due to adverse event (see details in Safety section). Another withdrawal from risperidone group and another two in the placebo group were due to insufficient response. The following table represents those who were assessed on the primary variable.

Enumeration of Patients Rated on the Primary Variable over Time

Time Interval & Disposition	Risperidone (N=40) N	Placebo (N=39) N
Baseline	37	38
Week 1	38	37
Week 2	36	36
Week 3	39	33
Week 5	39	33
Week 7	34	32
Week 8	34	31

Dosing Information

Mean dose of risperidone exposure is 0.038±0.0108mg/kg/day, which is equivalent to 1.170±0.4697mg/day. Risperidone dose range was 0.02-0.05mg/kg/day, that is 0.56-3.19mg/day. Mean dose data by visit was not available.

Concomitant Medications

Among all the subjects in this study, the most common concomitant medications were lorazepam (20 subjects, 25.3%), paracetamol (20 subjects, 25.3%), and salbutamol (6 subjects, 7.5%); an additional six subjects were taking other unspecified antiasthmatic medication.

Lorazepam was used in 9 subjects (23.1%) in placebo group and 11 subjects (27.5%) in risperidone. Two of these patients were diagnosed with other PDD's and the remainder were autistic. Antiepileptics (valproate) was used for unspecified period for seizure in one patient who was in risperidone group. No subject was on antidepressants, other antipsychotics, or other sedatives.

Table. Lorazepam Prescribed in Study CAN-23

Lorazepam Use	Risperidone N (%)	Placebo N (%)	Total N (%)
Autism	10 (37.0%)	8 (28.6%)	18 (32.7%)
Other PDDs	1 (3.7%)	1 (3.6%)	2 (9.1%)
Total	11 (27.5%)	9 (23.1%)	20 (25.3%)

Indications for using lorazepam were “anxiety during lab work/blood tests” or “prophylactic for extreme anxiety –lab work”. One case was due to “extreme anxiety during blood pressure” measurement. Most of these 20 patients were prescribed lorazepam for only one day or less than 30 days, but 7 subjects were prescribed lorazepam for more 30 days and no starting dates were indicated for 3 subjects.

Efficacy Results

The sponsor designates changes from baseline to endpoint of the Irritability subscale of ABC as the primary variable. Among the 40 subjects in risperidone group, 3 of them didn’t have baseline or post-baseline measurements and thus, only the scores of 37 of them have valid analysis. Likewise, one of the 39 subjects in placebo group didn’t have post-baseline measurement. Thus, only the scores of 38 subjects in placebo group are evaluable.

Summaries of the results from the analysis of the Irritability subscale of ABC scale are presented in **Appendices VI-1, VI-2, and VI-3** for 3 patient samples: all patients, autistic patients, and non-autistic patients, respectively. Risperidone was superior to placebo in reducing the Irritability Subscale of the ABC for both the LOCF and Observed Cases (OC) datasets at most time points in all 3 samples.

It is noted that the intergroup difference at week 8 in the non-autistic group was not significant (p=0.112). However, the number of patients still in-study at that visit in this sample was small (12 risperidone and 9 placebo patients). Also, risperidone was numerically superior to placebo by almost the same margin as in the autistic sample.

The sponsor also evaluated the consistency in treatment effects across study centers graphically. The FDA

statistician, Kun He, Ph.D., concludes that risperidone was numerically better than placebo across all sites.

Conclusions

Study CAN-23 demonstrates the superiority of risperidone over placebo in the treatment of irritability symptoms in children with autism.

2. Study US-150 Part I

Investigators/Sites

This is a multicenter study that involved five different sites in the U.S. from May 1999 to Apr. 2001. The following table lists the principal investigators from each site and the number of subjects recruited from each of them.

Principal Investigators	Sites	Number of Subjects
McDougle, Christopher J. M.D.	1	20
Aman, Michael G. Ph.D.	2	23
Tierney, Elaine M.D.	3	15
McCracken, James M.D.	4	24
Scahill, Lawrence D. M.S.N. Ph.D.	5	19

Objectives:

The sponsor's primary objective of the study was to compare the relative safety and efficacy of risperidone and placebo in the treatment of behavioral symptoms, such as impulsive aggression, agitation, self-injurious behavior, and troublesome repetitive behavior, in children and adolescents with Autistic Disorder and anticipate that risperidone would cause more transient sedation and weight gain than placebo.

Patient Sample

The sponsor planned to enroll approximately 100 subjects for this study.

In addition to consents signed by subject's parent, main inclusion criteria are:

- Children, male or female, age 5 to 17 years and 2 months old, with a body weight of at least 15kg
- Meeting DSM-IV Axis I diagnosis of Autistic Disorder (established by clinical assessment, corroborated by standard cutoff scores on the Autistic Diagnostic Interview or ADI)

- A mental age of at least 18 months, as measured by either the age-appropriate form of the Wechsler Intelligence test (whenever possible) or by the Revised Leiter or Mullen test
- A CGI score of at least 4 and a score of 18 or greater on the Irritability Scale of the ABC
- Inpatient or outpatient subject, physically healthy based on screening physical examination and medical history
- Free of all psychotropic medication for at least two weeks (four weeks for fluoxetine or depot neuroleptics)
- On a stable dosage of anticonvulsant for 4 weeks and seizure free for at least 6 months if seizure disorder is present.

Subjects with the following conditions are excluded:

- DSM-IV diagnosis of schizophrenia or other psychotic disorders, or a PPD other than Autistic Disorder.
- DSM-IV diagnosis of substance abuse
- Subjects with a significant medical condition such as hypertension, heart or pulmonary disease, liver or renal failure, or unstable seizure disorder identified by history, physical examination or laboratory tests
- History of known hypersensitivity to risperidone or a potentially serious adverse effects such as significant tachycardia or neuroleptic malignant syndrome
- History of prior adequate study with risperidone (defined as duration of 2 weeks or more at a dose of at least 1mg per day)
- Female patients with a positive beta-HCG pregnancy test
- QTc >450msec on ECG or 3-fold increase of liver enzymes.
- Clinical follow-up shows serious adverse events including severe side effects such as dyskinesia, weight gain exceeded the 95th percentile for age and increased more than 20% above baseline, seizure disorder becomes unstable, and clinical symptoms become more distressing and dangerous.

Study Design

This is an 8-week, randomized, double-blind, parallel-group, multicenter trial. The study medication dosage was

flexible, based on weight category, ranging from 0.25mg to 2.5mg (for weight between 20kg and 45kg) or 0.5mg to 3.5 mg/day (for 45kg and over) of risperidone tablets versus placebo. The number of subjects in each group was balanced within each center by each of the following randomization stratification factors: sex, pre- or post-pubertal, and anticonvulsant use.

Dose Schedule

Dosing was dependent on baseline body weight (15-20kg, =20kg to <45kg, or =45kg). Risperidone was started as a bedtime dose of 0.25 mg for patients in the lowest weight category or 0.5mg for patients in the two higher weight categories. On day 4, the dose was increased to 1.0 mg/day, given as 0.5 mg bid, for patients in the middle and high body weight groups. Thereafter, the dosage was gradually raised to a maximum of 2.5 mg/day for the middle weight group or 3.5 mg/day for the high weight group by days 22 and 23, respectively. Except for the starting dose, dosing for the low body weight group was not clearly specified in the study report. From day 4 onward, doses were split on a bid schedule. Where necessary, the larger portion was given in the evening (2.5 mg/day was split as 1.0mg in the AM and 1.5mg in the PM).

All patients could have been prescribed benztropine up to 1.0mg tid for dystonia or other extrapyramidal symptoms.

Assessments

Primary efficacy parameters were the change from baseline to end point on the Irritability subscale of the ABC scored by a parent or care giver and the CGI-C rated by the clinician investigator. These two measures are designated as co-primary variables and positive results on both were required to declare a positive study. The Aberrant Behavior Checklist (ABC) was performed at screening, baseline, and weeks 2, 4, 6, and 8, but the Clinical Global Impression (CGI-C) was assessed at baseline and then on weekly basis. The time allowed between screening and baseline was 7-14 days.

A responder on the CGI-C was defined by a clinical global improvement score of “Much improved” or “Very much improved.”

Secondary efficacy parameters were mainly assessed at baseline, week 2, 4, 6, and 8.

- Secondary efficacy parameters were the changes at endpoint versus baseline on the four other ABC subscale scores (Hyperactivity/Noncompliance, Inappropriate Speech, Lethargy/Social Withdrawal, and Stereotypic Behavior, the Compulsion subscale of Yale-Brown Obsessive Compulsive Scale (C-Y-BOCS) rated by clinicians, the Ritvo-Freeman Real Life Rating Scale for various symptoms of autism, including sensory-motor behaviors, social relationships, affect reactions, sensory responses, and language; and the Maladaptive Behavior domain scores from Vineland scale.

Analysis

The null hypothesis was that there would be no difference between the risperidone and placebo groups in the change from baseline to end point on the Irritability scale of the ABC or in the percentage of subjects with CGI-C ratings of much improved or very much improved. For the Irritability Subscale, the statistical test was interpreted at the 5% significance level, two tailed, with 80% power. For CGI-C, analysis was based on 5% significance level, two tailed, with power of 95%.

The intent-to-treat (ITT) population comprised all randomized subjects who received at least one dose of study drug. This was the primary sample for efficacy analyses.

The first primary efficacy variable, the Irritability subscale of the ABC, includes 15 items with each item rated on a scale of 0-3 (0 = no problem, 1 = slight problem, 2 =moderate problem, 3 = severe problem) yielding a total maximum score of 45 (see list below):

Items of the Irritability Subscale of the ABC

Injures self on purpose	Cries over minor annoyances and hurts
Aggressive to others (verbal/physical)	Mood changes quickly
Screams inappropriately	Cries and screams inappropriately
Temper tantrums	Stamps feet or bangs objects or slams doors
Irritable and whiny	Deliberately hurts himself/herself
Yells at inappropriate times	Does physical violence to self
Depressed mood	Tantrums when does not get own way
Demands must be met immediately	

Although the protocol specified primary analysis method for this primary variable was repeated measures model, the sponsor changed it to analysis of covariance (ANCOVA), with treatment and center as factors and the baseline score as covariate, according to the request of the FDA prior to this submission. The treatment by center interaction was examined graphically. Any departure from the assumptions of the ANCOVA model was performed via a quantile-quantile plot of the residuals versus the normal distribution and an assessment of the homogeneity of variance. A nonparametric Van Elteren test was to be used in case of severe violation of the underlying model assumptions.

CGI contains CGI-C (clinical global impression for change), which is the other co-primary variable, and the CGI-S (severity of pervasive development symptoms), both of which were scored by the clinician on a seven-point scale: absent to extremely severe for CGI-S and very much worse to very much improved for CGI-C. The CGI-C was used to give an impression of the change in the subject's condition compared to baseline. The percentage of responders on the CGI-C by treatment group, as defined above, was analyzed utilizing a Cochran-Mantel-Haenszel chi-square test.

The sponsor included the four other subscales of ABC, including as secondary efficacy variables Lethargy and social withdrawal; Stereotypic behavior; Hyperactivity/ noncompliance; Inappropriate speech.

Baseline Demographics

The majority patients in this study were Caucasian (66.3%). Most were male (81.2%). Almost all were in the 5-12 year old range (94.1%). Average age is 8.3 years-old (range 5-16 years). The risperidone group and placebo group are comparable with respect to age, race, sex, and baseline body mass index. The following table exhibits the demographics at baseline.

Subject Demographics at Baseline

Demographic Data		**Risperidone** (N=49)	**Placebo** (N=52)	**Total** (N=101)
Age (years)	Mean	8.1	8.5	8.3
	Median	7.0	8.0	8.0
	Range	5 - 16	5 - 14	5 – 16
Sex N (%)	Female	10 (20.4)	9 (17.3)	19 (18.8)
	Male	39 (79.6)	43 (82.7)	82 (81.2)
Race N (%)	Black	4 (8.2)	6 (11.5)	10 (9.9)
	Caucasian	34 (69.4)	33 (63.5)	67 (66.3)
	Hispanic	2 (4.1)	5 (9.6)	7 (6.9)
	Oriental	5 (10.2)	4 (7.7)	9 (8.9)
	Other	4 (8.2)	4 (7.7)	8 (7.9)

Baseline Severity of Illness

Mean scores at baseline on the Irritability Subscale of the ABC were comparable between treatment groups. The investigators used ADI to confirm subjects' diagnosis of Autism. Cognitive intelligence tests, including Mullen Test, Revised Leiter International Performances Scales, Wechsler Intelligence Scale for Children, and the Wechsler Preschool Primary Scale of Intelligence (WPPSI-R) were administered to the subjects at baseline. Although 96% (97/101) subjects had cognitive tests, only 54.5% (55/101) had IQ scores listed (see table below). The numbers of subjects in each of the treatment group who received each of the above tests were comparable. The number of subjects that belong to different levels of IQ are comparable in both treatment groups except those with IQ level at or below 49, where significantly more subjects were assigned to the placebo group (31.0% versus 19.2%). Mean IQ in placebo group was higher according to the sponsor (82.4 versus 65.8 in Risperidone group). Vineland adaptive behavioral scores are also comparable in both groups at baseline.

Baseline Illness Characteristics		Risperidone	Placebo
Autism Diagnostic Interview (with cut-off scores)	Reciprocal Social Interaction subscale (10)	26.2 (3.1)	26.3 (3.6)
	Verbal Score (8)	18.2 (3.46)	19.1 (4.3)
	Non-verbal Score (7)	11.8 (3.5)	12.1 (2.7)
	Mean Repetitive behavior/Stereotype (3)	7.7 (2.7)	8.0 (2.7)
Cognitive Tests --IQ (Intelligence Quotient)	Number of Subjects	26	29
	Mean	65.8	82.4*
	Moderate to Severe Retardation =49 (%)	5 (19.2)	9 (31.0)
	Mild Retardation 50 – 70 (%)	13 (50.0)	12 (41.4)
	Borderline IQ 71 – 84 (%)	5 (19.2)	4 (13.8)
	Average and above > 84 (%)	3 (11.5)	4 (13.8)
ABC Irritability Subscale	Number of Subjects	49	52
	Mean	26.1	25.0

*According to the sponsor that there were two misrecorded values as 1 and 736 here.

Patient Disposition

The sponsor enrolled a total of 101 subjects and randomized 49 to risperidone group, 52 to placebo group. Drop-out rate was 6.1% from the risperidone group and 34.6% from placebo group. But, only one patient from each group dropped out due to adverse event (see details in Safety section). Another 2 patients withdrew from risperidone group was due to insufficient response versus 12 patients who dropped out from the placebo group for this reason. Noncompliance, loss of follow-up and withdrawn consent or becoming ineligible to continue the trial were among others for discontinuation in the placebo group. The following table represents those who were assessed on the CGI at each visit.

Enumeration of Patients Rated on the Primary Variable over Time

Time Interval & Disposition	Risperidone (N=49) N	Placebo (N=52) N
Baseline	49	52
Week 1	47	49
Week 2	46	51
Week 3	46	48
Week 4	46	48
Week 5	48	41
Week 6	44	36
Week 7	45	36
Week 8	46	34
Endpoint	49	52

Dosing Information

The mean dose of risperidone was 0.055 (±0.019) mg/kg/day, translating to 1.670 (±0.432) mg/day. Risperidone dose range was 0.71-2.81 mg/day. Information regarding the mean dose by baseline weight or by visit was not provided.

Concomitant Medications

Among all the subjects in this study, the most common concomitant medications were paracetamol (11 subjects, 22.4% in risperidone group versus 12 subjects, 23.1% in placebo group), systemic antibacterials including amoxicillin, azithromycin, penicillin and others (10 subjects, 20.4% in risperidone group versus 9 subject, 17.3% in placebo group), and ibuprofen (7 subjects in each treatment group, 7% in risperidone group versus 7.4% in placebo group).

Lorazepam was used by only one subject in the risperidone group for sedation before blood drawn and by none in placebo group. Chloral hydrate was used in four patients, two in risperidone group and two in placebo group, mainly (3) for blood draw and EEG, one for insomnia. Another subject needed thiopental for shunt placement.

About 4% (4/101) of patients were on anticonvulsants for seizure disorder: in placebo group, one patient took

carbamazepine and one took lamotrigine and, in risperidone group, one took valproate sodium and one took gabapentin.

No subject was on antidepressants, other antipsychotics, or other sedatives.

Efficacy Results

The sponsor designated changes from baseline to endpoint of the Irritability subscale of ABC and that of the CGI-C as co-primary variables. Results on these variables by visit are displayed below. Risperidone was consistently superior to placebo on both variables.

Mean Change in ABC Irritability Subscale Scores

Treatment	**PLACEBO**				**RISPERIDONE**				
Irritability			Change from Treatment baseline				Change from Treatment baseline		Overall P-value(b)
	N	Mean	Mean Diff	P (a)	N	Mean	Mean Diff	P (a)	
Baseline	52	25.0			49	26.1			0.470
Week 2 OC	46	22.0	-3.1	0.005	46	17.4	-9.0	<0.001	<0.001
Week 2 LOCF	47	22.0	-3.0	0.005	46	17.4	-9.0	<0.001	<0.001
Week 4 OC	43	19.7	-5.6	<0.001	41	14.1	-12.1	<0.001	<0.001
Week 4 LOCF	52	20.3	-4.7	<0.001	49	13.9	-12.2	<0.001	<0.001
Week 6 OC	34	21.0	-4.5	<0.001	37	12.8	-14.3	<0.001	<0.001
Week 6 LOCF	52	21.2	-3.8	<0.001	49	12.3	-13.9	<0.001	<0.001
Week 8 OC	34	21.4	-4.8	0.002	45	10.8	-15.8	<0.001	<0.001
Week 8 LOCF	52	21.6	-3.5	0.003	49	11.3	-14.9	<0.001	<0.001

(a) Two sided P-value for paired t-test on change from treatment baseline.
(b) P-value for the intergroup difference from the ANCOVA analysis.

Percentage Responders on the CGI-C

	PLACEBO	RISPERIDONE	p-value
Week 2 OC	11.8%	32.6%	0.013
Week 2 LOCF	11.5%	33.3%	0.009
Week 4 OC	16.7%	65.2%	<0.001
Week 4 LOCF	15.4%	63.3%	<0.001
Week 6 OC	16.7%	63.6%	<0.001
Week 6 LOCF	13.5%	63.3%	<0.001
Week 8 OC	17.6%	80.4%	<0.001
Week 8 LOCF	11.5%	75.5%	<0.001

The sponsor didn't designate any key secondary variables. A review of scales included as secondary variables also showed positive results.

The sponsor evaluated the consistency in treatment effects across study centers graphically. The FDA statistician, Kun He, Ph.D., concludes that risperidone was numerically better than placebo across all sites.

Conclusions

Study USA-150/Part I demonstrates the superiority of risperidone over placebo in the treatment of irritability in children with autism.

(b) (4)

8 pages immediately following withheld - b(4)

C. Summary of Data Pertinent to Important Clinical Issues

1. Predictors of Response

Demographic Characteristics

The pool of all autistic patients from studies CAN-23 and USA-150/Part I with baseline and post baseline data was divided into two age subgroups: 5-12 years and older than 12 years. Mean changes in the ABC Irritability subscale are shown below. Risperidone was superior to placebo in the 5-12 subgroup by a statistically significant margin ($p<0.001$). Statistical testing was not done in the older subgroup due to the small sample size but risperidone was numerically superior to placebo by a large margin there as well.

AGE SUBGROUP	TREATMENT	N	MEAN CHANGE
5-12	Placebo	77	-4.9
5-12	Risperidone	70	-14.6
>12	Placebo	3	-4.0
>12	Risperidone	3	-10.3

A similar analysis for gender subgroups is shown below. Risperidone was superior to placebo to a statistically significant degree in both females and males ($p=0.012$ and $p<0.001$, respectively).

GENDER SUBGROUP	TREATMENT	N	MEAN CHANGE
Female	Placebo	13	-5.1
Female	Risperidone	18	-14.6
Male	Placebo	67	-4.9
Male	Risperidone	55	-14.3

This analysis was repeated for three racial subgroups (Black, Caucasian, and Other). The results are displayed below. Risperidone was superior to placebo in all three subgroups ($p=0.033$, $p<0.001$, and $p=0.004$, respectively).

RACE SUBGROUP	TREATMENT	N	MEAN CHANGE
Black	Placebo	12	-4.5
Black	Risperidone	7	-15.6
Caucasian	Placebo	51	-5.0
Caucasian	Risperidone	49	-14.2
Other	Placebo	17	-4.7
Other	Risperidone	17	-14.6

Type of Disorder: Autism vs. Other PDD's

Since all subjects in USA-150/Part I were diagnosed with autism, the analysis comparing autism versus other PDD subgroups was conducted only in study CAN-23. The mean changes in the ABC Irritability subscale by diagnostic subgroup are displayed below. In both the autistic and other PDD subgroups, risperidone was superior to placebo (p=0.002 and p=0.032, respectively).

DX SUBGROUP	TREATMENT	N	MEAN CHANGE
Autism	Placebo	28	-7.5
Autism	Risperidone	24	-13.5
Other PDD	Placebo	10	-3.7
Other PDD	Risperidone	13	-9.7

Presence or Absence of Somnolence

The pool of all autistic patients from studies CAN-23 and USA-150/Part I with baseline and post baseline data was divided into two subgroups based on the presence or absence of somnolence as a reported adverse event. Mean changes in the ABC Irritability subscale in each subgroup are shown below. Due to the imbalance in the number of patients by treatment and subgroup (i.e., many more risperidone than placebo patients with somnolence and many more placebo than risperidone patients without somnolence), these data were analyzed by computing the Least Squares mean difference between treatment arms with the 95% confidence interval for the difference. In the somnolence subgroup, the difference was -7.4 (-11.6, -3.2) and, in the "without somnolence" subgroup, -10.7 (-14.4, -7.0).[8] Thus, risperidone was superior to placebo in both subgroups.

[8] Negative treatment group differences indicate better effect for risperidone than placebo.

SOMNOLENCE SUBGROUP	TREATMENT	N	MEAN CHANGE
With Somnolence	Placebo	18	-5.9
	Risperidone	49	-14.3
Without Somnolence	Placebo	62	-4.6
	Risperidone	24	-14.7

Intelligence Quotient

The above analysis was repeated using IQ (=84 vs. >84) to define subgroups. Please note that a substantial proportion of the patients (37% overall) were missing an IQ score at baseline. Also, most of the patients had an IQ of 84 or less. The changes from baseline in the ABC Irritability subscale by intelligence subgroup are displayed below. In both subgroups, risperidone was superior to placebo ($p<0.001$ and $p=0.007$, respectively).

IQ SUBGROUP	TREATMENT	N	MEAN CHANGE
=84	Placebo	43	-4.4
	Risperidone	40	-13.4
>84	Placebo	10	-5.1
	Risperidone	3	-13.7

In summary, the superiority of risperidone over placebo in reducing the ABC Irritability subscale score appears to be independent of age, gender, race, type of disorder, somnolence, and IQ.

2. Size of Treatment Effect

A primary efficacy measure in both pivotal studies was the ABC Irritability subscale, which consists of 15 items, each rated on a scale from 0 to 3, with a maximum score of 45.

The mean changes from baseline to week 8 (LOCF) in the ABC Irritability subscale in the two pivotal trials (CAN-23 and USA-150/Part I) are displayed below. (The mean decreases from baseline are also represented as fractions of the baseline values.)

TRIAL/TIMEPOINT	RISPERIDONE	PLACEBO
CAN-23/Autism		
Baseline	20.6	21.6
Week 8	-13.5 (-66%)	-7.5 (-35%)
USA-150/Part I		
Baseline	26.1	25.0
Week 8	-14.9 (-57%)	-3.5 (-14%)

In both studies, the mean decreases in the Irritability subscale score were greater than 50% of the baseline value for the risperidone group. Changes of such magnitude are likely to be clinically significant.

3. Choice of Dose

Since both pivotal efficacy studies utilized flexible dosing, an examination of dose-response is not possible.

(b) (4)

D. Conclusions Regarding Efficacy

Studies CAN-23 and USA-150/Part I provide strong evidence of the efficacy of risperidone in treating symptoms grouped in the Irritability subscale of the ABC over a period of 8 weeks in children and adolescents with autism. These symptoms are repeated below for the convenience of the reader.

(b) (4)

Items of the Irritability Subscale of ABC	
Injures self on purpose	Cries over minor annoyances and hurts
Aggressive to others (verbal/physical)	Mood changes quickly
Screams inappropriately	Cries and screams inappropriately
Temper tantrums	Stamps feet or bangs objects or slams doors
Irritable and whiny	Deliberately hurts himself/herself
Yells at inappropriate times	Does physical violence to self
Depressed mood	Tantrums when does not get own way
Demands must be met immediately	

Approval of a psychotropic agent for such a symptom cluster begs the question of whether this represents a pseudospecific claim, that is, a claim for clinical symptoms common to many disorders that are “specific” to autism in name only as opposed to representing a distinct clinical entity unique to autism. We have generally been disinclined to approve medications for pseudospecific indications.

It is conceivable that some combination of the above symptoms may be unique to Autistic Disorder. To my knowledge, that has not been demonstrated.

Autism is somewhat unique among the major psychiatric illnesses, however, in that there is no approved treatment for the core symptoms of the disorder itself. Furthermore, the above symptoms can produce significant disability in autistic patients. Thus, an approved treatment for this aspect of this illness would meet an important public health need. Therefore, I consider the treatment of irritability in autism to be an acceptable indication.

VII. Integrated Review of Safety

A. Methodology of the Safety Review

Within the original supplement submission, deaths and other serious adverse events were examined from all completed and

ongoing Phase 1 and Phase 2/3 studies. Then, adverse events that led to dropout, common adverse events, laboratory test, vital sign, and ECG data and special safety analyses were evaluated. When possible, these evaluations focused on the pool of autistic patients from the two pivotal trials. When results for this patient pool were not provided by the sponsor, the review focused on analyses from the pool of double-blind, placebo-controlled studies. Also from the original submission, all serious adverse experiences from the sponsor's summary of pediatric postmarketing data were examined as well as the results of the sponsor's literature search.

Separately from the above review of data in the original submission, this safety review presents an examination of data contained in the 4-5-04 four-month Safety Update. This submission encompassed an update of the literature search, pharmacovigilance (postmarketing) data, and clinical trials data.

B. Safety Findings

1. Deaths

There were no deaths in the clinical trials.

2. Non-Fatal Serious Adverse Events (SAE's)

In the double-blind, placebo-controlled studies, 1.4% (3/222) of risperidone and 1.7% (4/237) of placebo patients experienced a serious adverse event. The serious events in the risperidone group were extrapyramidal disorder, appendicitis, and aggressive reaction. The only event considered probably drug-related was the extrapyramidal disorder, which is described below:

Patient 4150 from study CAN-23 was a 5 year-old boy with autism randomized to risperidone group. After he was given risperidone 2mg, instead of 0.2mg, patient's developed oculogyric crisis, swollen tongue, difficulty in talking and neck pain. He was successfully treated with benztropine and symptoms resolved the next day. Study participation was terminated.

In the placebo group, the following serious adverse events were reported, each in one patient: convulsions, headache,

vomiting, somnolence, excessive blood alcohol level, condition aggravated, injury, and medication error.

Across all Phase 2/3 studies in the original safety database (Nris=821), 9.4% of the risperidone patients reported at least one serious adverse experience. These events are enumerated in **Appendix VII-1**.[9] SAE's reported in at least 1% of these patients were condition aggravated (reported in 2.2% of patients) and aggressive reaction (1.3%). Other remarkable SAE's in the Phase 2/3 database were suicide attempt (0.5%), convulsions (0.2%), sepsis (0.2%), oculogyric crisis (0.2%), pleurisy (0.1%), bloody diarrhea (0.1%), pancreatic secretion decreased (0.1%), glomerulonephritis (0.1%), granulocytopenia (0.1%), pancytopenia (0.1%), and glaucoma (0.1%). The latter five events are considered unexpected and are summarized below.

Pancreatic Secretion Decreased

Patient A03417 in study INT-41 was a 13 yo female with a 2 year history of recurrent abdominal pain and nausea. After receiving risperidone for 154 days, it was noted that she had mild pancreatic exocrine hypofunction. She was treated with pancreatin 300mg tid. She continued risperidone therapy for a total duration of 1 year. During the trial, her weight increased from 66.3kg to 74.7kg.

Glomerulonephritis

Patient A03269 in study INT-41 was a 8 year-old boy with conduct disorder, ADHD and mild mental retardation and a medical history of enuresis. He was diagnosed with severe glomerulonephritis and hypertension (BP 118-100/70-74mmHg) after 129 days of risperidone treatment and hospitalized. He recovered after 8 days. The patient completed the trial without interruption.

Granulocytopenia

Patient A03223 in INT-41 was a 9 year-old boy with ADHD and moderate MR and history of cellulitis and other infections and some surgical operations. Patient was treated with risperidone 1.5mg/day but developed neutropenia with WBC 3,400/mm^3 and neutrophils 1.53/nl after about 11months of treatment. Despite the immediate discontinuation of risperidone, his neutrophils dropped further to 0.6/nl 9

[9] The reader is reminded that this enumeration does not include the Parts 2/3 of study USA-150 or the two ongoing studies. Nonetheless, SAE's from these latter trials were evaluated by the undersigned and are discussed in this review if deemed appropriate.

days later, but went back to 3,700/mm^3 on the 12th day of the event. No concomitant medications were used within 4 to 5months of the event. Hematological consult considered this event as immunological.

Pancytopenia

Patient A03105 in INT-41 was a 9 year-old boy with ADHD and borderline intellectual functioning and history of constipation and cough. On June 16, 1999, while he was treated with risperidone 1.5mg/day and developed pancytopenia: Hemoglobin/Hematocrit(H/H) 9.4g/dl/27.8%, Platelets $1.13*10^5/mm^3$, WBC 3,300/mm^3 with neutrophils 34.3%. Concomitant medications include Denoral (which can lead to agranulocytosis, leukopenia, hemolytic anemia, and thrombocytopenia), rifamycin drops and fusafungine spray on June 8-19 1999. His pancytopenia was resolved without discontinuation of risperidone.

Glaucoma

Patient A03703 in study INT-41 was a 9 year-old boy with ADHD, ODD and borderline intellectual functioning who was treated with risperidone and methylphenidate concomitantly. Patient was found to have increased intraocular pressure (30) on the 79^{th} day of the treatment. Glaucoma was resolved with treatment of timolol eye drops one week later. Though methylphenidate is contraindicated in glaucoma, it was discontinued 6 days after the glaucoma was resolved in this case.

An examination of all adverse events in the Phase 2/3 safety database for other clinically important events that were not classified as serious revealed five subjects on risperidone (0.6% or 5/821) who experienced syncope (AE verbatim terms were fainting, fainted, collapse, and loss of consciousness for three minutes). They were all on risperidone, dosing from 0.8-2.9mg/day. Only one of them (L6003 in USA-150) had been diagnosed with autism. In the placebo-controlled studies, 0.9% (2/222) of risperidone and 0% (0/237) of placebo patients reported syncope: this difference was not statistically significant (p=0.2). Despite none of these were reported as serious adverse events, I consider these events to be clinically significant.

3. Adverse Events Leading to Study Dropout

Among the patients with autism in the pool of studies USA-150/Part I and CAN-23, 2.6% (2/76) of the risperidone and 2.5% (2/80) of the placebo patients dropped out due to adverse experiences. One of the two risperidone dropouts is described in the previous section (Patient 4150 from study CAN-23 who dropped out after an extrapyramidal disorder following an accidental overdosage of risperidone). The other risperidone group dropout is described below:

Patient N5130 in USA-150 was a 9 year-old boy with autism randomized to risperidone group and was started on 0.5mg/day. This patient discontinued the study on Day 42 due to ineffectiveness and increased crying and irritability since Day 6 when he was on 1mg po bid. From CRF obtained, patient's mood was rated as moderately - severely depressed on the ABC-Community rating scale since 12 days into the treatment. This patient also experienced lethargy, somnolence, hypertonia, flushing, constipation, vomiting, rhinitis, acne and epistaxis during the treatment period. Upon discontinuation, his dosage was 1.5mg/day.

The two placebo patients with autism who dropped out (Patient 07018 from USA-150 and Patient 4155 from CAN-23) discontinued due to cerebral surgery for removal of a shunt and accidental overdosage of study medication, respectively.

4. Common Adverse Events

a. Coding of Adverse Events

Treatment emergent adverse event verbatim terms were coded by the sponsor to preferred terms using WHO-ART(WHO Adverse Reaction Terminology dictionary). The sponsor translated most of the verbatim terms appropriately. However, translations of several terms warrant attention. "Concentration difficulty" was translated as thinking abnormally; "mental distress" was translated into anxiety; "impulsive behavior" (9 cases) and "attitude change"(4 cases) were coded to personality disorder. "Behavior hyperactive," "akathesia" (25 cases) and "activity motor exaggerated" were all translated into hyperkinesia while "marked restlessness" was coded as agitation. In addition,

“mood swing” and “worsening of self-injury behavior” were coded to emotional lability.

b. Study Pooling

The two pivotal studies are both short term (8-week), randomized, double blind, placebo controlled studies. Study USA-150 only included pediatric patients with autism. Study CAN-23 included the pediatric patients with autism (70%) and patients with other PDDs. Both studies were flexible dosing based on body weight categories: 0.5-3.5mg/day for USA-150 and 0.01-0.06mg/kg/day for CAN-23. Thus, it seems reasonable to pool the both studies together for analysis.

c. Common, Drug-Related Adverse Events

Treatment emergent adverse events (TEAE’s) were examined in the primary safety database by comparing the reporting rates of placebo group and the risperidone group among patients diagnosed with autism in the pool of the two pivotal studies. **Appendix VII-2** displays the reporting rates for those events reported in at least 1% of the risperidone-treated patients.

Events that were reported by at least 5% of risperidone treated autistic patients and at a rate that was at least twice the placebo rate were considered common and drug related adverse events. These events are enumerated below.

Common and Drug Related Adverse Events in the Primary Placebo Controlled Pooled Database (occurrence rate of ≥5% and at least twice placebo)

Adverse Events	**Risperidone**	**Placebo**
	N total=76 n (%)	**N total=80 n (%)**
Somnolence	51 (67.1)	18 (22.5)
Appetite Increased	37 (48.7)	15 (18.8)
Extrapyramidal Symptoms*	33 (43.4)	8 (10%)
Fatigue	32 (42.1)	10 (12.5)
Upper Respiratory Tract Infection	26 (34.2)	12 (15.0)
Saliva Increased	17 (22.4)	5 (6.3)
Constipation	16 (21.1)	6 (7.5)
Mouth Dry	10 (13.2)	5 (6.3)

Dizziness	7 (9.2)	2 (2.5)
Automatism	5 (6.6)	1 (1.3)
Tachycardia	5 (6.6)	0
Confusion	4 (5.3)	0
Weight Increase	4 (5.3)	0

*See above footnote.

d. Dose-Relatedness

Since neither of the two pivotal studies utilized a fixed dose design, the relationship between adverse event reporting rates and administered dose could not assessed.

e. Demographic Effects on Adverse Event Reporting Rates

The sponsor provided some raw data that are not properly analyzed. The sponsor should be requested to do an appropriate analysis in the pool of placebo-controlled studies, specifically a computation of the drug:placebo odds of each common, drug-related adverse event (as defined above) within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

5. Laboratory Data

a. Extent of Laboratory Testing

Laboratory tests conducted in the pivotal studies are displayed in **Appendix VII-3**. These were performed received the following laboratory tests at baseline and week 8 or at endpoint.

The sponsor does not mention the rationale for not having the result of serum glucose level. The glucose results from the 17 subjects mentioned in the ISS were from other studies. Prolactin level was not obtained in CAN-23 and the results of USA-150 are still pending. Please note that available prolactin and glucose data are discussed below under Special Safety Analyses.

The analyses below are based on the pool of double-blind, placebo-controlled studies; separate analyses for the autistic patients were not provided.

b. Potentially Clinically Significant Laboratory Changes

Appendix VII-4 and **Appendix VII-5** illustrate the criteria and proportions of outliers for the chemistry and hematology tests, respectively, from all the double-blind placebo controlled studies in the original safety database.

In addition to low bicarbonate patients that appear more in risperidone group, the rate of increased liver enzyme and direct bilirubin was also slightly higher in risperidone group. None of these differences were statistically significant.
Slightly higher percentages of risperidone patients had outlying values on two lab tests: low MCV and increased eosinophils. However, the differences between risperidone and placebo were not statistically significant.

Though the mean value of urine specific gravity (normal range1.001-1.035) was slightly higher in risperidone group (71 versus 64), no subject was abnormal.

c. Mean Change from Baseline in Laboratory Values

Mean changes from baseline in laboratory test values in the placebo-controlled trials are displayed in **Appendix VII-6**. There were small differences between risperidone and placebo in terms of the mean change from baseline in ALT, alkaline phosphatase, and uric acid. Overall, the mean values of the laboratory tests in controlled studies on pediatric patients with autism and other DBDs in the original safety database have no significant changes from baseline to endpoint.(See the table below.)

d. Dropouts due to Abnormal Laboratory Findings

No subject dropped from the pivotal studies primarily due to abnormal laboratory findings based on above mentioned tests.

6. Vital Sign Data

a. Vital Sign Assessments

In the study reports, the sponsor provides the following items for vital sign assessments: Body temperature, pulse, and systolic and diastolic blood pressure all measured at sitting position. These were measured at screening,

baseline, and at all study visits. Neither orthostatic measurement of blood pressure nor respiratory rate was mentioned in the protocol or study report.

The sponsor analyzed data from autistic patients separately for both pulse rate and blood pressure. The table below shows the outliers of the vital signs in autism.

b. Potentially Clinically Significant Vital Sign Changes

The autistic patients in risperidone group have had an apparently higher rate of pulse increase compared to those in placebo group (43.1% versus 14.7%). This difference is highly statistically significant (p=0.0001, MH Chi-Square).

Risperidone group also has had slightly higher incidence of abnormally low diastolic blood pressure than placebo group (6.1% versus 4.2%); this difference was not statistically significant. No further information was provided on body temperature.

PCS Vital Signs in Autistic Patients

Vital Signs (and Criteria of Changes)	**Risperidone**	**Placebo**
	n (%)	**N (%)**
Pulse Rate	72	75
Abnormally Low (decrease from baseline of =15 to a value =65)	3 (4.0)	3 (4.2)
Abnormally High (increase from baseline of = 15 to a value 120)	31 (43.1)	11(14.7)
Blood Pressure	66	72
Systolic Abnormally Low (decrease from baseline of =15 to a value = 90)	8 (12.1)	9 (12.5)
Abnormally High (increase from baseline of = 15 to a value =180)	0	0
Diastolic Abnormally Low (decrease from baseline of =15 to a value = 50)	4 (6.1)	3 (4.2)
Abnormally High **(**increase from baseline of = 15 to a value =105)	0	1 (1.4)

The following table shows the mean values of vital signs in patients with autism:

c. Mean Change from Baseline in Vital Sign Measures

There was a significant greater mean change in pulse rate for risperidone vs. placebo group in the pool of autism patients.

Mean Change from Baseline in Vital Sign Measures in Autism

Vital Signs	Risperidone		Placebo	
	Subjects	Mean	Subjects	Mean
Body Temperature (^{o}F)	N=42	0.1	N=46	0
Pulse Rate (bpm)	N=72	7.4	N=75	-0.7
Respiratory Rate (times/min)	**N/A**		**N/A**	
Blood Pressure (sitting)				
• **Systolic** (mmHg)	N=66	2.6	N=72	0
• **Diastolic** (mmHg)	N=66	1.0	N=72	-0.2

d. Dropouts due to Vital Sign Abnormalities

No subject dropped out due to vital sign abnormalities.

7. ECG Data

a. ECG Assessments

In the double-blind, placebo-controlled studies, 12-lead ECG's were recorded at baseline and week 8 (or endpoint). However, quantitative ECG data in CAN-23 was not analyzed by the sponsor for some unknown reason. Thus, the analyses below are for the pool of only studies CAN-19, USA-150/Part I, and USA-93. Also, data for USA-150/Part I is presented separately since patients in this trial were diagnosed with autism.

The sponsor adjusted the QT interval for heart rate using a number of methods: Bazett's formula (QTcB), Fridericia's formula (QTcF), Sagie's formula (QTcL), and a linear-derived model (QTcLD). Under the latter model, baseline QT interval values and heart rate data for all subjects (except those in extension studies) were utilized to derive the regression equation QT=a + ß*(60/HR). The estimated slope from this linear model (ß) was then used to compute the QTcLD from the equation QTcLD= QT + ß*(1-(60/HR)), where QT interval are measured in msec and HR in bpm. This review will focus on QT interval analyses based on data from the Fridericia correction as well as the linear-

derived model since these adjustments may be more appropriate for drugs that increase the heart rate.

b. Potentially Clinically Significant ECG Changes

Potentially clinically significant (PCS) changes in ECG parameters were defined by the following criteria:

PCS CRITERIA FOR ECG CHANGES

ECG Parameter	Low (shortened)	High (prolonged)
HR (bpm)	=65	=120
PR (msec)	--	=210
QRS (msec)	=50	=120
QT (msec)	=200	=500
QTc (males)	--	>450
QTc (females)	--	>470

From the pool of studies CAN-19, USA-150/Part I, and USA-93, the proportions of patients who met these criteria at endpoint are displayed in the table below. The incidence of a PCS increase in heart rate was higher in the risperidone group versus placebo (11.6% vs. 9.5%) but this difference was not statistically significant (p=0.7). Risperidone was comparable to placebo on other measures. One patient (L6003 in USA-150/Part I) had a high QTcLD value at endpoint (see below).

PROPORTIONS OF PATIENTS MEETING PCS ECG CRITERIA AT ENDPOINT (DB, PC STUDIES except CAN-23)

Parameter	Placebo			Risperidone		
	Ntot	Npcs	%pcs	Ntot	Npcs	%pcs
HR (low)	147	9	6.1	138	9	6.5
HR (high)	147	14	9.5	138	16	11.6
PR (high)	147	0	0.0	138	0	0.0
QRS (low)	147	0	0.0	138	1	0.7
QRS (high)	147	0	0.0	138	1	0.7
QT (low)	147	0	0.0	138	0	0.0
QT (high)	147	0	0.0	138	0	0.0
QTcF (high)	147	0	0.0	138	0	0.0
QTcLD (high)	147	0	0.0	138	1	0.7

The sponsor also analyzed the proportion of patients categorically by the degree of change in QTc from baseline to endpoint. The results are shown below. A slightly greater proportion of risperidone versus placebo patients had changes in QTc of 30-60 msec and greater than 60 msec for QTcF and 30-60 msec for QTcLD; the latter was of

borderline statistical significance (p=0.1). Only one patient experienced a change greater than 60 msec on the QTcF; none did so based on the linear-derived adjustment of QT.

PROPORTIONS OF PATIENTS BY CATEGORICAL CHANGE IN QTc at ENDPOINT (DB, PC STUDIES except CAN-23)

Parameter	Placebo			Risperidone		
	Ntot	Ncat	%cat	Ntot	Ncat	%cat
QTcF						
<30 msec	142	136	95.8	133	124	93.2
30-60 msec	142	6	4.2	133	8	6.0
>60 msec	142	0	0.0	133	1	0.8
QTcLD						
<30 msec	142	139	97.9	133	125	94.0
30-60 msec	142	3	2.1	133	8	6.0
>60 msec	142	0	0.0	133	0	0.0

The next table displays the results of the PCS analysis based on data from only study USA-150/Part I. Again, risperidone was associated with a higher fraction of patients with a PCS increase in heart rate (34.1% vs. 20.9%; p=0.2). One child, an 11 year old boy (subject L6003), had a prolonged QTcLD at endpoint (455 msec at week 8 versus 422 msec at baseline).

PROPORTIONS OF PATIENTS MEETING PCS ECG CRITERIA AT ENDPOINT (STUDY USA-150/Part I)

Parameter	Placebo			Risperidone		
	Ntot	Npcs	%pcs	Ntot	Npcs	%pcs
HR (low)	43	0	0.0	44	0	0.0
HR (high)	43	9	20.9	44	15	34.1
PR (high)	43	0	0.0	44	0	0.0
QRS (low)	43	0	0.0	44	1	2.3
QRS (high)	43	0	0.0	44	1	2.3
QT (low)	43	0	0.0	44	0	0.0
QT (high)	43	0	0.0	44	0	0.0
QTcF (high)	43	0	0.0	43	0	0.0
QTcLD (high)	43	0	0.0	43	1	2.3

The display of categorical change in QTc among patients in USA-150/Part I is provided below. There were no major differences between the treatment groups in this study.

PROPORTIONS OF PATIENTS BY CATEGORICAL CHANGE IN QTc (USA-150/Part I)

Parameter	Placebo			Risperidone		
	Ntot	Ncat	%cat	Ntot	Ncat	%cat
QTcF						
<30 msec	43	41	95.3	43	42	97.7
30-60 msec	43	2	4.7	43	1	2.3
>60 msec	43	0	0.0	43	0	0.0
QTcLD						
<30 msec	43	41	95.3	43	41	95.3
30-60 msec	43	2	4.7	43	2	4.7
>60 msec	43	0	0.0	43	0	0.0

c. Mean Change in ECG Measures

The mean changes from baseline in the above ECG parameters were computed for the pool of studies CAN-19, USA-150/Part I, and USA-93 as well as for the autism study USA-150/Part I alone. The results are displayed in the next two tables, respectively. Differences between risperidone and placebo were not remarkable.

MEAN CHANGE FROM BASELINE TO ENDPOINT IN ECG PARAMETERS (DB, PC STUDIES except CAN-23)

Parameter	Placebo		Risperidone	
	N	Mean Change	N	Mean Change
HR (bpm)	142	+2.1	133	+1.0
PR (msec)	142	+0.7	133	+2.3
QRS (msec)	142	+0.3	133	-0.8
QT (msec)	142	-0.5	133	+1.3
QTcF (msec)	142	+1.4	133	+2.2
QTcLD (msec)	142	+2.0	133	+2.6

MEAN CHANGE FROM BASELINE TO ENDPOINT IN ECG PARAMETERS (STUDY USA-150/Part I)

Parameter	Placebo		Risperidone	
	N	Mean Change	N	Mean Change
HR (bpm)	43	+6.5	44	+8.4
PR (msec)	43	-2.5	44	+1.0
QRS (msec)	43	-1.7	44	-3.4
QT (msec)	43	-6.9	44	-10.1
QTcF (msec)	43	-0.2	44	-2.7
QTcLD (msec)	43	+2.3	44	+0.1

d. Dropouts due to ECG Abnormalities

No patients in the double-blind, placebo-controlled studies dropped out due to an ECG abnormality.

8. Special Safety Analyses

a. Extrapyramidal Symptoms (EPS)

The sponsor defined four EPS-related adverse event terms, each of which encompasses certain WHO preferred terms:

• tremor (WHO preferred term tremor).
• akathisia (WHO preferred term hyperkinesia).
• parkinsonism (WHO preferred terms extrapyramidal disorder, hypokinesia, and bradykinesia).
• dystonia (WHO preferred terms dystonia, hypertonia, oculogyric crisis, involuntary muscle contractions, tetany, and tongue paralysis).

The proportion of patients reporting these events, in addition to the rates for the preferred terms dyskinesia and tardive dyskinesia, are depicted in the table below for the autism patients in the pool of studies USA-150 and CAN-23. Except for akathisia and tardive dyskinesia, the reporting rates are considerably higher in the risperidone patients compared to the placebo patients.

Adverse Event	Placebo N=80	Risperidone N=76
Dystonia	6.3%	11.8%
Tremor	1.3%	11.8%
Parkinsonism	0.0%	7.9%
Dyskinesia	0.0%	6.6%
Akathisia	1.3%	1.3%
Tardive Dyskinesia	1.3%	0.0%

The two placebo-controlled autism trials utilized different scales to rate EPS: USA-150/Part I used the Simpson-Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS) whereas CAN-23 used the Extrapyramidal Symptom Rating Scale (ESRS).

In study USA-150, the mean changes from baseline to endpoint in the SARS total score at endpoint were -0.1 for placebo (N=51) and +0.2 for risperidone (N=49). This difference was not statistically significant (p=0.161).

Similarly, the mean changes in the AIMS score at endpoint were -0.1 for placebo (N=52) and -0.2 (N=49) for risperidone. This difference was also not statistically significant (p=0.586). The median change from baseline to endpoint for both the SARS and the AIMS was 0 for both risperidone and placebo.

In study CAN-23, the mean changes from baseline to endpoint in ESRS total score and subscores among the patients with autism are displayed in the next table. Mean changes were comparable between the risperidone and placebo groups.

ESRS Score	Placebo N=28	Risperidone N=27
Total ESRS	-0.4	-0.3
Parkinsonism	-0.5	-0.3
Dystonia	0.0	0.0
Dyskinesia	+0.1	0.0

It is curious that the EPS scale data are not very consistent with the reporting of EPS-like symptoms as adverse events. The latter suggest that dystonia, tremor, Parkinsonism, and dyskinesia are associated with risperidone treatment in this population.

b. Glucose Metabolism

The sponsor performed a search for adverse events suggesting a disorder of glucose metabolism. Glucose-related adverse events encompassed the following preferred terms: acidosis, lactic acidosis, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus reactivated, abnormal glucose tolerance, glycosuria, hyperglycemia, hypoglycemia, hypoglycemic reaction, ketosis, diabetic coma, neonatal hyperglycemia, neonatal hypoglycemia, phenylketonuria, increased plasma osmolality, hypoglycemic coma, blood glucose false positive, and breath odor ketones.

No event which was coded to any of the above terms was reported in either of the pivotal autism studies.

In other Phase 2/3 trials, only one patient experienced a glucose-related event: Patient A3132 experienced ketonuria following 190 days of risperidone treatment in study USA-97. No treatment was given and the patient continued in the trial with subsequent resolution of the event.

An examination of the study protocols and study reports revealed that serum glucose levels were not assessed in either of the pivotal autism studies.

In the pool of double-blind, placebo-controlled studies, few patients had baseline and post-baseline random glucose levels (15 placebo patients and 18 risperidone patients). In these patients, the mean change from baseline to endpoint in glucose levels was -0.2 mg/dl for risperidone and -3.7 mg/dl for placebo. None of the patients with post baseline glucose levels met a criterion for a potentially clinically important serum glucose reading (<50 or >200 mg/dl).

In my opinion, the assessment of the effects of risperidone on glucose metabolism in pediatric patients was inadequate.

c. Prolactin Elevation

In adults treated with risperidone, risperidone elevates prolactin levels and the elevation persists during chronic administration.[10] This is most likely due to dopamine D_2 receptor blockade in the tuberoinfundibular pathway which results in increased secretion of prolactin by the anterior pituitary. This, in turn, may produce a number of clinical effects, such as gynecomastia.

Prolactin data were not available from the placebo-controlled autism studies but were available from the studies in patients with DBD and other PDD's. In the latter double-blind, placebo-controlled studies, the mean prolactin levels at baseline and endpoint were very similar in the placebo patients: 8.083 and 8.064 ng/ml, respectively (N=108 at endpoint). However, in the risperidone group, the mean value increased from 8.107 at baseline to 29.330 ng/ml at endpoint (N=91). Additionally, a higher percentage of patients in the risperidone group (43.4% or 36/83) had an increase from normal range at baseline to above normal range at endpoint compared to placebo (2.0% or 2/98).

The sponsor examined the incidence of adverse events that were considered to be potentially prolactin-related in the clinical trials. These events included the following: gynecomastia, nonpuerperal lactation, breast discharge,

[10] See Risperdal labeling.

impotence, libido decreased, male breast pain, female breast pain, anorgasmia, dysmenorrhea, ejaculation failure, abnormal sexual function, and hyperprolactinemia. These events were reported in 6.3% (14/222) of risperidone patients and 2.1% (5/237) of placebo patients in the double-blind, placebo-controlled studies. By far, the most common specific event in the risperidone group was hyperprolactinemia (5.9% of risperidone and 0.4% of placebo patients).[11] Other events, which were each reported in less than 1% of patients, were gynecomastia and dysmenorrhea.

Interestingly, none of these events were reported in patients over the age of 12 years in the placebo-controlled studies. Also, the odds of reporting an event was higher among male patients (6.9% for risperidone vs. 1.1% in placebo) than in females, where the placebo rate was actually higher (4.3% for risperidone vs. 5.9% for placebo).

Among all 821 patients exposed to risperidone in Phase 2/3 studies in the original ISS database, 117 (14.3%) experienced one of these events.

As in adults, risperidone appears to produce prolactin elevation in children and adolescents.

d. Somnolence

In the patients with autism from studies USA-150/Part I and CAN-23, somnolence was reported as a treatment-emergent adverse event in 67% (51/76) of risperidone and 23% (18/80) of placebo patients. This difference is highly statistically significant ($p<0.001$). None of these patients dropped out due to somnolence.

In the pool of all placebo-controlled studies, 50% (110/222) of risperidone and 14% (32/237) of placebo patients reported somnolence. In the risperidone group, somnolence was rated as mild in 63 patients, moderate in 43 patients, and severe in 4 patients. Two risperidone patients (0.9%) and no placebo patients discontinued treatment due to somnolence. A Kaplan-Meier analysis of

[11] Presumably reports of hyperprolactinemia were based on blood levels and, thus, derive solely from the non-autism studies. Therefore, the stated percentages likely underestimate the true incidence of prolactin elevation since Autistic patients were included in the rate denominators but were not assessed for prolactin elevation.

the time to the first occurrence of somnolence revealed that the incidence was highest during the first 2 weeks of treatment in risperidone patients. In all risperidone patients with somnolence, the mean duration of somnolence was 18.7 days (range 1 to 57 days). This represented about 39% of the total duration of drug exposure.

In study CAN-23, changes in the dosing regimen were permitted in patients who experienced somnolence. The recommended schedule of once daily in the morning could be changed to once daily in the evening or to a bid schedule, with one-half the dose in the morning and one-half the dose in the evening. In the risperidone group, 20 subjects (of 29 with somnolence) had changes in dosing during reports of somnolence. Somnolence resolved in 18 subjects after the change in dosing. Of the other 2 patients, with had persistent somnolence and the other had resolution followed by recurrence.

In two placebo-controlled studies (USA-93 and CAN-19), sedation was rated on a 100mm Visual Analog Scale (0=absent and 100=severe). At baseline, ratings were comparable (6.8mm for placebo (N=117) and 6.1 for risperidone (N=98)). At each subsequent assessment, there was a mean decrease in the rating for placebo and a mean increase for risperidone. In the risperidone group, there was a progressive increase through week 4 and then a progressive decrease through week 6. At endpoint, the mean change was -2.4mm for placebo and +6.9mm for risperidone.

e. Seizures

Seizure disorder is a common comorbid condition in autism, occurring in as many as 25% of autistic patients.

The sponsor provided an enumeration of all patients who experienced adverse events coded to the preferred term “convulsions.” However, an examination of all adverse event verbatim terms that suggested a possible seizure occurrence revealed three additional patients who may have had seizures. These patients are listed below. The incidence figures which follow are adjusted to include these three patients.

Table. Subjects with Possible Seizures

Adverse Events Verbatim	Coded Preferred Terms	Age	Sex	Diagnosis	Treatment	CRF ID
Staring Spells	Thinking Abnormal	6	F	DBD/Other PDD	Risperidone 1-1.2mg/day	CAN-19/A3641
Staring Spells	Thinking Abnormal	8	M	Autistic Disorder	Placebo	USA-150/N5027
Clouding of Consciousness for 15seconds	Absences	8	M	DBD/Other PDD	Risperidone 1.8mg/day	INT-41/A03315

In the double-blind, placebo-controlled trials, one risperidone patient and two placebo patients experienced a seizure. These numerators include two patients listed above (A3641 and N5027). Thus, the reporting rates in this study pool are 0.5% (1/222) for risperidone and 0.8% (2/237) for placebo. In this pool of studies, 4 patients in the risperidone group and 3 patients in the placebo group took anticonvulsant medication. Among these, 3 risperidone patients and 2 placebo patients had autism.

Overall, the incidence rate for seizures was 1.0% (8/821) in the Phase 2/3 safety database.

Although the incidence of seizure appears high, the higher incidence in the placebo group in the placebo-controlled studies suggests that this is not related to risperidone treatment.

f. Gastrointestinal Disorders

Children and adolescents with Autistic Disorder experience higher rates of gastrointestinal disorders than their peers without Autism.

In the pivotal studies, 62% of the patients who received risperidone experienced a gastrointestinal adverse event compared to 48% of placebo patients. Specific gastrointestinal adverse events reported in at least 5% of the risperidone patients with autism in the pivotal studies are depicted below. None of these patient dropped out due to a gastrointestinal adverse event.

	Placebo (N=80)	Risperidone (N=76)
Vomiting	21%	25%
Increased saliva	6%	22%
Constipation	8%	21%
Dry mouth	6%	13%
Diarrhea	20%	13%
Nausea	8%	8%
Dyspepsia	10%	5%

Events that are probably drug-related (occurring at an incidence at least twice that of placebo) are increased salivation, constipation, and dry mouth.

In the Phase 2/3 safety database (Nris=821), 1% of patients had a gastrointestinal event classified as serious. These events were: abdominal pain (4 patients), appendicitis (2 patients), and vomiting (2 patients). The following events were serious in one patient each: constipation, diarrhea, bloody diarrhea, nausea, pancreatic secretion decreased, and saliva increased.

g. Body Weight, Height, and Body Mass Index

For autistic patients in the two pivotal studies, 5.3% of risperidone patients and no placebo patients reported weight gain as an adverse event. In these patients, the mean changes from baseline to endpoint in body weight were +2.6kg for risperidone (N=76) and +0.9kg for placebo (N=80). Using a 7% increase or decrease from baseline in body weight as a criterion, 66.7% of risperidone patients and 11.4% of placebo patients had an abnormal increase in weight; 1.4% of risperidone and 2.5% of placebo patients had an abnormal weight loss.

The mean changes in height for these patients were +1.1cm for 48 risperidone patients and +1.2cm for 51 placebo patients.

Mean changes in body mass index (BMI) in this sample were +1.2 for 48 risperidone patients and +0.1 for 51 placebo patients.

Changes in body weight and BMI for the DBD/PDD patients in double-blind, placebo-controlled studies were similar.

In longer-term, open-label studies (up to 36 months), baseline and endpoint BMI assessments were available for 450 patients treated with risperidone. A cross-tabulation of BMI category at baseline and endpoint is shown below. BMI categories were defined as normal (<25), overweight (25 to <30), and obese (=30). Most (428) were normal at baseline. At endpoint, however, 26 (6%) of these patients had shifted to the overweight category and 4 (1%) to the obese category. Three of the 17 patients who were overweight at baseline shifted to the obese category at endpoint.

Endpoint BMI Cat.	**Baseline BMI Category**			
	Normal	**Overweight**	**Obese**	**Total**
Normal	398	1	0	399
Overweight	26	13	0	39
Obese	4	3	5	12
Total	428	17	5	450

Results from the 8-week, double-blind, placebo-controlled studies were similar: 141 risperidone and 175 placebo patients were normal at baseline and, among these patients at endpoint, 9 (6%) of risperidone and 2 (1%) of placebo patients had shifted to the overweight category.

Thus, risperidone appears to be associated with an increase in body weight and BMI.

Although there was little difference between risperidone and placebo in terms of height increase in short-term trials, longer-term studies are likely to be more sensitive detecting effects on height. The evaluation of changes in height are complicated since increases in these measures are normally expected to occur in the age range of these patients. One approach to addressing this concern is to utilize z-scores, where the z-score is the number of standard deviations from a patient’s gender/age-standardized mean. The z-score is determined at baseline and at the end of the observation period. If the mean change in z-score is negative, then the group did not gain height as expected based on population norms.

Thus, it is suggested that the sponsor be requested to analyze height data by computing the changes from baseline to endpoint in z-scores for all patients who received

risperidone for a certain continuous period of time (e.g., 3 months).

h. Cognitive Function

Cognitive tests were performed in several studies to assess whether risperidone treatment had an adverse effect on attention, concentration, and/or verbal memory. However, testing was performed in only two placebo-controlled trials, USA-93 and CAN-19, which enrolled mentally retarded children with conduct disorder. These data were not available for either of the two pivotal autism studies.

In the pool of USA-93 and CAN-19, the mean changes from baseline to endpoint on the easy CPT (Continuous Performance Test), hard CPT, and MVLT (Modified Verbal Learning Test) were generally small and similar between treatment groups.[12]

It is not clear whether these results can be extrapolated to patients with autism. Thus, the assessment of these measures in autistic patients is considered inadequate.

i. Suicidality

There were no adverse events related to treatment-emergent suicidality in the pivotal autism studies based on an examination of both verbatim and preferred adverse experience terms from those trials.

In the larger pool of double-blind, placebo-controlled studies (Nris=222), there were no adverse events coded to suicide attempt.

In the Phase 2/3 safety database, the incidence of adverse events coded to suicide attempt in risperidone-treated patients was 0.7% (6/821). All occurred in open-label extension studies. The timing of these events by 3-month interval is shown below. Most of these events occurred in the first 12 months. However, this is not unexpected since the number of patients still in-study at month 13 was less than half the original sample (331/821). Reporting rates by 3-month interval in the first 12 months were not substantially different. The high rate in the 25-27 month

[12] These data will not be presented here but can be found in Appendix Tables 2.7.4.153 - 2.7.4.155 of the sponsor’s Summary of Clinical Safety.

interval is based on only one patient and is not considered a stable estimate.

Interval (months)	N/n[13]	%
1-3	1/821	0.1%
4-6	1/621	0.2%
7-9	2/565	0.4%
10-12	1/525	0.2%
25-27	1/62	1.6%

Finally, since suicidal-related adverse events have been coded to the WHO-ART preferred term “emotional lability” in other development programs, all verbatim event terms that had been coded to this preferred term were surveyed in the Phase 2/3 safety database. Only one verbatim term suggesting suicidality was identified: “worsening of self-injurious behavior,” which was reported in Patient A3098 during open-label treatment in study USA-97.

In sum, there is no signal for suicidality from the double-blind, placebo-controlled studies and no temporal clustering of suicide attempts in the open-label trials.

j. Treatment-Emergent Aggression

Verbatim adverse event terms that were coded to the preferred term “aggressive reaction” include the following: increased aggression, increased oppositional behavior, worsening mood, fighting, hitting, scratching, spitting, screaming, loud, cruelty to animals, sexually touching others, throwing things, verbally aggressive, outburst, grouchy, violent, and temper tantrums.

In the 2 pivotal studies, the reporting rates of events coded to aggressive reaction are provided below by type of disorder and study.

Type of Disorder	Placebo	Risperidone
USA-150/Autism	0/52 (0.0%)	1/49 (2.0%)
CAN-23/Autism	3/28 (10.7%)	1/27 (3.7%)
CAN-23/Other PDD	5/11 (45.5%)	2/13 (15.4%)

In USA-150/Part I, the risperidone rate was higher than the placebo rate but not to a statistically significant degree (p=0.485). In CAN-23, the placebo rates were about three-

[13] N=number of events. n=number of patients entering that 3-month interval. %=N/n X 100%.

fold higher than the risperidone rates for both autistic patients and patients with other PDD's.

The reporting rate for agitation in the autism patients who participated in the pivotal studies was 3.9% (3/76) in the risperidone group and 8.8% (7/80) in the placebo group. In all placebo-controlled trials, agitation was reported in 2.3% (5/222) of risperidone patients and 4.6% (11/237) of placebo patients.

Finally, a search of the entire Phase 2/3 database for adverse events described by verbatim terms that contained "homicide," "homicidal," "murder,", or "kill" revealed no such events.

These data do not suggest that risperidone treatment was associated with treatment-emergent aggression.

9. Overdose Experience

The sponsor performed no systematic examination of overdose potential in this sNDA.

Only one autistic patient experienced an overdose of risperidone: Patient 4150 in study CAN-23. This patient is described above under section VII.B.2 (Non-Fatal Serious Adverse Events).

10. Human Reproductive Data

No information relevant to the effect of risperidone on human reproduction was provided in this supplement.

11. Withdrawal Phenomena/Abuse Potential

No data pertaining to discontinuation effects or abuse liability was presented in this sNDA.

12. Postmarketing Data

There were 241 reports with 444 adverse events coded among child and adolescent patients from 14 different countries. Classification of these 241 reports by diagnosis is shown below.

Autistic Spectrum Diagnosis	Number of Cases Received
Autism/Autistic spectrum	198
Asperger's syndrome	20
Pervasive developmental disorder (PDD)	17
Autism/PDD	3
Autism/Asperger's syndrome	3

These cases were reported with increasing frequency over more recent years, as displayed below.

Calendar Year	Number of Cases Received
1993[a]	0
1994	0
1995	5
1996	10
1997	17
1998	18
1999	31
2000	28
2001	28
2002	63
2003[b]	41

a: beginning 01 May
b: through 30 Aug

Among these reports, 34 cases were serious and 207 non-serious.

Among the 34 serious case reports, 85 events were reported. None of these events had a fatal outcome. A line listing of these 34 cases is presented in **Appendix VII-7**. An examination of the primary clinical events reported in these cases was completed to detect any pattern of serious adverse events.

The most common serious adverse event was extrapyramidal symptoms:

- tardive dyskinesia (4 cases).
- dystonia (4 cases).
- EPS (2 cases)
- tremor (1 case).
- NMS (1 case).

Other notable serious adverse events, each of which was reported in one case, were:

- diabetic coma.
- neutropenia.
- leukopenia.
- thrombocytopenia.

The patient with diabetic coma had a pre-treatment history of brittle diabetes mellitus and experienced poor control of blood sugar levels after discontinuation of risperidone. Neither case of decreased white blood cell count was reported to progress to agranulocytosis (total WBC =1,000mm^3 or ANC =500/mm^3). The patient with thrombocytopenia exhibited chronically low platelet counts during three years of risperidone therapy with no bleeding tendencies noted.

On the whole, these data do not suggest the occurrence of any previously unknown serious adverse events likely to be associated with risperidone in autistic spectrum patients.

13. Literature Search Results

A total of 628 articles were identified and, after elimination of duplicate articles, 319 remained. These articles were reviewed and categorized and, after further elimination of certain types of articles (e.g., those with no clinical data), 163 articles remained.

Safety results were reported in 125 of these articles. In general, the adverse events described in these articles were deemed by the sponsor to be consistent with adverse experiences previously reported with risperidone or the various concomitant medications administered.

No deaths were reported.

Serious adverse events were described for a total of 10 subjects. These were NMS (5 subjects), tardive dyskinesia (2 subjects), acute dystonia (1 subject), and viral encephalitis (versus NMS) (1 subject). In the remaining subject, toxic carbamazepine levels were reported after starting risperidone treatment. However, an interaction

study did not demonstrate that risperidone produces an elevation of carbamazepine levels.[14]

Overdoses (accidental or intentional) were described in 4 cases. None were fatal. Amounts of risperidone ingested ranged from 4mg (in a 3 year old boy) to 60mg. Associated adverse events included tachycardia, dystonia, lethargy, upward eye gaze, jerky limb movements, motor restlessness, decreased blood pressure, and bradycardia.

Adverse events leading to discontinuation of risperidone were reported in 38 articles. The most frequent events leading to dropout were weight gain, extrapyramidal symptoms, sedation, drowsiness, separation anxiety, and NMS.

The most frequently reported adverse events were weight gain (37 articles), sedation (27 articles), and extrapyramidal symptoms (24 articles).

In sum, this literature search did not reveal any previously unreported serious adverse events likely to be causally associated with risperidone.

14. Four-Month Safety Update

The four-month Safety Update, which was submitted on 4-5-04, contains additional safety data from two clinical trials that were ongoing at the time of the original supplement submission as well as updates of the above literature search and spontaneously reported postmarketing safety data (see section IV. for further details).

Clinical Trials Update

At the time of this update, one of the two ongoing trials (INT-79) had been completed and the other (INT-84) was still ongoing.

INT-79[15]

INT-79 enrolled children and adolescents, ages 5-17, with Conduct Disorder or other DBD. This study consisted of three phases:

[14] See Risperdal labeling.

[15] The Clinical Study Report for INT-79 is not yet complete. The safety data summarized in this update is based on the final, validated database.

• acute treatment with open-label risperidone for 6 weeks.
• responders from the first phase received an additional 6 weeks of single-blind risperidone treatment.
• sustained responders from the first phase were randomized to risperidone or placebo for up to 6 months of double-blind treatment.

A total of 527 patients were enrolled. Of these, 436 entered the second phase and, of these, 335 were randomized into the third phase (172 to risperidone and 163 to placebo).

Risperidone dosing was done by weight category (less than 50kg and 50kg or more). In the former category during the third (maintenance) phase, the mean dose was 0.811 mg/day with a range 0.20 to 1.50 mg/day (N=116). In the latter category during the maintenance phase, the mean dose was 1.218 mg/day with a range of 0.05 to 1.50 mg/day (N=56).

The mean duration of exposure to risperidone during the maintenance phase was 133.1 days (range of 2 to 252 days).

No subject died during this study.

Remarkable adverse experiences that were classified as serious during the first two phases of this trial were: suicide attempt (2), syncope (1), convulsions (1), stupor (1), and granulocytopenia (1). The latter two cases are further described below.

Stupor: Patient A30068 was a 15 year old Black male who experienced a depressed level of consciousness after head trauma secondary to an accident riding his bike.

Granulocytopenia: Patient A30045 was a 7 year old white male who experienced a baseline WBC count of 3,900/mm^3 and 3,400/mm^3 (ANC=1,340/mm^3) after 12 weeks of risperidone therapy. He was subsequently randomized to placebo but study medication was stopped on study day 120 due to neutropenia. No other WBC counts were provided. Other adverse experiences reported during the trial included GI tract infection, fever, and cough. A causal role of risperidone in producing this slight drop in WBC count could not be excluded.

During the maintenance phase, only one remarkable serious adverse events was reported among the patients randomized to risperidone: ECG abnormal (1). This was reported in Patient A30255, an overweight 12 year old Caucasian male, who received methylphenidate concomitantly. After 288 days of risperidone treatment, he was found to have ventricular premature beats on routine ECG and was hospitalized. This finding was not seen on previous tracings. These were considered possibly related to risperidone by the investigator and drug was discontinued.

An examination of adverse events that led to dropout from all three phases revealed only two other notable events: QT prolonged (1) and hepatic enzymes increased (1). These are described below.

QT Prolongation: Patient A30225 was a 10 year old Caucasian male who was discontinued from the study after 84 days of risperidone treatment after QT prolongation was detected on ECG: QT=470 ms, QTcF=510 ms, and QTcLD=499 ms; baseline values were 440 ms, 450 ms, and 449 ms, respectively. Two weeks later, the QTc was still prolonged but no longer greater than 500 ms (470, 480, and 476, respectively). The QT prolongation was consider possibly related to risperidone by the investigator. Relevant adverse events during the study were dizziness, weakness, and nausea and vomiting.

Elevated Liver Enzymes: Patient A30159 was a 13-year old white boy with ODD. Concomitant medications included methylphenidate hydrochloride and cough and cold preparations. He received oral risperidone for a total of 82 days, up to 0.6mg/day. Study medication was discontinued on Day 84 during the maintenance phase due to hepatic enzymes increased. He was found to have an increase in SGPT/GGT. The SGPT was 351 U/L on Day 84 and 78 U/L when redrawn 8 days after the last dose of risperidone treatment. The GGT was 186 U/L at day 84 and 105 U/L when redrawn 8 days after the last dose of risperidone treatment. (Baseline liver enzymes were not provided.) Cough and cold medications were discontinued on Day 81. The increase of SGPT/GGT was considered not resolved. He subsequently discontinued from the study on Day 90 as a result of the adverse event of hepatic enzymes increased. A causal relationship could not be excluded.

INT-84

INT-84 was a one-year, open-label follow-up study of INT-79 in children and adolescents (ages 5-17 years) with Conduct Disorder or other DBD. Risperidone dosing was in the range of 0.02 to 0.06 mg/kg/day. This study is till ongoing. Serious adverse events through 12-31-03 are described in this update.

No deaths were reported in this study.

Examination of a listing of new serious adverse events (i.e., since 7-31-03) revealed only one unexpected serious adverse experience, aseptic meningitis, in one patient. No further information was provided for this patient.

Literature Update

A total of 40 articles were identified. After removal of duplicates, 34 articles remained and were categorized. As in the original search, certain classes of articles were eliminated from further consideration and the number of publications was further reduced to 14. Safety results were reported in 6 articles.

No deaths were reported.

There were no reports of tardive dyskinesia or overdose. One of the 6 articles specifically stated that there were no serious adverse events.

Discontinuation of treatment due to adverse events was described in 3 articles. The adverse experiences that led to dropout were increased serum prolactin levels, loss of consciousness with a suspected seizure, neck dystonia, tachycardia, flushing, subjective reports of visual changes which were not specified, weight gain, enuresis, rigidity, hypoactivity, and severely blunted affect.

The most commonly reported adverse events in these publications were weight gain (4 articles), sedation (4 articles), increased appetite (3 articles), and tremor (2 articles).

Postmarketing Update

In this update of the pharmacovigilance database, a total of 23 cases were retrieved. Two of these were serious and

21 were non-serious. Among these cases, a total of 47 adverse events were reported.

There were no adverse events with fatal outcomes.

The two serious cases are summarized below.

Tardive dyskinesia: A 10 year old boy received risperidone for 5 months for the treatment of autism when he experienced tardive dyskinesia. Sodium valproate was a concomitant medication. Risperidone was stopped and the symptoms disappeared, only to reappear 2 days later. As of one week later, the symptoms persisted.

Another 10 year old boy received risperidone for Tourette's Disorder for 5 months when he experienced hyperglycemia. (Laboratory data were not provided.) No concomitant medications were reported. Risperidone was discontinued and the patient was hospitalized and treated with insulin. Insulin was still administered as of one month later.

Update Conclusions

This update contains reports of important adverse findings that may be causally related to risperidone treatment, specifically QT interval prolongation, elevated liver enzymes, and hyperglycemia.

QT prolongation and hyperglycemia have been reported among adult patients who received risperidone and, thus, are not considered entirely unexpected.

Although the report of elevated liver transaminases is unexpected, the occurrence of one such case is insufficient to draw a conclusion about the causal role of risperidone in producing hepatocellular damage.

Overall, this update provides no evidence of any new significant hazard that can be reasonably attributed to risperidone.

C. Adequacy of Patient Exposure and Safety Assessments

The number of pediatric patients exposed to risperidone and the duration of their exposure across all studies in this sNDA exceed ICH guidelines: 565 patients were exposed for 7

months of longer and 331 patients were exposed for 13 months or longer.[16]

The safety assessments were inadequate with respect to measuring serum glucose levels. In placebo-controlled studies, glucose values were available for only 18 risperidone and 17 placebo patients. Given the risk of hyperglycemia with most atypical antipsychotics in adults, this data is inadequate to rule out a similar, if not higher, risk in children and adolescents.

No data was collected on orthostatic measurement of blood pressure. By virtue of its alpha receptor antagonist properties, risperidone may be associated with large orthostatic changes in blood pressure, as has been observed in adults. In the placebo-controlled studies, syncope was reported in 0.9% (2/222) of risperidone and 0.0% (0/237) of placebo patients.

Also, no data was obtained with respect to respiratory rate. Given the propensity of risperidone to be associated with somnolence or sedation, mild respiratory depression could be related to risperidone treatment.

D. Assessment of Data Quality and Completeness

An audit of the consistency of adverse event information across three documents (CRF's, Narrative Summaries, and Adverse Event CRT's) in 7 patients revealed no discrepancies.[17]

The report of the clinical site inspections by the Division of Scientific Investigations is not yet complete.

One deficiency in terms of data completeness was the lack of systematically analyzed ECG data from CAN-23. The sponsor pooled ECG data from only one of the two pivotal autism studies with the two other double blind studies. An examination of the study report for CAN-23 reveals only the clinical diagnosis of ECG and dates. No ECG parameters were specified or analyzed by the sponsor.

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[16] ICH guidelines recommend 300-600 patients exposed for at least 6 months and 100 patients exposed for at least one year.

[17] The seven audited patients were: CAN-23/4155, INT-41/A03541, INT-41/A03306, INT-41/A03637, INT-41/A03053, INT-41/A03457, and USA-93/A03181.

Additionally, demographic subgroup effects on adverse event reporting rates were not properly analyzed (see above).

With respect to data quality, there were numerous errors in the footnotes for tables. Many table titles were also confusing. For instance, among tables purported to contain data from "double blind placebo controlled studies," there were tables containing data from: 1) only one pivotal study pooled with two other phase III controlled studies, 2) both phase II and III controlled studies, and 3) only phase III controlled studies. This required extra vigilance on the part of the undersigned reviewers to insure the accuracy of data summarized in this review.

E. Summary of Important Safety Findings

This safety review revealed no previously unrecognized, significant safety findings associated with risperidone therapy in pediatric patients that would preclude approval of this sNDA or require a major revision to Risperdal labeling.

VIII. Dosing, Regimen, and Administrative Issues:

Dosing:
Note that any subject who weighed 15kg or less was excluded from the studies. (b) (4) A cautionary statement for low-weight patients may be the most appropriate way to address this issue.

(b) (4)

Data on submitted PK study show significant differences in clearance between the autistic children and those with DBD. The sponsor has not yet submitted the pop PK drawn from study US-150. Further confirmation of dosing is needed once pop PK is available for analysis. (Please refer to the upcoming biopharmaceutics review.)

Regimen and Administration:
Regimen and administration of risperidone are reasonable.

IX. Using in Special Populations

This submission is for the studies in children and adolescents ages 5-16 year-old. The sponsor didn't submit studies in other special populations in this submission.

X. Review of Proposed Labeling

The following review is based on revisions to Risperdal labeling proposed by the sponsor and conveyed to the Agency in a 3-26-04 submission.

(b) (4)

1 page immediately following withheld - b(4) Draft Labeling

(b) (4)

XI. Conclusions and Recommendations

From a clinical perspective, it is recommended that this sNDA be granted approvable status.

Prior to final approval, the sponsor should be requested to address the following clinical issues:

1) Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose (b) (6) . These discrepancies should be explained.

2) Relapse data from Part III of study USA-150 should be reanalyzed using a definition for relapse that incorporates only Aberrant Behavior Checklist Irritability subscale criteria since this is the efficacy outcome of interest. This should include a Kaplan-Meier survival analysis of relapse using the interim dataset. Additionally, the sponsor should compute the mean duration of continuous response status for patients randomized into Part III.

3) The sponsor should provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of the drug:placebo odds of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

4) An analysis of quantitative ECG data from study CAN-23 should be submitted for our review.

5) The sponsor should analyze height data from pediatric patients who have been treated with risperidone continuously for at least 6 months utilizing z-scores to

better assess the potential effect of risperidone on growth in the pediatric population.

Additionally, the following Phase 4 clinical commitments are recommended:

1) It is recommended that the sponsor conduct a study in children and adolescents which includes a substantial proportion of patients with Autistic Disorder and which assesses fasting serum glucose levels to evaluate the effect of risperidone on glucose metabolism in the pediatric population.
2) It is further recommended that the sponsor conduct a closely monitored study of cognitive function in patients with Autistic Disorder who are treated with risperidone.

June Cai, M.D.
May 15, 2004

Gregory M. Dubitsky, M.D.
May 15, 2004

cc: NDA 20-272
HFD-120/Division File
HFD-120/JCai
/GDubitsky
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NDA 20-272/S-036
RISPERIDONE TABLETS
IN THE TREATMENT OF
AUTISM

SECTION XII:
APPENDICES TO THE
REVIEW AND EVALUATION OF CLINICAL DATA

NDA DATA SOURCES

APPENDIX IV-1:
TABLE OF STUDIES

Study	Design and Dosage	Number of Subjects[a] (Treatment)
COMPLETED STUDIES IN CHILDREN AND ADOLESCENTS WITH AUTISTIC DISORDER		
Phase 3 Efficacy And Safety Studies		
RIS-USA-150 Part 1	8-week, randomized, double-blind, placebo-controlled, multicenter study in children and adolescents (5 years - 17 years and 2 months) with Autistic Disorder. Flexible-dose risperidone 0.5 – 3.5 mg/day, based on body weight categories: ≤45 kg: 0.5-2.5 mg/day >45 kg: 0.5-3.5 mg/day versus placebo	N = 101 (PLAC n=52; RIS n=49)
Part 2	4-month, open-label follow-up for responders to risperidone in Part 1 and for PNR who responded to risperidone in 8-week PNR phase. Flexible-dose risperidone 0.5 – 3.5 mg/day, based on body weight categories	N = 63 (RIS responders n=30) (PNR n=33)
Part 3	8-week, randomized, double-blind, placebo-controlled, discontinuation period subsequent to Part 2. Subjects randomized to receive: • Placebo (risperidone dosage during the last week of Part 2 was tapered to placebo over 3 weeks, followed by 5 weeks placebo) or • Risperidone (dosage during the last week of Part 2 for 8 weeks) Flexible-dose risperidone 0.5 – 3.5 mg/day, based on body weight categories	N = 39 (PLAC n=20; RIS n=19)
RIS-CAN-23	8-week, randomized, double-blind, placebo-controlled, multicenter study in children (5-12 years) with Autistic Disorder or other PDDs Flexible-dose risperidone 0.01 – 0.06 mg/kg/day versus placebo	N = 79 (Autistic Disorder n=55; other PDDs n=24) (PLAC n=39; RIS n=40)
Open-Label Phase 2 Pilot Study		
RIS-BEL-22	4-week, open-label study in children (3-12 years) with Autistic Disorder Flexible-dose risperidone 0.01 – 0.12 mg/kg/day	N = 7 (RIS n=7)
Pharmacokinetic Study		
RIS-BEL-21	Single-dose risperidone 0.015 or 0.03 mg/kg in children (3-12 years) with Autistic Disorder.	N = 6 (RIS n=6)

[a] Includes all subjects who received at least 1 dose of study medication.

continued

Study	Design and Dosage	Number of Subjects[a] (Treatment)
COMPLETED STUDIES IN CHILDREN AND ADOLESCENTS WITH DBD		
Double-Blind, Placebo-Controlled Phase 3 Studies		
RIS-CAN-19	6-week, randomized, double-blind, placebo-controlled, multicenter study in children (5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD Risperidone 0.02 – 0.06 mg/kg/day versus placebo	N = 110 (PLAC n=57; RIS n=53)
RIS-USA-93	6-week, randomized, double-blind, placebo-controlled, multicenter study in children (5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD Risperidone 0.02 – 0.06 mg/kg/day versus placebo	N = 118 (PLAC n=63; RIS n=55)
Double-Blind, Placebo-Controlled Phase 2 Studies		
RIS-NED-9	6-week, randomized, double-blind, placebo-controlled study in adolescents (12-18 years) with an IQ of 60 to 90 inclusive and a diagnosis of Conduct Disorder, ADHD, or ODD Risperidone 1 – 10 mg/day versus placebo	N = 38 (PLAC n=19; RIS n=19)
RIS-BEL-24	4-week, randomized, double-blind, placebo-controlled study in children and adolescents (6-14 years) with mental retardation and behavior disturbances. Risperidone 0.01 – 0.1 mg/kg/day versus placebo	N = 13 (PLAC n=7; RIS n=6)
Long-Term, Open-Label, Phase 3 Studies		
RIS-CAN-20	1-year, open-label, extension study of RIS-CAN-19 in children (5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD Risperidone 0.02 – 0.06 mg/kg/day	N = 77 (PLAC-RIS[b] n=39; RIS-RIS[c] n=38)
RIS-USA-97	48-week, open-label, multicenter, extension study of RIS-USA-93 in children (5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD Risperidone 0.02 – 0.06 mg/kg/day	N = 107 (PLAC-RIS[b] n=59; RIS-RIS[c] n=48)
RIS-INT-41	1-year, open-label, multicenter, extension study of RIS-CAN-19 (23 subjects) and supportive study (481 subjects) in children and adolescents (5-14 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD Risperidone 0.02 – 0.06 mg/kg/day	N = 504 (PLAC-RIS[b] n=13; RIS-RIS[c] n=10; RIS[d] n=481)

Study	Design and Dosage	Number of Subjects[a] (Treatment)
COMPLETED STUDIES IN CHILDREN AND ADOLESCENTS WITH DBD (Continued)		
Long-Term, Open-Label, Phase 3 Studies (Continued)		
RIS-INT-70	1-year, open-label extension study of RIS-INT-41 to acquire additional long-term safety data for children and adolescents (6-15 years) who completed RIS-INT-41 Risperidone 0.02 – 0.06 mg/kg/day	N = 48 children (RIS n=48)
RIS-HUN-4	2-year, open-label extension study of RIS-INT-41 to acquire additional long-term safety data for children and adolescents (5-14 years) who completed RIS-INT-41 Risperidone 0.02 – 0.06 mg/kg/day	N = 35 (RIS n=35)
COMPLETED PHASE 1 STUDY IN CHILDREN AND ADOLESCENTS WITH PSYCHOTIC AND BEHAVIORAL DISORDERS		
Pharmacokinetic Study		
RIS-USA-160	Multiple-dose pharmacokinetic study of risperidone 0.01 to 0.08 mg/kg in children and adolescents (5-17 years) with behavioral and psychotic disorders	N = 24 (RIS n=24)
ONGOING STUDIES[b] IN CHILDREN AND ADOLESCENTS		
Phase 3, Secondary, Long-Term Studies in Children and Adolescents with DBD		
RIS-INT-79	Long-term, relapse-prevention study in children and adolescents (5-17 years) with Conduct Disorder or other DBD, with a 6-month randomized discontinuation design Risperidone 0.25 – 1.5 mg/day versus placebo	Planned N = 225
RIS-INT-84	1-year, open-label, follow-up study of RIS-INT-79 in children and adolescents (5-17 years) with Conduct Disorder or other DBD, to document the long-term safety of risperidone Risperidone 0.02 – 0.06 mg/kg/day	Planned N = 225

APPENDIX IV-2
PATIENT ENUMERATION BY STUDY

Type of Study and Subjects	Name of Study	Risperidone	Placebo
Double-blind in Autism	RIS-USA-150 Part I	49	52
Double-blind in Autism & DBD	RIS-CAN-23	40 (27 Autistic)	39 (28 Autistic)
Open-label in Autism	RIS-USA-150 Part II	63	0
Double-blind, discontinuation in Autism (Cont'd from 150 Part II)	RIS-USA-150 Part III	19	20
Open-label in Autism	RIS-BEL-22	7	0
PK study in Autism	RIS-BEL-21	6	0
PK study in Non-Autistics	RIS-USA-160	24	0
Double-blind in Non-Autistics	RIS-CAN-19	53	57
Double-blind in Non-Autistics	RIS-CAN-93	55	63
Double-blind in Non-Autistics	RIS-NED-9	19	19
Double-blind in Non-Autistics	RIS-BEL-24	6	7
Open-label, long term in Non-Autistics	RIS-CAN-20	38	39
Open-label, long term in Non-Autistics	RIS-USA-97	48	59
Open-label, long term in Non-Autistics	RIS-INT-41	491	13
Open-label, long term in Non-Autistics	RIS-INT-70	48	0
Open-label extension study of completers from RIS-INT-41	RIS-HUN-4	35	0

APPENDIX IV-3
DEMOGRAPHIC FEATURES
DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES

	Placebo (N=237)	Risperidone (N=222)	Total (N=459)
Sex, n (%)			
N	237	222	459
Female	51 (21.5)	47 (21.2)	98 (21.4)
Male	186 (78.5)	175 (78.8)	361 (78.6)
Age, years			
N	237	222	459
Category, n (%)			
<=12 years	220 (92.8)	201 (90.5)	421 (91.7)
>12 years	17 (7.2)	21 (9.5)	38 (8.3)
Mean (SD)	8.8 (2.76)	8.8 (2.82)	8.8 (2.79)
Median	8.0	9.0	8.0
Range	5 - 18	5 - 17	5 - 18
Weight, kg			
N	235	218	453
Mean (SD)	34.78 (16.713)	35.41 (17.319)	35.08 (16.991)
Median	31.00	30.70	30.90
Range	15.4 - 163.1	15.0 - 113.0	15.0 - 163.1
Height, cm			
N	190	176	366
Mean (SD)	135.37 (18.816)	137.15 (18.446)	136.23 (18.635)
Median	134.30	134.60	134.60
Range	45.0 - 185.0	104.0 - 200.0	45.0 - 200.0
Body mass index, kg/m^2			
N	190	175	365
Mean (SD)	19.63 (11.595)	18.55 (4.625)	19.11 (8.963)
Median	17.60	17.20	17.40
Range	13.0 - 157.0	8.8 - 36.1	8.8 - 157.0
Race, n (%)			
N	218	202	420
Black	37 (17.0)	33 (16.3)	70 (16.7)
Caucasian	149 (68.3)	136 (67.3)	285 (67.9)
Hispanic	8 (3.7)	5 (2.5)	13 (3.1)
Oriental	5 (2.3)	6 (3.0)	11 (2.6)
Other	19 (8.7)	22 (10.9)	41 (9.8)
Domiciliary status: lives with, n (%)			
N	218	203	421
Other	40 (18.3)	33 (16.3)	73 (17.3)
Parents	178 (81.7)	170 (83.7)	348 (82.7)
Geographic region, n (%)			
N	237	222	459
Canada	81 (34.2)	82 (36.9)	163 (35.5)
Europe	26 (11.0)	25 (11.3)	51 (11.1)
Other (Israel & S. Africa)	5 (2.1)	4 (1.8)	9 (2.0)
United States of America	125 (52.7)	111 (50.0)	236 (51.4)
Intelligence quotient			
N	210	189	399
Mean (SD)	68.7 (49.60)	68.1 (15.60)	68.4 (37.51)
Median	68.0	71.0	70.0
Range	1 - 736[a]	15 - 118	1 - 736[a]
Type of disorder, n (%)			
N	237	222	459
Autistic Disorder	80 (33.8)	76 (34.2)	156 (34.0)
DBD/other PDD	157 (66.2)	146 (65.8)	303 (66.0)

APPENDIX IV-4
DEMOGRAPHIC FEATURES
RISPERIDONE PATIENTS IN PHASE 2/3 STUDIES

Sex, n (%)	
N	821
Female	156 (19.0)
Male	665 (81.0)
Age, years	
N	821
Category, n (%)	
<=12 years	720 (87.7)
>12 years	101 (12.3)
Mean (SD)	9.3 (2.59)
Median	9.0
Range	3 - 17
Weight, kg	
N	815
Mean (SD)	35.43 (14.473)
Median	32.00
Range	13.6 - 113.0
Height, cm	
N	753
Mean (SD)	137.80 (16.907)
Median	136.90
Range	45.0 - 200.0
Body mass index, kg/m^2	
N	752
Mean (SD)	18.27 (6.353)
Median	17.20
Range	8.8 - 157.0
Race, n (%)	
N	801
Black	88 (11.0)
Caucasian	624 (77.9)
Hispanic	14 (1.7)
Oriental	8 (1.0)
Other	67 (8.4)
Domiciliary status: lives with, n (%)	
N	790
Other	141 (17.8)
Parents	649 (82.2)
Geographic region, n (%)	
N	821
Canada	121 (14.7)
Europe	347 (42.3)
Other (Israel & S. Africa)	108 (13.2)
United States of America	245 (29.8)
Intelligence quotient	
N	780
Mean (SD)	65.3 (14.14)
Median	68.0
Range	15 - 118
Type of disorder, n (%)	
N	821
Autistic Disorder	83 (10.1)
DBD/other PDD	738 (89.9)

APPENDIX IV-5
MODAL DOSE VS. DURATION OF EXPOSURE
RISPERIDONE PATIENTS IN PHASE 2/3 STUDIES

	Risperidone							
	Total	Mode Dose, n (%)						
Duration	(N=821) n (%)	<= 0.5 (N=43)	>0.5 to <=1.0 (N=150)	>1.0 to <=1.5 (N=218)	>1.5 to <=2.0 (N=190)	>2.0 to <=2.5 (N=93)	> 2.5 (N=124)	Not defined[a] (N=3)
<= 3 months	200 (24.4)	23 (53.5)	43 (28.7)	56 (25.7)	28 (14.7)	22 (23.7)	25 (20.2)	3 (100)
4-6 months	56 (6.8)	3 (7.0)	15 (10.0)	10 (4.6)	11 (5.8)	11 (11.8)	6 (4.8)	0
7-9 months	40 (4.9)	0	3 (2.0)	7 (3.2)	7 (3.7)	4 (4.3)	19 (15.3)	0
10-12 months	194 (23.6)	9 (20.9)	35 (23.3)	52 (23.9)	62 (32.6)	16 (17.2)	20 (16.1)	0
13-15 months	247 (30.1)	6 (14.0)	41 (27.3)	75 (34.4)	56 (29.5)	29 (31.2)	40 (32.3)	0
16-18 months	6 (0.7)	2 (4.7)	1 (0.7)	2 (0.9)	0	1 (1.1)	0	0
19-21 months	6 (0.7)	0	0	1 (0.5)	2 (1.1)	1 (1.1)	2 (1.6)	0
22-24 months	10 (1.2)	0	1 (0.7)	2 (0.9)	3 (1.6)	1 (1.1)	3 (2.4)	0
25-27 months	38 (4.6)	0	5 (3.3)	10 (4.6)	13 (6.8)	6 (6.5)	4 (3.2)	0
28-30 months	4 (0.5)	0	3 (2.0)	0	1 (0.5)	0	0	0
> 33 months	20 (2.4)	0	3 (2.0)	3 (1.4)	7 (3.7)	2 (2.2)	5 (4.0)	0

ITEMS UTILIZED IN THE REVIEW

APPENDIX V-1 ITEMS UTILIZED IN THE REVIEW	
SUBMISSION DATE	**ITEM DESCRIPTION**
12-19-03	Application Summary Financial Disclosure Information Proposed Labeling Integrated Summary of Safety Integrated Summary of Efficacy Phase 1, 2, and 3 Study Reports CRT's (.xpt files) CRF's
2-19-04	CRF for USA-150 Patient K8007
3-5-04	Response to 2-25-04 Filing Comments
3-26-04	Revised Proposed Labeling
4-5-04	4-month Safety Update
4-14-04	CRF's for USA-150 Patients L6009 and L6011

EFFICACY

APPENDIX VI-1
CHANGES FROM BASELINE IN THE ABC IRRITABILITY SUBSCALE/ALL PATIENTS
STUDY CAN-23

	PLACEBO						RISPERIDONE						
				Change from Treatment baseline						Change from Treatment baseline			Overall
	N	Mean	SD	Mean	SD	P (a)	N	Mean	SD	Mean	SD	P (a)	P-value(b)
IRRITABILITY													
TREATMENT													
BASELINE	38	21.2	9.74				37	18.9	8.84				0.478
WEEK 1	37	17.4	10.40	-4.0	8.28	0.006	38	13.4	8.73	-5.7	6.06	<0.001	0.068
WEEK 1 LOCF	37	17.4	10.40	-4.0	8.28	0.006	38	13.4	8.73	-5.7	6.06	<0.001	0.068
WEEK 2	36	16.0	10.89	-5.7	8.60	<0.001	36	9.4	7.27	-8.9	6.41	<0.001	0.017
WEEK 2 LOCF	38	15.5	10.87	-5.7	8.37	<0.001	39	10.1	7.49	-9.0	6.43	<0.001	0.016
WEEK 3	33	15.1	11.54	-6.1	8.92	<0.001	39	8.7	6.94	-10.5	5.97	<0.001	0.003
WEEK 3 LOCF	38	15.4	11.04	-5.8	8.59	<0.001	39	8.7	6.94	-10.5	5.97	<0.001	<0.001
WEEK 5	33	14.5	11.58	-6.2	7.72	<0.001	39	8.3	6.18	-10.9	5.70	<0.001	0.001
WEEK 5 LOCF	38	15.6	11.40	-5.7	7.51	<0.001	39	8.3	6.18	-10.9	5.70	<0.001	<0.001
WEEK 7	32	15.3	11.84	-6.8	8.19	<0.001	34	7.7	5.81	-11.6	5.90	<0.001	0.002
WEEK 7 LOCF	38	15.4	11.19	-5.8	8.02	<0.001	39	7.7	5.60	-11.4	5.94	<0.001	<0.001
WEEK 8	31	14.5	12.29	-7.5	8.29	<0.001	34	7.1	5.93	-12.1	5.96	<0.001	0.004
WEEK 8 LOCF	38	14.7	11.46	-6.5	8.41	<0.001	39	7.0	5.59	-12.1	5.84	<0.001	<0.001
END POINT	38	14.7	11.46	-6.5	8.41	<0.001	39	6.9	5.52	-12.1	5.81	<0.001	<0.001

APPENDIX VI-2
CHANGES FROM BASELINE IN THE ABC IRRITABILITY SUBSCALE/AUTISTIC PATIENTS
STUDY CAN-23

	PLACEBO						RISPERIDONE						
				Change from Treatment baseline						Change from Treatment baseline			Overall
	N	Mean	SD	Mean	SD	P (a)	N	Mean	SD	Mean	SD	P (a)	P-value(b)
IRRITABILITY													
TREATMENT													
BASELINE	28	21.6	10.17				24	20.6	8.07				0.741
WEEK 1	27	16.9	10.66	-5.0	8.11	0.004	26	14.5	9.13	-6.9	6.54	<0.001	0.165
WEEK 1 LOCF	27	16.9	10.66	-5.0	8.11	0.004	26	14.5	9.13	-6.9	6.54	<0.001	0.165
WEEK 2	27	15.8	10.85	-6.0	7.45	<0.001	24	10.2	7.49	-9.7	7.08	<0.001	0.062
WEEK 2 LOCF	28	15.6	10.70	-6.0	7.31	<0.001	26	10.9	7.71	-10.0	7.13	<0.001	0.045
WEEK 3	23	14.4	11.70	-7.3	8.18	<0.001	26	9.4	7.49	-11.8	6.03	<0.001	0.028
WEEK 3 LOCF	28	15.0	11.01	-6.6	7.91	<0.001	26	9.4	7.49	-11.8	6.03	<0.001	0.009
WEEK 5	23	13.7	11.12	-7.4	6.55	<0.001	26	9.1	7.08	-11.9	4.17	<0.001	0.012
WEEK 5 LOCF	28	15.2	11.03	-6.4	6.57	<0.001	26	9.1	7.08	-11.9	4.17	<0.001	0.001
WEEK 7	22	14.0	11.83	-9.1	6.75	<0.001	24	8.1	6.09	-13.0	5.43	<0.001	0.035
WEEK 7 LOCF	28	14.4	10.96	-7.2	7.22	<0.001	26	8.3	6.03	-12.7	5.33	<0.001	0.003
WEEK 8	22	13.8	12.21	-8.8	7.01	<0.001	22	7.8	6.16	-13.9	5.05	<0.001	0.019
WEEK 8 LOCF	28	14.1	11.33	-7.5	7.59	<0.001	26	7.4	5.76	-13.5	5.23	<0.001	0.002
END POINT	28	14.1	11.33	-7.5	7.59	<0.001	26	7.4	5.76	-13.5	5.23	<0.001	0.002

APPENDIX VI-3
CHANGES FROM BASELINE IN THE ABC IRRITABILITY SUBSCALE/NON-AUTISTIC PATIENTS
STUDY CAN-23

	PLACEBO						RISPERIDONE						
				Change from Treatment baseline						Change from Treatment baseline			Overall
	N	Mean	SD	Mean	SD	P (a)	N	Mean	SD	Mean	SD	P (a)	P-value(b)
IRRITABILITY													
TREATMENT													
BASELINE	10	20.0	8.81				13	15.6	9.58				0.318
WEEK 1	10	18.8	10.08	-1.2	8.51	0.666	12	11.1	7.66	-3.3	4.23	0.020	0.308
WEEK 1 LOCF	10	18.8	10.08	-1.2	8.51	0.666	12	11.1	7.66	-3.3	4.23	0.020	0.308
WEEK 2	9	16.6	11.66	-4.9	11.93	0.254	12	7.8	6.82	-7.3	4.73	<0.001	0.204
WEEK 2 LOCF	10	15.1	11.92	-4.9	11.25	0.202	13	8.5	7.02	-7.2	4.54	<0.001	0.361
WEEK 3	10	16.6	11.63	-3.4	10.35	0.326	13	7.5	5.74	-8.2	5.24	<0.001	0.045
WEEK 3 LOCF	10	16.6	11.63	-3.4	10.35	0.326	13	7.5	5.74	-8.2	5.24	<0.001	0.045
WEEK 5	10	16.5	12.96	-3.5	9.76	0.286	13	6.5	3.41	-9.1	7.65	0.001	0.025
WEEK 5 LOCF	10	16.5	12.96	-3.5	9.76	0.286	13	6.5	3.41	-9.1	7.65	0.001	0.025
WEEK 7	10	18.2	11.95	-1.8	9.17	0.550	10	6.6	5.21	-8.5	6.00	0.002	0.014
WEEK 7 LOCF	10	18.2	11.95	-1.8	9.17	0.550	13	6.5	4.63	-9.1	6.50	<0.001	0.002
WEEK 8	9	16.2	13.04	-4.4	10.65	0.246	12	5.8	5.51	-9.3	6.44	<0.001	0.112
WEEK 8 LOCF	10	16.3	12.29	-3.7	10.32	0.286	13	6.1	5.35	-9.5	6.25	<0.001	0.042
END POINT	10	16.3	12.29	-3.7	10.32	0.286	13	5.9	5.09	-9.7	6.24	<0.001	0.032

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SAFETY

APPENDIX VII-1
SAE's from Phase 2/3 Studies

Adverse Event System Organ Class Adverse Event Preferred Term	All Risperidone (N=821) n (%)
Total number of subjects with serious adverse events	77 (9.4)
Body as a whole - general disorders	25 (3.0)
Condition aggravated	18 (2.2)
Fever	3 (0.4)
Asthenia	1 (0.1)
Fatigue	1 (0.1)
Injury	1 (0.1)
Leg pain	1 (0.1)
Pallor	1 (0.1)
Psychiatric disorders	21 (2.6)
Aggressive reaction	11 (1.3)
Suicide attempt	4 (0.5)
Depression	3 (0.4)
Agitation	1 (0.1)
Anorexia	1 (0.1)
Confusion	1 (0.1)
Drug abuse	1 (0.1)
Emotional lability	1 (0.1)
Manic reaction	1 (0.1)
Somnolence	1 (0.1)
Central & peripheral nervous system disorders	16 (1.9)
Extrapyramidal disorder	3 (0.4)
Convulsions	2 (0.2)
Dyskinesia	2 (0.2)
Dyskinesia tardive	2 (0.2)
Headache	2 (0.2)
Hypertonia	2 (0.2)
Oculogyric crisis	2 (0.2)
Dizziness	1 (0.1)
Dystonia	1 (0.1)
Hypokinesia	1 (0.1)
Respiratory system disorders	11 (1.3)
Asthma	4 (0.5)
Pharyngitis	4 (0.5)
Bronchitis	2 (0.2)
Dyspnea	1 (0.1)
Pleurisy	1 (0.1)
Respiratory disorder	1 (0.1)
Upper respiratory tract infection	1 (0.1)
Gastro-intestinal system disorders	9 (1.1)
Abdominal pain	4 (0.5)
Appendicitis	2 (0.2)
Vomiting	2 (0.2)

Adverse Event System Organ Class Adverse Event Preferred Term	All Risperidone (N=821) n (%)
Gastro-intestinal system disorders (continued)	9 (1.1)
Constipation	1 (0.1)
Diarrhea	1 (0.1)
Diarrhea bloody	1 (0.1)
Nausea	1 (0.1)
Pancreatic secretion decreased	1 (0.1)
Saliva increased	1 (0.1)
Resistance mechanism disorders	8 (1.0)
Infection viral	4 (0.5)
Sepsis	2 (0.2)
Abscess	1 (0.1)
Infection	1 (0.1)
Otitis media	1 (0.1)
Secondary terms	5 (0.6)
Medication error	3 (0.4)
Surgical intervention	2 (0.2)
Musculo-skeletal system disorders	3 (0.4)
Arthritis	1 (0.1)
Bone disorder	1 (0.1)
Myalgia	1 (0.1)
Skin and appendages disorders	2 (0.2)
Rash pustular	1 (0.1)
Urticaria	1 (0.1)
Urinary system disorders	2 (0.2)
Face edema	1 (0.1)
Glomerulonephritis	1 (0.1)
Cardiovascular disorders, general	1 (0.1)
Hypertension	1 (0.1)
Heart rate and rhythm disorders	1 (0.1)
Tachycardia	1 (0.1)
Metabolic and nutritional disorders	1 (0.1)
Weight decrease	1 (0.1)
Red blood cell disorders	1 (0.1)
Pancytopenia	1 (0.1)
Vision disorders	1 (0.1)
Glaucoma	1 (0.1)
White cell and RES disorders	1 (0.1)
Granulocytopenia	1 (0.1)

APPENDIX VII-2
PROPORTIONS OF PATIENTS REPORTING COMMON TREATMENT-EMERGENT ADVERSE EVENTS (AUTISTIC PATIENTS FROM USA-150 & CAN-23)

Adverse Events	Risperidone	Placebo
	N total=76 n (%)	N total=80 n (%)
Somnolence	51 (67.1)	18 (22.5)
Appetite Increased	37 (48.7)	15 (18.8)
Extrapyramidal Symptoms*	33 (43.4)	8 (10.0)
Fatigue	32 (42.1)	10 (12.5)
Rhinitis	27 (35.5)	18 (22.5)
Upper Resp Tract Infection	26 (34.2)	12 (15.0)
Vomiting	19 (25.0)	17 (21.3)
Coughing	18 (23.7)	14 (17.5)
Urinary Incontinence	17 (22.4)	16 (20.0)
Saliva Increased	17 (22.4)	5 (6.3)
Constipation	16 (21.1)	6 (7.5)
Fever	15 (19.7)	15 (18.8)
Insomnia	12 (15.8)	21 (26.3)
Anxiety	12 (15.8)	12 (15.0)
Headache	11 (14.5)	9 (11.3)
Diarrhea	10 (13.2)	16 (20.0)
Mouth Dry	10 (13.2)	5 (6.3)
Rash	8 (10.5)	6 (7.5)
Dizziness	7 (9.2)	2 (2.5)
Anorexia	6 (7.9)	6 (7.5)
Nausea	6 (7.9)	6 (7.5)
Thirst	6 (7.9)	5 (6.3)
Automatism	5 (6.6)	1 (1.3)
Tachycardia	5 (6.6)	0
Dyspepsia	4 (5.3)	8 (10.0)
Confusion	4 (5.3)	0
Weight Increase	4 (5.3)	0
Agitation	3 (3.9)	7 (8.8)
Nervousness	3 (3.9)	4 (5.0)
Epistaxis	3 (3.9)	3 (3.8)
Conjunctivitis	3 (3.9)	2 (2.5)
Influenza-Like Symptoms	3 (3.9)	1 (1.3)
Muscle Contractions Involuntary	3 (3.9)	1 (1.3)
Concentration Impaired	3 (3.9)	0
Menstrual Disorder**	1 (3.2)	0
Amenorrhea**	1 (3.2)	0

Vulva Disorder**	1 (3.2)	0
Aggressive Reaction	2 (2.6)	3 (3.8)
Abdominal Pain	2 (2.6)	3 (3.8)
Pharyngitis	2 (2.6)	1 (1.3)
Asthma	2 (2.6)	1 (1.3)
Flushing	2 (2.6)	1 (1.3)
Flatulence	2 (2.6)	0
Speech Disorder	2 (2.6)	0
Micturition Frequency	2 (2.6)	0
Acne	2 (2.6)	0
Palpitation	2 (2.6)	0
Tinnitus	2 (2.6)	0
Otitis Media	1 (1.3)	3 (3.8)
Emotional Lability	1 (1.3)	2 (2.5)
Pain	1 (1.3)	2 (2.5)
Fecal Incontinence	1 (1.3)	2 (2.5)
Eczema	1 (1.3)	2 (2.5)
Gynecomastia	1 (1.3)	2 (2.5)
Ear Ache	1 (1.3)	2 (2.5)
Paroniria	1 (1.3)	1 (1.3)
Neurosis	1 (1.3)	1 (1.3)
Thinking Abnormal	1 (1.3)	1 (1.3)
Hallucination	1 (1.3)	1 (1.3)
Tooth Ache	1 (1.3)	1 (1.3)
Edema	1 (1.3)	1 (1.3)
Bullous Eruption	1 (1.3)	1 (1.3)
Burn	1 (1.3)	1 (1.3)
Personality Disorder	1 (1.3)	0
Dysphasia	1 (1.3)	0
Crying Abnormal	1 (1.3)	0
Malaise	1 (1.3)	0
Syncope	1 (1.3)	0
Allergy Aggravated	1 (1.3)	0
Breath Odor, Nos	1 (1.3)	0
Chest Pain	1 (1.3)	0
Leg Pain	1 (1.3)	0
Hypotonia	1 (1.3)	0
Respiratory Disorder	1 (1.3)	0
Hematuria	1 (1.3)	0
Urine Abnormal	1 (1.3)	0
Pruritus	1 (1.3)	0
Skin Dry	1 (1.3)	0
Rash Maculo-Papular	1 (1.3)	0
Eye Abnormality	1 (1.3)	0
Arrhythmia	1 (1.3)	0

Moniliasis	1 (1.3)	0
Eosinophilia	1 (1.3)	0
Lymphadenopathy	1 (1.3)	0
Abrasion, Nos	1 (1.3)	0
Hepatic Enzyme Increased	1 (1.3)	0

*Includes (in descending order): tremor, hypertonia, dyskinesia, extrapyramidal disorders, involuntary muscle contractions, ataxia, hypokinesia, hypotonia, akathisia, apathy, abnormal gait, dystonia, , bradykinesia, hyperkinesia, oculogyric crisis, parkinsonism, tongue disorder

**Adjusted for gender.

APPENDIX VII-3
LABORATORY TEST ASSESSMENTS (USA-150 & CAN-23)

Tests	US-150 (Part I)	CAN-23
Sodium	X	x
Potassium	X	x
Bicarbonate	Unavailable	x
Chloride	X	x
Blood urea nitrogen	X	x
Creatinine	X	x
Glucose	Unavailable	Unavailable
AST	X	x
ALT	X	x
Alkaline phosphatase	Unavailable	X
GGT	Unavailable	X
Direct bilirubin	X	Unavailable
Total bilirubin	X	X
Total protein	Unavailable	X
Albumin	Unavailable	Unavailable
Lactate dehydrogenase	Unavailable	X
Uric acid	Unavailable	X
Calcium	Unavailable	X
CPK	X	Unavailable
Prolactin	Unavailable	Unavailable
RBC	X	X
Hemoglobin	X	x
Hematocrit	X	x
MCV, MCH and MCHC	Unavailable	x
WBC with differentials	X	x
Platelet counts	X	x
Urinary analysis	X	x

APPENDIX VII-4
PCS LABORATORY TEST CHANGES/CHEMISTRY

Clinical Chemistry	Risperidone	Placebo
Tests and Criteria	n (%)	n (%)
Sodium 125-154 (mmol/L)	196	211
Within	196 (100)	211 (100)
Potassium 3-6 (mmol/L)	192	206
Within	192 (100)	206 (100)
Chloride 90-115 (mmol/L)	183	198
Within	183 (100)	198 (100)
Bicarbonate 18-36 (mmol/L)	126	133
Below	3 (2.4)	1 (0.8)
Within	123 (97.6)	132 (99.2)
Blood urea nitrogen 2-40(mmol/L)	196	210
Within	196 (100)	210 (100)
Creatinine 0.2-2.5 (umol/l)	195	209
Within	195 (100)	209 (100)
Glucose 50-200 (mmol/L)	18	17
Within	18 (100)	17 (100)
AST (SGOT) 0-100 (U/L)	197	208
Within	197 (100)	208 (100)
ALT (SGPT) 0-110 (U/L)	196	209
Within	195 (99.5)	209 (100)
Above	1 (0.5)	0
Alkaline phosphatase (U/L)[18]	149	166
Within	149 (100)	166 (100)
GGT 0-120 (U/L)	150	164
Within	150 (100)	164 (100)
Total bilirubin 0-2.5(umol/L)	185	200
Within	185 (100)	200 (100)
Total protein 4-9.5(g/L)	150	169
Within	150 (100)	169 (100)
Lactate dehydrogenase 0-500(U/L)	130	142
Within	130 (100)	142 (100)
Calcium 7.5-11.6(mmol/L)	133	149
Within	133 (100)	149 (100)
Uric Acid 1.5-10(umol/L)	57	53
Within	57 (100)	53 (100)

[18] Criteria for alkaline phosphatase: 0-800U/L for females age 2-8 and 14-16,and males age 2-9 and 17-18; 0-1200U/L for females age 9-13 and males 10-16; 0-280U/L for females over 17 and males over 19.

APPENDIX VII-5
PCS LABORATORY TEST CHANGES/HEMATOLOGY

Hematology	Risperidone	Placebo
	N (%)	N (%)
RBC 3.3-6.8(tera/L)	179	197
Within	179 (100)	197 (100)
Hemoglobin 10-20(g/dL)	183	200
Within	183 (100)	200 (100)
Hematocrit 30-60(vol-%)	179	193
Within	179 (100)	193 (100)
MCV 73-117(fl)	122	137
Below	1 (0.8)	0
Within	121 (99.2)	137 (100)
MCH 26-40(pg)	121	137
Within	121 (100)	137 (100)
MCHC 233-368(g/L)	125	142
Within	125 (100)	142 (100)
WBC 3-15(giga/L)	182	201
Below	0	1 (0.5)
Within	182 (100)	200 (99.5)
Neutrophils 30-90(%)	178	187
Below	2 (1.1)	8 (4.3)
Within	176 (98.9)	179 (95.7)
Lymphocytes 10-60(%)	185	197
Below	0	1 (0.5)
Within	184 (99.5)	192 (97.5)
Above	1 (0.5)	4 (2.0)
Monocytes 0-20(%)	199	187
Within	199 (100)	187 (100)
Eosinophils 0-10(%)	175	182
Within	167 (95.4)	176 (96.7)
Above	8 (4.6)	6 (3.3)
Basophils 0-6(%)	171	186
Within	171 (100)	186 (100)
Platelet count 100-600(giga/L)	180	193
Within	180 (100)	192 (99.5)
Above	0	1 (0.5)

APPENDIX VII-6
MEAN CHANGES FROM BASELINE IN LABORATORY TEST VALUES

Laboratory Tests	Risperidone		Placebo	
	Subjects	Mean	Subjects	Mean
Sodium (mmol/L)	N=196	-0.63	N=208	0.04
Potassium (mmol/L)	N=192	-0.01	N=203	0.01
Bicarbonate (mmol/L)	N= 128	-0.68	N=140	0.10
Chloride (mmol/L)	N=183	-0.40	N=197	-0.21
BUN (mmol/L)	N=196	-0.18	N=207	0.20
Creatinine (umol/L)*	N=195	-0.14	N=206	1.12
Glucose (mmol/L)	N=18	-0.01	N=17	-0.21
AST (U/L)	N=197	1.12	N=205	-0.62
ALT (U/L)	N=196	5.07	N=206	0.33
Alkaline phosphatase (U/L)	N=149	13.52	N=163	1.99
GGT (U/L)	N=151	0.87	N=161	-0.17
Direct bilirubin (umol/L)	N=38	-0.04	N=34	-0.12
Total bilirubin (umol/L)	N=185	-0.27	N=197	-0.16
Total protein (g/L)	N=150	-0.53	N=166	-0.12
Lactate dehydrogenase (U/L)	N=130	0.63	N=142	-2.73
Uric acid (umol/L)	N=57	3.62	N=50	-0.77
Calcium (mmol/L)	N=133	-0.01	N=149	-0.01
CPK (U/L)	N=42	-0.33	N=36	-9.06
Prolactin (ng/ml)	N=83	20.46	N=98	-0.18
Growth hormone (ug/L)	N=29	1.73	N=34	0.27
RBC (tera/L)	N=179	-0.07	N=194	0.03
Hemoglobin (g/L)	N=184	-1.36	N=199	0.38
Hematocrit (vol %)	N=180	-0.32	N=191	0.12
MCV (fl)	N=125	0.18	N=142	-0.09
MCHC (mmol/L)	N=125	0.004	N=142	0.04
MCH (pg)	N=124	0.01	N=141	0
WBC (giga/L)	N=185	-0.38	N=200	-0.24
Neutrophils (%)	N=181	1.59	N=188	-1.51
Lymphocytes (%)	N=187	-2.31	N=196	1.47
Monocytes (%)	N=187	0.48	N=196	-0.16
Eosinophils (%)	N=184	0.12	N=191	-0.11
Basophils (%)	N=171	0.02	N=185	0.03
Platelet counts (giga/L)	N=180	-4.44	N=190	-4.93
Urine Gravity	N=71	-.002	N=65	0.001

APPENDIX VII-7
POSTMARKETING SAE'S

Case Number	Country	Age (yrs)	Sex	Dose (mg)	Latency (days)	Primary Clinical Event
JAUSA18533	USA	7	M	Unkn	125	Convulsion NOS
JAUSA24939	USA	11	F	2.0	Unkn	Glucocorticoids increased NOS
JAUSA32222	USA	7	M	10.0	1	Convulsions NOS
JACGBR1999000319	UK	14	M	1.0	10	Extrapyramidal disorder
JAFRA42799	France	13	M	Unkn	510[a]	Hypertonia
JAOCAN1999000276	Canada	14	M	1.5	Unkn	Epistaxis
JAOCAN2000000801	Canada	9	M	1.0	380[a]	Tardive dyskinesia
JRFBEL2000001595	Australia	13	M	4.0	Unkn	Tardive dyskinesia
JRFUSA2000003302	USA	14	M	2.0	644[a]	Neuroleptic malignant syndrome
APCDSS2001001508	Australia	16	M	Unkn	1000[a]	Testicular disorder NOS
EMADSS2001003642	Belgium	Child	Unkn	0.2	Unkn	Coma
EMADSS2001004170	France	10	M	1.0	1	Epistaxis
NSADSS2001002131	USA	12	F	1.5	850[a]	Suicidal ideation
NSADSS2001013710	USA	6	M	2.0	365[a]	Tardive dyskinesia
EMADSS2002000627	UK	9	Unkn	4.0	925[a]	Dystonia
EMADSS2002001788	Netherlands	17	M	2.0	Unkn	Neuralgia NOS
EMADSS2002003340	UK	15	M	1.0	2	Dystonia
EMADSS2002003364	UK	10	M	0.5	Unkn	Tic
EMADSS2002005683	Finland	14	M	1.0	49	Tremor
NSADSS2001009025	Canada	5	M	0.5	Unkn	Urinary frequency
NSADSS2002009993	USA	8	M	Unkn	Unkn	Aggression
NSADSS2002026254	USA	11	M	Unkn	Unkn	Pyrexia
NSADSS2002028667	USA	8	M	0.5	1	Diabetic coma NOS
EMADSS2003000047	UK	10	M	1.5	3	Dystonia
EMADSS2003002045	Portugal	14	M	3.0	730[a]	Extrapyramidal disorder
EMADSS2003002188	Netherlands	14	M	0[b]	30	Delusion NOS
EMADSS2003002919	France	16	M	6.0	873[a]	Neutropenia
EMADSS2003003910	UK	14	F	5.0	1	Somnolence
EMADSS2003004088	Netherlands	9	M	1.0	Unkn	Sedation
EMADSS2003004564	Germany	14	M	2.0	610[a]	Leukopenia NOS
DE-JNJFOC-20030803985	Germany	11	F	Unkn	Unkn	Thrombocytopenia
DE-JNJFOC-20030804000	Germany	17	M	1.0	30[a]	Tardive dyskinesia
FR-JNJFOC-20030601578	France	15	M	2.0	21[a]	Grand mal convulsion
GB-JNJFOC-20030705737	UK	14	F	5.0	1	Convulsions NOS

M=Male; F=Female; Unkn=Unknown

a: approximation due to imprecise or incomplete information

b: off risperidone 4 days at time of event

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

/s/

Greg Dubitsky
5/18/04 11:06:37 AM
MEDICAL OFFICER

June, Please sign-off. It will then go to Paul
for his signature. Thanks, Your Mentor Greg

June Cai
5/19/04 05:08:43 PM
MEDICAL OFFICER
Too bad that the system didn't work well. Here it is again.

Paul Andreason
6/7/04 09:03:06 AM
MEDICAL OFFICER
I recommend that the Division consider an approvable action
for this supplement. Please see my memo to
the file dated June 7, 2004.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

CHEMISTRY REVIEW(S)

NDA 21-444, SE1-008
NDA 20-588, SE1-024
NDA 20-272, SE1-036

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-444 **DATE REVIEWED:** 3/19/04
NDA #: 20-588
NDA #: 20-272

REVIEW #: 1 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Efficacy	19-DEC-2003	19-DEC-2003	23-DEC-2003

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

DRUG PRODUCT NAME:

Proprietary: **NDA 21-444**: RISPERDAL••M-TAB™ Orally Disintegrating Tablets
NDA 20-588: RISPERDAL••Oral Solution
NDA 20-272: RISPERDAL••Tablets

USAN [1989]: risperidone

PHARMACOL. CATEGORY/INDICATION: Autism

DOSAGE FORM: **NDA 21-444**: Disintegrating Tablet
NDA 20-588: Solution
NDA 20-272: Tablet

STRENGTHS:

NDA 20-272

0.25 mg (dark yellow, tablet, imprinted **RIS 0.25**)
0.5 mg (red-brown, tablet, imprinted **RIS 0.5**)
1.0 mg (white, tablet, imprinted **R 1**)
2.0 mg (orange, tablet, imprinted **R 2**)
3.0 mg (yellow, tablet, imprinted **R 3**)
4.0 mg (green, tablet, imprinted **R 4**)

NDA 20-588

30 mL, 1 mg/mL

NDA 21-444

0.5 mg (light coral, round, biconvex, tablet, etched **R0.5**)
1.0 mg (light coral, square, biconvex, tablet, etched **R1**)
2.0 mg (light coral, round, biconvex, tablet, etched **R2**)

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: *Rx*

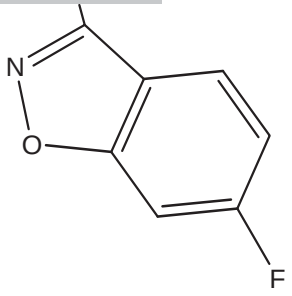
SPECIAL PRODUCTS: __Yes xx No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2a]pyrimidin-4-one

Molecular formula: $C_{23}H_{27}FN_4O_2$
Molecular Weight: 410.48
CAS: 106266-06-2

(b) (4)



RELATED APPLICATIONS: IND 31,931

CONSULT: None

SUPPLEMENT PROVIDES FOR: A new indication for Risperdal• •in the treatment of autism.

CONCLUSIONS: Recommend Approval from the CMC Standpoint.

2 Pages Immediately Following Withheld - b(4)

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/s/

Donald Klein
3/19/04 10:54:41 AM
CHEMIST

Review Chemist mistakes corrected

Thomas Oliver
3/19/04 03:48:11 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20-272 (S-036)**
SERIAL NUMBER:	**S-036**
DATE RECEIVED BY CENTER:	**08/10/06**
PRODUCT:	**Risperidone**
INTENDED CLINICAL POPULATION:	**Children and adolescent with autism**
SPONSOR:	**Johnson & Johnson** **Pharmaceutical Research & Development, L.L.C.** **1125 Trenton-Harbourton Rd,** **P.O.Box 200** **Titusville, NJ 08560**
DOCUMENTS REVIEWED:	**Response to approvable letter**
REVIEW DIVISION:	**Division of Psychiatric Drug Products (HFD-130)**
PHARM/TOX REVIEWER:	**Ikram Elayan**
PHARM/TOX SUPERVISOR:	**Barry Rosloff**
DIVISION DIRECTOR:	**Tom Laughren**
PROJECT MANAGER:	**Doris Bates**

Date of review submission to Division File System (DFS): 9-27-2006

Summary

In the response to the approvable letter the sponsor has agreed to conduct a juvenile animal study in rats with a higher dose and a juvenile animal study in dogs as a phase IV commitment (see the following pages as provided by the sponsor in the Complete Response document of August 10, 2006 submission S-036):

Complete Response To FDA 14 July 2006 Approvable Action For Autism

3. PHASE 4 COMMITMENTS

3.1. Nonclinical Juvenile Rat Toxicology Study (Higher Dose)

In the 14 July 2006 Approvable Letter, the FDA stated:

"We have completed our review of your juvenile animal toxicology study [rat]. We consider this study to be less than optimal based on the following information: A dose higher than the HD of 0.63 mg/kg could have and should have been used. In a range finding study, a dose of 2.5 mg/kg produced similar toxicity to the next lowest dose of 0.63 mg/kg, the only clear difference being cold body surface and cold/dark extremities transiently (during the first few days of dosing only) at the 2.5 mg/kg dose. Bodyweight gains were decreased at both doses, with the effects at 2.5 mg/kg equal to or slightly less than those at 0.63 mg/kg. Plasma AUC values (for parent drug + 9-OH risperidone) at the 0.63 mg/kg dose are estimated to be roughly similar to those in humans receiving the currently proposed maximum dose; based on data from the range finding study achievable levels at 2.5 mg/kg are about 3X greater than those at 0.63 mg/kg.

We are therefore requesting that you perform an additional juvenile rat study, at a higher dose, as a Phase 4 Commitment. This study should be performed using doses greater than 0.63 mg/kg; based on range finding data, it appears that a dose of 2.5 mg/kg would be tolerated.[…]"

The Company commits to perform an additional juvenile toxicity study in the rat at the requested higher dose of 2.5 mg/kg/day. The outline of the protocol, as presented in , is identical to the design of the juvenile toxicity study that was submitted and reviewed by the FDA (protocol submitted to the FDA on 2 April 2004, comments received on 26 May 2004).

The Company will provide the study report for this rat juvenile toxicity study to the FDA in March 2009, together with the report of the dog juvenile toxicity study.

Table 1: Protocol Outline for a Juvenile Rat Toxicity Study With Risperidone.

Description	**Details**
Test article	Risperidone
Species	Crl. CD rat, males and females
Number/sex /group	Main study animals - 36/sex/group Subset I - 12/sex/group Subset II - 12/sex/group Subset III - 12/sex/ group Satellites (TK) - as required
Number of groups	2: Control group and 2.5 mg/kg/day dosage group
Route of administration	Oral gavage
Commencement of dosing	Day 12 post-partum
Duration of dosing	Day 12 – 50 of age (subsets I to III)
Dose volume	5 ml/kg
Age at initiation	Observations to commence Day 7 post-partum Post-coital age to be evenly distributed through groups
Allocation	All group in a litter
Culling	Litters culled Day 4 post-partum to appropriate even numbers of males and females
Weaning	Day 21 post-partum
Observations	**Timing**
Routine clinical observation	Daily
Bodyweight	Daily during lactation and twice weekly thereafter
Food consumption	Twice weekly from weaning
Long bone growth	Every two days during lactation and weekly thereafter
Reflex ontogeny	At least two measures assessed pre-weaning
Eyes open	From Day 12
Vaginal opening	From Day 30
Preputial separation	From Day 40
Sensory function	According to standard procedures, at least once post-weaning and again post-treatment in Subset II
Locomotor activity (Rotarod)	Assessed during the treatment (Subset I) and post-treatment period (Subset II)
Figure 8 Activity Maze	Assessed during post-treatment period (Subset III)
Learning and memory (Morris Water Maze)	Assessed during the treatment (Subset I) and post-treatment period (Subset II)
Hormone assessment (prolactin)	Onset of puberty (Subset II)
Toxicokinetics	During lactation (Day 16)
Mating Phase	Commencing when animals are at least 10 weeks old and after completion of the neurobehavioural assessments (Subset III)
Gross pathology – Organ weights	Subset I – At the end of treatment (Day 50) Subset II – After completing post-treatment behavioral assessments (~Day 75) Subset III – After the mating period (males once fertility is confirmed, females Day 13/14 of pregnancy)
Histopathology	Full battery of tissues, including detailed examination of male and female genital tract (Subsets I-II)

3.2. Nonclinical Juvenile Dog Toxicology Study

In the 14 July 2006 Approvable Letter, the FDA stated:

"In addition, we have evaluated the need for a juvenile dog toxicology study, and have determined that this study also should be conducted as a Phase 4 Commitment. Effects on reproductive organs were seen in both the juvenile rat study submitted here, and in previous adult dog toxicity studies. A juvenile dog study should therefore be performed to evaluate the effects of risperidone on the development of the organs of reproduction; such a study should include a recovery period."

The Company will conduct a juvenile dog toxicity study, details of which are provided in Table 7.

Dog pups will be dosed from 10 weeks on, up to the age of 10 months when they have reached sexual maturity. The dose levels proposed for the dog study are based on previous experience with risperidone in repeat-dose toxicity studies in dogs.

A 3-month repeat-dose toxicity study was conducted in dogs dosed with risperidone in gelatin capsules at dose levels of 0, 0.31, 1.25 and 5 mg/kg/day (Exp. No. 1735). Dose-related sedation was observed at all dose levels. At 5 mg/kg/day, a transient decrease in body weight gain was noted. At all dose levels, the female genital tract showed a more resting aspect than in controls. The testes displayed incomplete spermatogenesis at 1.25 and 5 mg/kg/day, while the prostate showed a more immature aspect.

In a 12-month repeat-dose toxicity study, dogs received risperidone in gelatin capsules at dose levels of 0, 0.31, 1.25 and 5 mg/kg/day (Exp. No. 1789). Dose-dependent sedation occurred at all dose levels during the entire study. A transient decrease in body weight gain was observed at all dose levels. In the testes, focally degenerated tubules were found at 1.25 mg/kg/day, while at 5 mg/kg/day 1 of 4 male dogs showed diffuse degeneration of the germinative epithelium with no spermatozoa in the epididymides. The prostate showed a more immature aspect at 1.25 and 5 mg/kg/day.

Based on this information, a juvenile toxicity study will be conducted in which risperidone will be administered in gelatin capsules to dog pups at dose levels of 0, 0.31, 1.25 and 5 mg/kg/day.

On 17 May 2004, the Company submitted a protocol outline for a juvenile dog toxicity study to the FDA. The FDA provided comments on this protocol outline by email (26 May 2004). The revisions proposed by the FDA have been accounted for in the outline presented in Table 7. As indicated in the protocol outline, the effects of risperidone on the development of the reproductive organs will be evaluated in this study.

The Company will provide the study report for this juvenile dog toxicology study to the FDA in March 2009.

Table 2: Protocol Outline for a Juvenile Dog Toxicity Study With Risperidone

Description	**Details**
Test article	Risperidone
Species	Beagle dog
Number of pups/sex/group	Subset I - 4/sex/group (main study phase) Subset II - 4/sex/group (recovery phase) (in total 32 pups/sex)
Number of dams	18 gravid dogs with litters of 2 males and 2 females where possible
Number of groups	4: Control and three treated groups
Proposed dose levels	0.31 – 1.25 – 5 mg/kg/day
Route of administration	Oral gelatine capsules
Commencement of dosing	~ 2 weeks post-weaning (approximately 10 weeks of age)
Duration of dosing	40 weeks (subsets I-II)
Duration recovery period	Up to 12 weeks (subset II)
Dose volume	5 ml/kg
Culling	Litters culled Day 4 post-partum to 4 pups (2 males and 2 females where possible)
Weaning	~ 8 weeks post-partum
Observations	**Timing**
Routine clinical observation	Daily cage-side and weekly detailed
Body weight	Weekly
Food consumption	Weekly
Observational Battery	At pretest and Weeks 4, 13, 26, 40 and 52 (recovery)
Neurological examination (incl. spinal reflexes, postural reactions, cranial nerves)	At pretest and Weeks 4, 13, 26, 40 and 52 (recovery)
Hematology, clinical biochemistry, urinalysis	At pretest and Weeks 4, 13, 26, 40 and 52 (recovery)
ECGs and heart rate	At pretest and Weeks 4, 13, 26, 40 and 52 (recovery)
Ophthalmology	Once during treatment and recovery phase
Hormone assessment	Serum testosterone and progesterone At Week 40 and 52 (recovery)
Sperm assessment	Sperm motility, count and morphology (CASA) At Week 40 and 52 (recovery)
Toxicokinetics	At start and end of dosing period
Gross pathology – Organ weights	Subset I – At the end of treatment (week 40)(age of 50 w) Subset II – At the end of recovery (week 52)(age of 62 w),
Histopathology	Full battery of tissues, including evaluation of male and female genital organs

Reviewer's comments:

The design of these studies is generally acceptable; however, the followings are recommendations that we would like to convey to the sponsor:

1. increase the number of animals in the different subsets in the rat juvenile study (i.e. the number of animals will be at least 15/subset).
2. measure motor activity using the Figure 8 Activity Maze during treatment as well as during the recovery period.

3. include a measurement for the levels of Insulin-like Growth Factor (IGF-1) in the hormone assessment section in both the rat and the dog study.
4. include a measurement to assess long bone growth in the dog study.

We would like to convey to the sponsor that we have not considered the proposed doses in the dog study in our evaluation of the proposed protocol design.

Recommendations:

The proposed designs of the juvenile animal studies in the rat and dog are generally acceptable. The previous recommendations are to be conveyed to the sponsor.

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/s/

Ikram Elayan
9/27/2006 03:59:03 PM
PHARMACOLOGIST

Barry Rosloff
9/27/2006 04:06:59 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20-272 (S-036)**
SERIAL NUMBER:	**S-036**
DATE RECEIVED BY CENTER:	**01/16/06**
PRODUCT:	**Risperidone**
INTENDED CLINICAL POPULATION:	C**hildren and adolescent with autism**
SPONSOR:	**Johnson & Johnson** **Pharmaceutical Research & Development, L.L.C.** **1125 Trenton-Harbourton Rd,** **P.O.Box 200** **Titusville, NJ 08560**
DOCUMENTS REVIEWED:	Juvenile studies in rats submitted in a CD format dated January 16, 2006 **(TOX6568 and TOX6569)**
REVIEW DIVISION:	**Division of Psychiatric Drug Products (HFD-130)**
PHARM/TOX REVIEWER:	**Ikram Elayan**
PHARM/TOX SUPERVISOR:	**Barry Rosloff**
DIVISION DIRECTOR:	**Tom Laughren**
PROJECT MANAGER:	**Doris Bates**

Date of review submission to Division File System (DFS): June 12, 2006

Appears this way on the original

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability:

The submitted rat juvenile study will be considered satisfactory but not optimal and will be accepted for approval; however, another study with more optimal doses and higher human safety factors is to be conducted as soon as possible after approval as phase IV commitment. In addition, a dog juvenile study is to be conducted as soon as possible after approval as a phase IV commitment based on the findings in the male reproductive system in adult dogs (see review of the original NDA submission by Dr. Lois Freed dated 4/30/93).

B. Recommendation for nonclinical studies: see recommendation on approvability

C. Recommendations on labeling: the effects of the treatment on prolactin levels and the effect on the mammary gland have been reported in adult animals and mentioned in the labeling. It is not clear if this finding in juvenile animals is to be added to the labeling as an effect seen in juvenile animals too. In addition, the other effects see in the reproductive system of juvenile F animals (vagina, ovary and uterus) were partially seen in some studies in adult animals (ovary) and it is not clear if these findings need to be described in the labeling. If these changes are to be described in the labeling, an addendum will follow this review as for the text that will be added to the labeling in this regard.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: See tabulated data at the end of Special toxicology studies: juvenile animal studies

B. Pharmacologic activity: not reviewed, see review of the original NDA submission for schizophrenia

C. Nonclinical safety issues relevant to clinical use:

From the findings of the submitted rat juvenile study, the drug at the doses used did not have a significant effect on a variety of tests performed. However, some effects that are known to be associated with risperidone treatment such as an increase in prolactin levels were seen in both M and F (in M at MD and HD only and in F at all tested doses) and acinar proliferation and secretory activity in mammary tissue in both M and F. Some histopathological changes were observed in the vagina (disturbed oestrus cycle) indicating pseudopregnancy and increased epithelial mucification of the vagina and cervix in some of the animals that

showed normal cycling and in the uterus (resting appearance). Increases in corpora lutea was also observed in the ovary of treated animals. These effects on the F reproductive system (ovary, vagina, and uterus) were not reflected on the reproductive activity of these animals, except for an increase in implantations and live embryos at HD which the sponsor considered incidental. It is possible that this increase in implantations and live embryos is drug related especially in view of the increase in the number of corpora lutea in the ovary (dose dependently) and the changes in vagina (states of pseudopregnancy and increased mucification). The mechanism by which the compound might be producing these effects on F reproductive organs is not known but it could be associated with the changes in prolactin via indirect drug effect on other systems (i.e. pituitary hypothalamic gonadal pathway). It should be noted that some of these effects (increase in corpora lutea) were seen in some (but not all) of the reproductive studies conducted in adult animals; however, the other changes in the vagina and uterus were not observed in these studies. It is possible that these observations in the juvenile animals (uterus and vagina) might be unique to this population and might not be reflected in mature animals.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

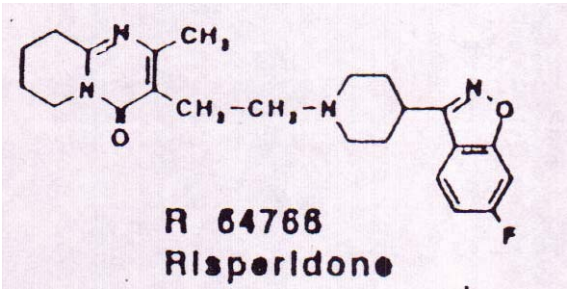
NDA number: 20272-S 036
Review number: 1
Sequence number/date/type of submission: CD submitted on January 16, 2006
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Johnson & Johnson Pharmaceutical Research & Development,
a division of Janssen Pharmaceutica N.V.,
Turnhoutseweg 30, B-2340 Beers (Belgium)
Manufacturer for drug substance:

Reviewer name: Ikram Elayan, Ph.D.
Division name: Division of Psychiatric Drug Products
HFD #: 130
Review completion date:

Drug:

Trade name: Risperidone
Generic name: R 64766
Code name: R 64766
Chemical name: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl-6,7,8,9-tetrahydro-2-methyl 4H-pyridol[1,2-a]pyrimidin-4-one
CAS registry number:
Molecular formula/molecular weight: $C_{23}H_{27}FN_4O_2$
MW = 410.4

Structure:



Relevant INDs/NDAs/DMFs: IND 31931, NDA 20272 N-000 (original NDA for risperidone in the treatment schizophrenia)

Drug class: antipsychotic (benzisoxazole derivative)

Intended clinical population: treatment of irritability associated with autism in children and adolescent ages 5-16

Clinical formulation: tablets and oral solutions are available

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: juvenile rat toxicity pilot study (R064766, tox-6568), and oral (gavage) juvenile toxicity study in the rat (R064766, tox-6569)

Studies not reviewed within this submission: **none (only the previously mentioned juvenile animal studies were submitted).**

Note: For NDA reviews, all section headings should be included.

Since an application for this compound was previously submitted and reviewed (NDA 20272, N-000 for the treatment of schizophrenia) information for the headings in the template here that are not present can be obtained from the original review by Dr. Freed or from the labeling of risperidone.

2.6.2 PHARMACOLOGY:

N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY:

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETIC:

N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY:

N/A

2.6.6 TOXICOLOGY

2.6.6.1 Special toxicology studies: Juvenile animal studies

1. Study title: Juvenile toxicity range finding study in the rat

Key study findings:

Study no.: JAB0073 (R064776- Tox-6568)
Volume #, and page #: CD format submitted January 16, 2006
Conducting laboratory and location: (b) (4)

Date of study initiation: July 2004
GLP compliance: no
QA reports: yes ( ) no (x)
Drug, lot #, and % purity: lot #ZR064766PUA373, according to certificate of analysis total impurities specification using HPLC was (b) (4)
Formulation/vehicle: solution/deionized water tartaric acid and NaOH

Methods: this study was conducted to investigate the effect of the test article on development of the juvenile rats following oral administration by gavage from day 12-25 of age inclusive in an attempt to select the appropriate doses for the main study.

Doses: 0, 0.04, 0.16, 0.63 and 2.5 mg/kg/day at a dose volume of 10 ml/kg

Study design: Sprague Dawley pups (8 males and 7-8 F per dose) were dosed orally by gavage once daily with the appropriate dose from day 12 to 25 of age inclusive. The following parameters were evaluated for the pups during the treatment period: clinical observations (daily for changes in behavior and appearance and for toxicity after dosing), mortality (twice daily), body weights (daily), and toxicokinetics (PND 25, pre-dose, 1, 4, & 8 h after dosing).

Results:

Mortality: no drug-related mortalities.

Clinical signs were observed daily after treatment and were described by the sponsor as following:

According to the sponsor's group clinical observation table (see attached table below), on the first or second day of dosing male pups receiving 2.5 mg/kg/day were cold all over; however, it should be noted that in the individual clinical observation table only 1M (#39) was described as having body surface cold (see attached table below). After the

first few days of dosing the extremities only were described as being cold and appearing dark (for M in the individual clinical observations table and for F in the group clinical observation table). These signs were not observed beyond day 17. One M (#39) receiving 2.5 mg/kg/day was dehydrated and had labored breathing on Day 14 of age as well as having a cold body and extremities and was not dosed on that day.

From day 19 until day 22 of age all pups receiving 0.63 mg/kg/day and all F pups receiving 2.5 mg/kg/day had decreased activity and partially closed eyes from approximately 3 hours post-dosing according the group clinical observation table; however, these observations were not listed in the individual clinical observation table (see attached tables below). No clinical signs were observed for one or two days after these signs finished.

On day 24 and/or day 25 of age all pups receiving 0.63 mg/kg/day and all F pups receiving 2.5 mg/kg/day were observed to have intermittently closed and partially closed eyes and rapid breathing. The effect on the eyes was observed at approximately half an hour after dosing and lasted all day. Rapid breathing was observed only at 2.5 to 7 hours post dosing. Rapid breathing was also observed in the pups receiving 0.16 mg/kg/day on day 25 of age only. It was observed at 3 hours post-dosing and lasted for the rest of the day.

Unsteady gait was reported in animals treated with 0.63 mg/kg/day and 2.5 mg/kg/day on days 24-25 and lasted from 0.5-1 h post dosing. According to the sponsor, one F (#72) receiving 0.63 mg/kg/day had splayed hindlimbs and decreased activity on day 25 of age. The following tables (group clinical observations and individual clinical observations) were obtained from the sponsor (pages 32 and 33):

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Annexe 1 - Group clinical observations

(Page 1 of 1)

Group : 1 2 3 4 5

Treatment : Control Risperidone

Dosage (mg/kg/day) : 0 0.04 0.16 0.63 2.5

Group	Animal number	Clinical sign	Day of age 12	13	14	15	16	17	18	19	20	21	22	23	24	25
3M, 3F	All	Rapid breathing														3 - 7
4M, 4F	All	Decreased activity								3 - 5	3	4	3.5			
		Partially closed eyes								3 - 5	3	4	3.5			
		Intermitant eyes closed and part closed														0.75 - 7
		Unsteady gait														1
		Rapid breathing														3 - 7
5M	33 - 36	Body surface - cold		X												
5F	73 - 76	Extremeties - cold			X											
		Extremeties - dark				X	X									
		Decreased activity								3 - 5	3	4	3.5			
		Partially closed eyes								3 - 5	3	4	3.5			
		Intermitant eyes closed and part closed														0.5 - 7
		Unsteady gait														0.5
		Rapid breathing														2.5 - 7
5M	37 - 40	Body surface - cold	X													
5F	77 - 80	Extremeties - cold		X												
		Extremeties - dark			X	X										
		Decreased activity							3 - 5	3	4	3.5				
		Partially closed eyes							3 - 5	3	4	3.5				
		Intermitant eyes closed and part closed													0.5 - 7	0.75
		Unsteady gait													0.5	0.75
		Rapid breathing													2.5 - 7	0.75

X=Present w=Brown 0.5, 2.5, 3, 3.5, 4 and 7 hours post-dose

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Annexe 2 - Individual clinical observations

(Page 1 of 1)

Group : 1 2 3 4 5

Treatment : Control Risperidone

Dosage (mg/kg/day) : 0 0.04 0.16 0.63 2.5

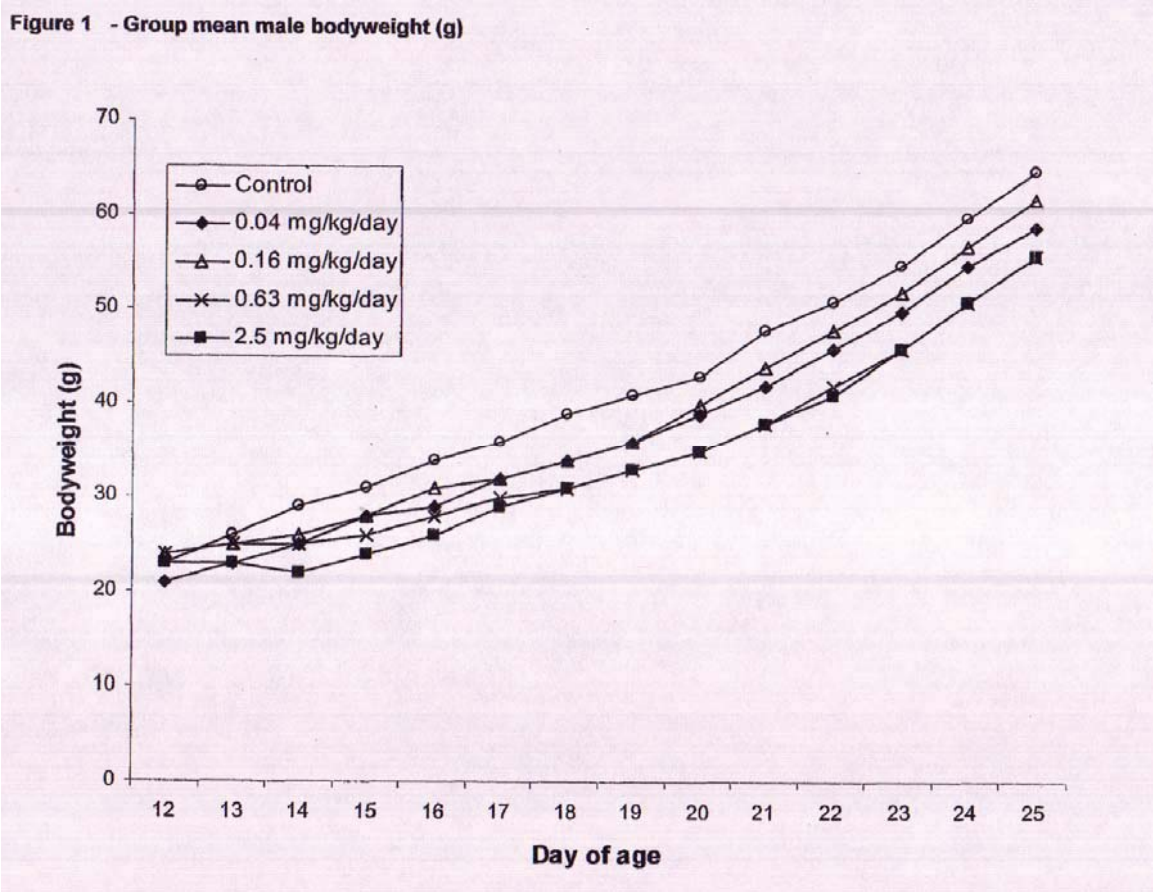
Group sex	Animal number	Clinical sign	Day of age 14	15	16	17	18	19	20	21	22	23	24	25
4F	72	Hindlimbs splayed												X
		Decreased activity												X
		Extremeties pale												X
5M	35	Extremeties cold		X										
		Extremeties cold - Pre-dose			X									
	36	Extremeties cold			X									
	37	Extremeties cold		X										
	38	Extremeties cold		X										
	39	Dehydrated	X											
		Body surface cold	X											
		Laboured breathing	X											
		Extremeties cold	X											
5F	73	Extremeties cold		X										
	77	Mouth - red discharge												X
		Laboured breathing												X
		Noisy breathing												X
		Caught in cage												X
		Euthanased												
	79	Extremeties cold	X											
	80	Extremeties cold	X											

X=Present

It is not clear why M treated with 2.5 mg/kg/day did not exhibit similar clinical signs to F treated with that dose (partially closed eyes and decreased activity) even though both M and F treated with 0.63 mg/kg/day exhibited comparable signs. It is also unclear the reason for discrepancy in data representation between the individual clinical signs table and the group clinical signs table.

Body weight: animals were weighed daily from day 12 to day 25 of age.

In M, over the treatment period pups receiving 0.63 or 2.5 mg/kg/day gained less weight than the control animals (a 21% reduction in body wt gain by the end of the study compared to control, however mainly seen during the first two days) resulting in a reduction in absolute body weight in both groups compared to the control group at the end of treatment (14% for both groups). The following Figure was provided by the sponsor (page 30):



Tabulated data for the effect on body wt gain and body wt in M is provided by the sponsor (page 24 and 26):

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Table 1 - Group mean male bodyweight (g)

(Page 1 of 1)

Group	:	1	2	3	4	5
Treatment	:	Control		Risperidone		
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63	2.5

Day of age	Group 1	2	3	4	5
N	8	8	8	8	8
12	23 ± 3	21 ± 3	24 ± 4	24 ± 2	23 ± 1
13	26 ± 3	23 ± 3	25 ± 4	25 ± 2	23 ± 1
14	29 ± 3	25 ± 3	26 ± 3	25 ± 2	22 ± 2
15	31 ± 3	28 ± 3	28 ± 4	26 ± 2	24 ± 3
16	34 ± 3	29 ± 3	31 ± 5	28 ± 3	26 ± 3
17	36 ± 3	32 ± 3	32 ± 4	30 ± 3	29 ± 3
18	39 ± 3	34 ± 3	34 ± 4	31 ± 3	31 ± 3
19	41 ± 3	36 ± 3	36 ± 4	33 ± 4	33 ± 4
20	43 ± 4	39 ± 4	40 ± 4	35 ± 4	35 ± 4
21	48 ± 4	42 ± 4	44 ± 4	38 ± 4 ↓21%	38 ± 5 ↓21%
22	51 ± 4	46 ± 4	48 ± 4	42 ± 4	41 ± 7
23	55 ± 4	50 ± 4	52 ± 4	46 ± 5 ↓16%	46 ± 8 ↓16%
24	60 ± 5	55 ± 5	57 ± 5	51 ± 5 ↓15%	51 ± 8 ↓15%
25	65 ± 5	59 ± 5	62 ± 5	56 ± 6 ↓14%	56 ± 9 ↓14%

N = number of animals in mean

Table 3 - Group mean male bodyweight gains (g)

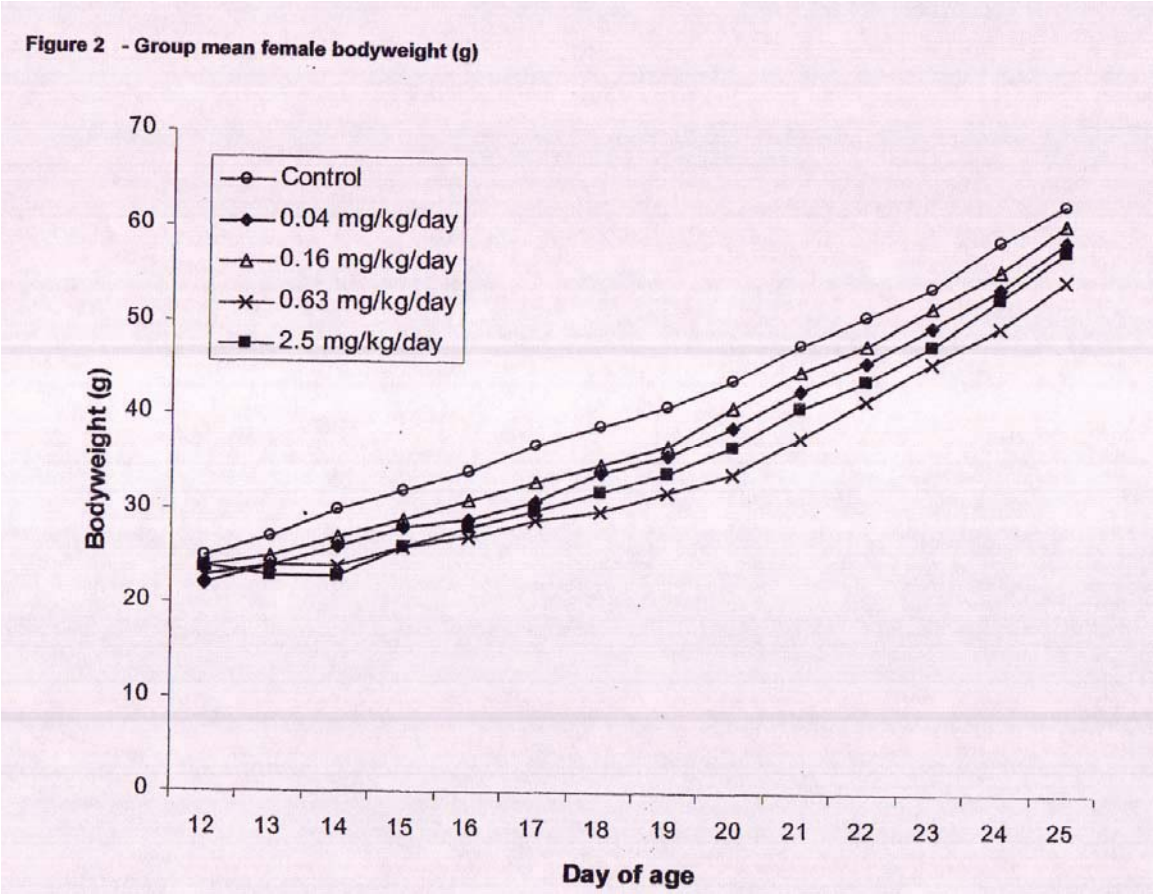
(Page 1 of 1)

Group	:	1	2	3	4	5
Treatment	:	Control		Risperidone		
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63	2.5

Day of age	Group 1	2	3	4	5
N	8	8	8	8	8
12 to 15	8 ± 1	6 ± 1	4 ± 1	2 ± 1	1 ± 2
15 to 18	8 ± 1	6 ± 1	6 ± 1	5 ± 1	6 ± 1
18 to 22	13 ± 2	12 ± 2	13 ± 2	11 ± 2	11 ± 5
22 to 25	14 ± 1	13 ± 3	14 ± 2	14 ± 3	15 ± 4
12 to 25	42 ± 2	38 ± 4	38 ± 2	33 ± 4 ↓21%	33 ± 8 ↓21%

N = number of animals in mean

In F treated with 2.5 mg/kg/day body weigh gain during the first two days was less than that observed in the control group (2 g in treated animals vs. 7 g in control). However, from day 15-25 there was no difference between the control and the treated group. At the end of treatment the difference in absolute body weight between control and F treated with 2.5 mg/kg was 8%. In F treated with 0.63 mg/kg the difference in body weight gain from the control was seen up to day 18 (3-4g in treated animals vs. 7 g in control). The decrease in absolute body weight in this group was 13-15% compared to control at the end of the study. It is apparent from these findings that in F the effect on body weight and body weight gain was not dose related. The following figure was provided by the sponsor (page 31).



The following tables represent the data for the body wt and body wt gain in F as provided by the sponsor (pages 25 and 27):

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Table 2 - Group mean female bodyweight (g)

(Page 1 of 1)

Group	:	1	2	3	4	5
Treatment	:	Control		Risperidone		
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63	2.5

Day of age	Group 1	2	3	4	5
N	7	7	8	8	8
12	25 ± 3	22 ± 1	24 ± 3	23 ± 1	24 ± 3
13	27 ± 3	24 ± 2	25 ± 3	24 ± 2	23 ± 3
14	30 ± 3	26 ± 2	27 ± 4	24 ± 2 ↓20%	23 ± 3 ↓23%
15	32 ± 3	28 ± 2	29 ± 4	26 ± 2	26 ± 4
16	34 ± 3	29 ± 2	31 ± 4	27 ± 2	28 ± 5 ↓15%
17	37 ± 3	31 ± 2	33 ± 4	29 ± 2	30 ± 5
18	39 ± 4	34 ± 3	35 ± 4	30 ± 3	32 ± 5
19	41 ± 3	36 ± 2	37 ± 4	32 ± 3 ↓22%	34 ± 6 ↓17%
20	44 ± 3	39 ± 3	41 ± 3	34 ± 3	37 ± 7
21	48 ± 3	43 ± 3	45 ± 2	38 ± 4	41 ± 8
22	51 ± 4	46 ± 3	48 ± 3	42 ± 4	44 ± 9
23	54 ± 4	50 ± 3	52 ± 3	46 ± 4 ↓15%	48 ± 10 ↓11%
24	59 ± 4	54 ± 3	56 ± 3	50 ± 4	53 ± 9
25	63 ± 3	59 ± 3	61 ± 3	55 ± 5 ↓13%	58 ± 9 ↓8%

N = number of animals in mean

Table 4 - Group mean female bodyweight gains (g)

(Page 1 of 1)

Group	:	1	2	3	4	5
Treatment	:	Control		Risperidone		
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63	2.5

Day of age	Group 1	2	3	4	5
N	7	7	8	8	8
12 to 15	7 ± 1	6 ± 1	5 ± 2	3 ± 1	2 ± 2
15 to 18	7 ± 0	6 ± 2	6 ± 1	4 ± 1	7 ± 2
18 to 22	12 ± 1	12 ± 1	13 ± 2	12 ± 2	11 ± 4
22 to 25	11 ± 2	13 ± 1	13 ± 1	13 ± 2	15 ± 2
12 to 25	37 ± 3	36 ± 3	37 ± 2	32 ± 4	35 ± 6

N = number of animals in mean

Toxicokinetics: the levels of risperidone, its active metabolite 9-hydroxy-risperidone (9-OH-risperidone) and the active moiety (risperidone + 9-OH-risperidone) were assessed on Day 25 of age. Blood samples were collected from the orbital sinus from two pups/group/sex/timepoint at the following time points: pre-dose, 1, 4, and 8h post dose.

Plasma levels for risperidone, 9-OH-risperidone and the active moiety were generally not quantifiable at 0.04 mg/kg/day in M juvenile rats. Maximum risperidone, 9-OH-risperidone and the active moiety concentrations were reached at 1-4h post dose. The systemic exposure to risperidone, 9-OH-risperidone and the active moiety increased with

increasing dose and were not markedly different from dose proportionality. There was no consistent evidence of a major sex difference in risperidone, 9-OH-risperidone or the active moiety at any level. 9-OH-risperidone concentrations were generally somewhat higher than those of risperidone at corresponding timepoints at all dose levels. The following tables were provided by the sponsor for the levels of risperidone, 9-OH-risperidone, and the active moiety (pages 102-104).

TABLE 2

Table 2A: Mean Plasma Concentrations (ng/mL) and Some Basic Pharmacokinetic Parameters of Risperidone in Rats on Day 25 of Age after Repeated Oral Dosing of 0.04, 0.16, 0.63 or 2.5 mg/kg/day Risperidone from Day 12 to Day 25 of Age of a Juvenile Toxicity Dose Range Finding Study in the Rat.

	Day 25 of Age							
Time (h) Dose Group	0.04 mg/kg/day 2		0.16 mg/kg/day 3		0.63 mg/kg/day 4		2.5 mg/kg/day 5	
Gender	Male	Female	Male	Female	Male	Female	Male	Female
0	<0.500	<0.500	<0.500	<0.500	<0.500	<0.500	<0.500	<0.500
1	2.04	1.96	7.86	6.75	29.3	63.6	132	126
4	<0.500	0.684	0.745	1.71	14.0	17.5	21.1	71.6
8	<0.500	<0.500	<0.500	<0.500	3.17	4.31	13.5	11.8
C_{max} (ng/mL)	-[1]	1.96	7.86	6.75	29.3	63.6	132	126
T_{max} (h)	-[1]	1	1	1	1	1	1	1
$t_{½ (4-8h)}$ (h)	-[1]	-[4]	0.9[2]	1.5[2]	1.9	2.0	-[4]	1.5
$AUC_{0-8 h}$ (ng.h.mL)	-[1]	6.09	13.9	17.5	106	177	314	484
$AUC_{0-24 h}$ (ng.h.mL)	-[1]	-[3]	13.9	18.1	114	189	-[3]	510
Male to Female Ratios (C_{max})	-[1]		1.2		0.5		1.0	
Male to Female Ratios (AUC_{0-8h})	-[1]		0.8		0.6		0.6	
Dose proportionality Ratios (C_{max})			-[1]	3.4	3.7	9.4	4.5	2.0
Dose proportionality Ratios (AUC_{0-8h})			-[1]	2.9	7.6	10.1	3.0	2.7

[1] Not appropriate or not calculable due to a lack of data points.
[2] Timepoints used to calculate half-life: 1 and 4 hours.
[3] Not appropriate as extrapolation value >25%.
[4] Half-lives could not be reliably calculated.

Table 2B: Mean Plasma Concentrations (ng/mL) and Some Basic Pharmacokinetic Parameters of 9-OH-Risperidone in Rats on Day 25 of Age after Repeated Oral Dosing of 0.04, 0.16, 0.63 or 2.5 mg/kg/day Risperidone from Day 12 to Day 25 of Age of a Juvenile Toxicity Dose Range Finding Study in the Rat.

	Day 25 of Age							
Time (h) Dose Group	0.04 mg/kg/day 2		0.16 mg/kg/day 3		0.63 mg/kg/day 4		2.5 mg/kg/day 5	
Gender	Male	Female	Male	Female	Male	Female	Male	Female
0	<0.500	<0.500	<0.500	<0.500	<0.500	<0.500	<0.500	<0.500
1	1.82	1.28	12.0	7.49	25.9	37.1	195	125
4	<0.500	1.43	4.76	5.67	35.1	33.2	53.9	105
8	<0.500	<0.500	2.23	2.32	15.7	14.8	51.9	42.4
C_{max} (ng/mL)	-[1]	1.43	12.0	7.49	35.1	37.1	195	125
T_{max} (h)	-[1]	4	1	1	4	1	1	1
$t_{½ (4-8h)}$ (h)	-[1]	-[1]	3.6	3.1	3.4	3.4	-[3]	3.1
$AUC_{0-8 h}$ (ng.h.mL)	-[1]	-[1]	42.8	38.3	201	215	637	681
$AUC_{0-24 h}$ (ng.h.mL)	-[1]	-[1]	53.9	48.4	-[2]	-[2]	-[2]	864
Male to Female Ratios (C_{max})	-[1]		1.6		0.9		1.6	
Male to Female Ratios (AUC_{0-8h})	-[1]		1.1		0.9		0.9	
Dose proportionality Ratios (C_{max})			-[1]	5.2	2.9	5.0	5.6	3.4
Dose proportionality Ratios (AUC_{0-8h})			-[1]	-[1]	4.7	5.6	3.2	3.2
9-OH-risperidone/ risperidone Ratios (C_{max})	-[1]	0.7	1.5	1.1	1.2	0.6	1.5	1.0
9-OH-risperidone/ risperidone Ratios (AUC_{0-8h})	-[1]	-[1]	3.1	2.2	1.9	1.2	2.0	1.4

[1] Not appropriate or not calculable due to a lack of data points.
[2] Not appropriate as extrapolation value >25%.
[3] Half-lives could not be reliably calculated.

Table 2C: Mean Plasma Concentrations (ng/mL) and Some Basic Pharmacokinetic Parameters of the Active Moiety (Risperidone + 9-OH-Risperidone) in Rats on Day 25 of Age after Repeated Oral Dosing of 0.04, 0.16, 0.63 or 2.5 mg/kg/day Risperidone from Day 12 to Day 25 of Age of a Juvenile Toxicity Dose Range Finding Study in the Rat.

	Day 25 of Age							
Time (h) Dose Group Gender	0.04 mg/kg/day 2		0.16 mg/kg/day 3		0.63 mg/kg/day 4		2.5 mg/kg/day 5	
	Male	Female	Male	Female	Male	Female	Male	Female
0	<1.00	<1.00	<1.00	<1.00	<1.00	<1.00	<1.00	<1.00
1	3.86	3.24	19.8	14.2	55.2	101	326	251
4	<1.00	2.11	5.51	7.38	49.1	50.7	74.9	176
8	<1.00	<1.00	2.23	2.66	18.8	19.1	65.4	54.1
C_{max} (ng/mL)	-[1]	3.24	19.8	14.2	55.2	101	326	251
T_{max} (h)	-[1]	1	1	1	1	1	1	1
$t_{½ (4-8h)}$ (h)	-[1]	-[3]	3.1	2.7	2.9	2.8	-[3]	2.3
$AUC_{0-8 h}$ (ng.h.mL)	-[1]	15.9	57.9	56.9	310	398	955	1170
$AUC_{0-24 h}$ (ng.h.mL)	-[1]	-[2]	67.5	67.1	387	475	-[2]	1350
Male to Female Ratios (C_{max})	-[1]		1.4		0.5		1.3	
Male to Female Ratios (AUC_{0-8h})	-[1]		1.0		0.8		0.8	
Dose proportionality Ratios (C_{max})			-[1]	4.4	2.8	7.1	5.9	2.5
Dose proportionality Ratios (AUC_{0-8h})			-[1]	3.6	5.4	7.0	3.1	2.9

[1] Not appropriate or not calculable due to a lack of data points.
[2] Not appropriate as extrapolation value >25%.
[3] Half-lives could not be reliably calculated.

Conclusion: The sponsor had concluded from the results of the dose ranging study that a dose of 2.5 mg/kg/day would be too high for the main juvenile toxicity study especially since the main study will be longer (Day 12 to Day 50 of age). The sponsor came to this conclusion based on the effect on body wt and clinical signs observed in M and F. The sponsor proposed the following doses for the main study: 0, 0.04, 0.16 and 0.63 mg/kg/day.

The reviewer believes that the clinical signs observed at the dose of 2.5 mg/kg/day in this study (decreased activity and cold body and extremities) might not be tolerated in pups if they were long lasting. However, these signs were observed for only few days during treatment after which they were no longer observed (i.e. transient). The effect on body wt was interestingly seen at both the MD and HD (0.63 and 2.5 mg/kg) in the same magnitude in M (~14% decrease on day 25) and in F the decrease at 0.63 mg/kg/day (13%) was somewhat slightly higher than that seen at 2.5 mg/kg/day (8%) on Day 25 compared to the control. In addition, the effect on absolute body wt at both doses was less dramatic on day 25 compared to the first few days when it was first observed (~20%

decrease on day 17 in M and ~14% decrease on day 25 at both 2.5 mg/kg/day and 0.63 mg/kg/day compared to the control group). The treated animals appeared to gain less wt compared to the control animals in the first few days of treatment but gained almost similar wt thereafter. The sponsor considered the dose of 2.5 mg/kg/day inadequate for the main study because of its effects on body wt and chose the dose of 0.63 mg/kg/day even though it had similar effects on body wt. Even though there were fewer clinical signs observed at a dose of 0.63 mg/kg/day, this will probably not favor it as a better dose for the main study (on the notion that the animals will better tolerate it) because all the clinical signs that were seen at the higher dose (2.5 mg/kg/day) were transient and thus will not limit the use of 2.5 mg/kg/day as the high dose for the main study. If the dose is to be considered an MTD it would have to be the maximum of the two doses with similar effects (in this case on body wt if we considered the clinical signs as not being the determining factor). If the sponsor considered the clinical signs observed with 2.5 mg/kg/day dose limiting it will probably not be sufficient in this case because they were not observed beyond the first few days. Therefore the reviewer considers that choosing 0.63 mg/kg/day as the high dose for the main study is not appropriate and the higher dose (2.5 mg/kg/day) which produced similar effects on body wt with some clinical signs even though not long lasting might be good enough to indicate that toxicity might be happening with increasing the dose. This potential HD dose could have been 2.5 or may be a slightly lower dose (i.e. 1.5 mg/kg/day) but a dose of 0.63 mg/kg/day might be low. The effect on body wt together with other observed clinical signs will make a dose of 2.5 mg/kg/day satisfactory as an MTD in the main study if the effect on body wt will be long lasting beyond weaning together with some observed dose limiting clinical signs. The findings of the proposed main study (proposed doses of 0, 0.04, 0.16, and 0.63 mg/kg/day) will either support or negate this conclusion by the reviewer.

2. Study title: oral (gavage) juvenile toxicity study in the rat

Key study findings: see summary table at the end of the study.

Study no.: R06466 (TOX6569 or JAB0074)
Volume #, and page #: CD format submitted January 16, 2006
Conducting laboratory and location: (b) (4)

Date of study initiation: 17 November 2004 (start of dosing December 6, 2004)
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Batch #ZR064766PUA373, impurities were reported as ≤ (b) (4)
Formulation/vehicle: Aqueous solution containing tartaric acid and NaOH

Methods

Doses: 0, 0.04, 0.16, and 0.63 mg/kg/day

Study design: Sprague Dawley pups (36/sex/group) were dosed with the appropriate dose orally by gavage (5 ml/kg) once daily from Day 12 to Day 50 of age inclusive. Each dose group was subdivided into 3 subsets (12 rats/sex/subset) according to different assessments followed as described here:

1) Subset I: development assessments (eye opening from day 11 of age until occurrence and pupillary light reflex on day 21 of age). Post-weaning behavioral tests [learning and memory (Morris water maze test) around day 46 of age, locomotive activity (rotarod) around day 29 of age, and Preyer reflex around day 36 of age] were conducted during the treatment period. At the end of the dosing (Day 50 of age) animals were necropsied and organs were weighed and tissues were retained for histopathological examination

2) Subset II: development assessments were conducted during treatment period and animals were assessed for onset of sexual maturity with blood samples being collected on the day that vaginal opening or balanopreputial separation occurred for measurement of hormone levels. At least 14 days after the end of treatment, behavioral tests (learning memory around day 68 of age, locomotor activity around day 64 of age, and Preyer reflex around day 65 of age) were conducted. Vaginal opening was observed starting on Day 30 of age until occurrence and balanopreputial separation was observed from Day 40 of age until occurrence. At necropsy, organs were weighed and tissues were retained for histopathological examination.

3) Subset III: at least 14 days after termination of treatment animals were tested in the Figure Eight activity maze (around day 64 of age). At approximately 10 weeks of age they were paired to assess reproductivity performance. Females were necropsied on Day 13 of gestation while M were necropsied following review of the F data.

Clinical observations and mortalities: pups were examined daily from Day 7 of age for changes in behavior and/or appearance. From day 12 of age (start of dosing) clinical signs of toxicity were also observed. No indication to the time of observations in relation to treatment but the results indicate that observations were reported according to the time during the day at which these signs were observed.

Body weight: M and F from subset I and II and M from subset III were weighed daily during lactation from Day 10 to Day 21 of age and twice weekly thereafter until necropsy. Subset III F were weighed daily during lactation from Day 10 to Day 21 of age and then twice weekly until confirmation of mating. On confirmation of mating, subset III F were also weighed on Days 0, 6, and 13 of gestation.

Food consumption: the amount of food for each cage was recorded twice weekly after weaning on Day 21 of age until the end of the dosing period (subset I), until necropsy (subset II) or until pairing (subset III).

Long bone growth was determined by measuring the distance between the hock and the heel after the start of dosing for 10 M (from 10 litters) and 10 F (from 10 litters) per group, every two days during lactation and then weekly thereafter until necropsy from all subsets.

Hormone assessment: blood samples were collected from 10M and 10 F per group in Subset II between 14 and 16 hours on the day that vaginal perforation or preputial separation was observed. Blood was collected from the orbital sinus under isofluorane anaesthesia.

Reproductive capacity: at approximately 10 weeks of age animals of Subset III were paired with each F paired with a M from the same dose group for up to seven days. Sibling pairings were avoided. Vaginal smears were taken daily until sperm were found in the smear. At this time the stage of the estrous cycle or presence of sperm were recorded. The stage of oestrus cycle was determined by the type of cell present and the stages were coded as described here:

P- pro-oestrus: predominance of small/medium round cells with centrally placed nuclei (leucocytes and mucus are rarely found).
O- oestrus: predominance of cornified cells with pyknotic nuclei (leukocytes and mucus are absent).
M- met-oestrus: predominance of leucocytes, anucleate cornified cells, and large oval anucleate cells.
D- di-oestrus: predominance of leucocytes (mucus and a few cornified and small round cells may be present).

The mating activity of the animals was assessed by recording the number of copulation plugs.

Post-mortem studies:

1. **Pup necropsy:** of the pups that were selected for the study, a necropsy was conducted on all pups sacrificed or found dead during lactation and after weaning.

2. **Male necropsy:** the males in Subset I were killed after the end of the completion of dosing (Day 50) and necropsy was performed. The males in Subset II were killed after completion of the post-treatment behavioral assessments (PND 64) and a necropsy was performed. The males in Subset III were killed approximately two weeks after the mating period, following review of the female data and a necropsy performed.

3. **Female necropsy:** females in Subset I were killed after the end of the completion of dosing and a necropsy was performed. Females in Subset II were killed after completion of post-treatment behavioral assessments and a necropsy was performed. Females in Subset III were killed on Day 13 of gestation. The following observations were made on this group in addition to the pathology procedures conducted on all groups (see below): pregnancy status, number of corpora lutea, and number of intrauterine position of implantations (classified as early resorptions or live embryos).

Pathology Procedures:

The following tissues were wax embedded, cut at a nominal thickness of 4/5 µm, stained with haematoxylin and eosin and examined microscopically from all control and HD animals, from all animals dying or killed during study, and all macroscopic abnormalities from all control and HD animals killed at termination and from all animals dying or killed during the study. Macroscopically abnormal tissues from animals of the low and intermediate dose groups that were euthanized at the scheduled kill(s) were preserved in neutral buffered formaldehyde.

2.8.6. PATHOLOGY PROCEDURES (GROUPS 1 TO 4) - SUBSETS I , II AND III

Tissue	Weigh	Fix	Slide Preparation	Microscopic Examination
adrenal glands	✓	✓	✓	✓
aorta		✓	✓	✓
bone marrow smear		✓	✓	✓
brain (3 levels examined) ¥	✓	✓	✓	✓
caecum		✓	✓	✓
colon		✓	✓	✓
duodenum		✓	✓	✓
epididymides		✓	✓	✓
eyes (incl. optic nerves)		✓	✓	✓
femur and joint (incl. marrow)		✓	✓	✓
Harderian glands		✓	✓	✓
heart	✓	✓	✓	✓

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Tissue	Weigh	Fix	Slide Preparation	Microscopic Examination
animal identification@				
ileum (incl. Peyer's patches)		✓	✓	✓
jejunum		✓	✓	✓
kidneys	✓	✓	✓	✓
lacrimal glands		✓	✓	✓
larynx		✓	✓	✓
liver	✓	✓	✓	✓
lungs (incl. mainstem bronchi)	✓	✓	✓	✓
mesenteric lymph node		✓	✓	✓
oesophagus		✓	✓	✓
ovaries	✓	✓	✓	✓
pancreas		✓	✓	✓
pituitary	✓	✓	✓	✓
prostate	✓	✓	✓	✓
rectum		✓	✓	✓
salivary gland (submandibular, parotid* and sublingual)	✓	✓	✓	✓
sciatic nerve		✓	✓	✓
seminal vesicles (incl. coagulating gland)	✓	✓	✓	✓$
site of mammary gland		✓	✓	✓
skeletal muscle		✓	✓	✓
skin		✓	✓	✓
spinal cord (3 levels examined)		✓	✓	✓
spleen	✓	✓	✓	✓
sternum (incl. bone marrow)		✓	✓	✓
stomach		✓	✓	✓
submandibular lymph nodes		✓	✓	✓
testes	✓	✓	✓	✓
thymus	✓	✓	✓	✓
thyroids (incl. parathyroids)#	✓	✓	✓	✓
tongue		✓	✓	✓
trachea		✓	✓	✓
ureters		✓	✓	✓
urinary bladder		✓	✓	✓
uterus (incl. uterine cervix and oviducts) §	✓	✓	✓	✓
vagina		✓	✓	✓
all gross lesions		✓	✓	✓

@retained * retained but not weighed
weighed after fixation $ examination excludes coagulating gland
¥ Three areas of the brain examined included the cerebrum, midbrain and cerebellum.
§ Gravid uterus weight also recorded

Following review of the data the Sponsor processed the following tissues from Subset I from the LD and MD groups: mammary tissue (M&F), vagina, uterus (includes uterine cervix and oviducts) and ovaries.

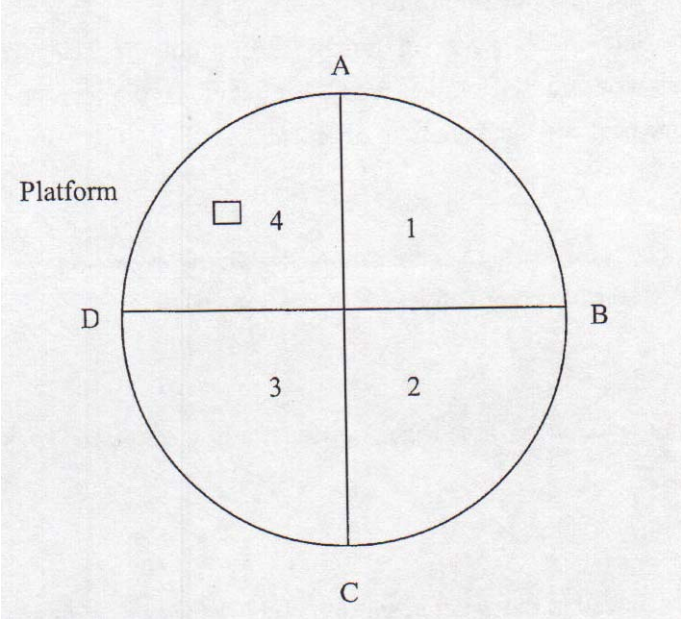
Bone marrow smears:

A full myelogram examination of the prepared bone marrow smears was performed for the animals in Groups 1 and 4 only from each subset.

Description of the different tests used in the study:

1) **Learning and memory test (Morris water maze)**: the following description was provided by the sponsor (pages 20-22):

Animals in Subset I were tested on Day 46 ± 2 of age and animals in Subset II were assessed on Day 68 ± 2 of age, approximately two weeks after the end of the dosing period. The Morris water maze was a pool of diameter 140 cm and depth 45 cm filled with 25 cm of water (24 °C ± 2 °C) made cloudy by the addition of powdered milk. The pool had a platform of 10 cm diameter, which stood 24 cm high, just below the surface of the water. There were cues around the outside of the pool to assist the rats in spatial orientation.



The letters A to D in the diagram show starting positions for the rats (approximately 5 cm inside from the wall of the pool). The quadrants were numbered 1 to 4.

The Operator always stood at point A and remained still during the swim as they were used by the rats as a spatial cue. The rats were placed onto the platform or into the water by the Operator. The Operator indicated to the Recorder (who was out of sight of the swimming rat) the number of the quadrant the rat had entered each time it changed quadrants, and the time taken for the rat to get onto the platform.

Day 1

- The rat was placed onto the platform by the Operator for 15 seconds to triangulate its position in relation to the spatial cues.
- The rat was then placed in the water at starting point A, approximately 5 cm from the wall of the pool and facing the side of the pool, and the timer started.
- Each time the rat entered a quadrant the number of the quadrant was recorded.
- When the rat climbed onto the platform the timer was stopped and the time recorded.
- If 60 seconds elapsed and the rat had not found the platform, the Operator gently guided the rat to the platform.
- The rat was left on the platform for 15 seconds before being removed.

The trial was repeated twice more, with 30 minutes having elapsed between the end of one trial and the beginning of the next.

Day2

The same procedures as Day 1 were followed with the exception that the rats were placed at starting point B for each of the three trials.

Day 3

Again, the rats underwent three trials, however they were placed in the water at starting point C.

Day4
The rats were placed in the water at starting point D for each of three trials.

2) **Preyer Reflex test**: the hearing ability of the animals was tested using this test. Any animal that failed was re-tested the following day.

3) **Locomotor activity test using the rota-rod test:** locomotor activity was assessed using a rota-rod. The rota-rod test monitors the coordination and fatigue resistance of the animals by recording the

length of time they can stay on a revolving and accelerating drum. Animals were given five consecutive runs on the equipment and the time taken until the animal either falls off or starts to revolve with the drum was recorded for each run.

4) **Figure Eight activity maze:** a "Figure 8" Activity System fitted with photobeam mountings (San Diego Instruments) was used to detect locomotor and rearing activity. The system was located in a separate room equipped with a white noise generator to control for extraneous background noise. The maze consisted of several interconnected alleyways forming a "figure 8" and elicited moderately high levels of spontaneous motor activity, thus detection of both increases and decreases in activity were possible.

Toxicokinetics:

Blood samples (0.6 ml) were collected from satellite pups on Day 12 and Day 16 at pre-dose, 1, 4, and 8h after dosing (3M and 3F on each sampling point) to assess the levels of risperidone, its active metabolite 9-hydroxy-risperidone and the active moiety (risperidone + 9-OH-risperidone).

Results:

Analysis of dosing formulations:

Samples of the dosing solutions were assessed for concentration and stability. The concentrations of the samples were between 96% and 99% of the nominal value. The stability of the dosing solutions was established for those samples prepared at the beginning of the study and according to the sponsor the formulations were "stable for a period exceeding the use period during the study."

Mortality:

A female (#270) from HD group died on Day 25 of age. The sponsor described this animal as "convulsing during dosing"; however, no findings at necropsy or histopathology indicated the cause of death. The sponsor considered this death as drug-unrelated "in view of the isolated nature of this finding." The reviewer agrees with the sponsor that this death might not be treatment related based on the fact that no deaths were observed at a higher dose in the dose ranging study (2.5 mg/kg/day) up to day 25 of age. Therefore, in view of the lack of any other findings to indicate the cause of death in this animal and because it was the only animal that died at this dose this death could be incidental. It should be pointed out that the convulsive state that the animal was in during dosing might be incidental and not drug related since convulsions were not observed in

adult rats treated with up to 10 mg/kg/day for 30 days in a subchronic study (see a review by Dr. Lois Freed for the original NDA 20272, dated 4/30/1993).

In addition to this animal, there were three early deaths that were considered by the sponsor to be associated with dosing trauma. Male #130 from HD group was found dead on Day 23 of age (described with left eye, right eye, abnormal color, dark), M #61 from LD group was necropsied on Day 29 of age (described with hunched posture on day 28 and dull, hunched posture, decreased activity, and body weight loss on day 29), and F #222 from MD group was found dead approximately 15 min after dosing on Day 13 of age (no clinical signs were described). According to sponsor, findings at necropsy for those animals were suggestive of dosing trauma (the following findings were described in the report: cloudy abnormal color of the lungs and pericardium with abnormal contents cloudy fluid for M#61, cloudy yellow fluid in thorax for M #130, and nothing was described for F #222).

Clinical observations:

In the HD group, partially closed eyes were observed in all treated pups starting day 18 of age onwards from approximately 2-3h after dosing until the end of the day, however, as the treatment period progressed the daily duration of this sign decreased. Periodic decreased activity was reported for all pups in the HD group starting from Day 20 of age to day 44 (almost daily, observed intermittently from ~1-3 h after dosing at different observation times but does not appear to be continuous and seemed to dissipate by the end of the day). The incidence of this finding (decreased activity) was decreased towards the end of the study. It should be noted that these observations were recorded only in the group clinical observations table (Table 1, page 59) but were not reflected on the individual clinical observations table (Annex 1, page 307).

At MD partially closed eyes were recorded between Day 20 and Day 25 of age with decreased activity present on Day 24 of age.

No drug-related clinical signs were observed at the LD.

Body Weight:

Body wt gains were lower in animals treated with 0.16 or 0.63 mg/kg/day when compared with controls from the start of treatment (Day 12 of age) until weaning on Day 21 of age. These decreases ranged from ~90% at the beginning of dosing to ~25% by day 21 in the HD groups compared to control and from ~50% to ~10% in the MD groups compared to control. Some decreases in body wt gain were also observed in the LD groups but only for the first few days of treatment and were ≤ 40% compared to control. In the period after weaning the effect on body wt gain seemed to disappear and treated animals appeared to gain wt comparable to the control animals.

Decreases in absolute body wt were also observed during the same period (day12-21 of age) in MD and HD groups compared to the control group. The decreases ranged from 10 to 20% at the HD compared to control (in M: ~10% in subset I, and ~20% in subsets II and III, in F: ~10% in subset I, 17% in subset II, and 15% in subset III) and from 5-13% in the MD group (in M: 5% in subset I, 13% in subset II and 9% in subset III; in F: 5% in subset I, 12% in subset II and 9% in subset III) compared to control. By the end of the treatment (Day 50 of age) the difference in absolute body wt between M treated with HD (subset II and III) and control animals ranged from 7-8% (no difference in subset I) while in F treated with the same dose there was no difference between treated and control animals. After cessation of treatment (after day 50) the effect on body wt appeared to diminish and mostly seen in subset III M only (~4% decreased compared to control with some occasional statistical significance). It is of interest that the effect on body wt was the most while the animals were suckling, there was no indication whether the animals' suckling behavior was affected or not.

In F of Subset III, at the time of gestation mean body wt gain between Day 0 and Day 6 of gestation was lower in all treated groups compared to control but there was no drug relationship and the sponsor did not consider it drug-related. Body wt gains between Day 6 and Day 13 of gestation were comparable with those of the controls.

The following figures and tabulated data were provided by the sponsor (pages 63-69 and 267-273).

Males:

Appears this way on the original

Figure 1 - Group mean male bodyweight change (g) - Subset I

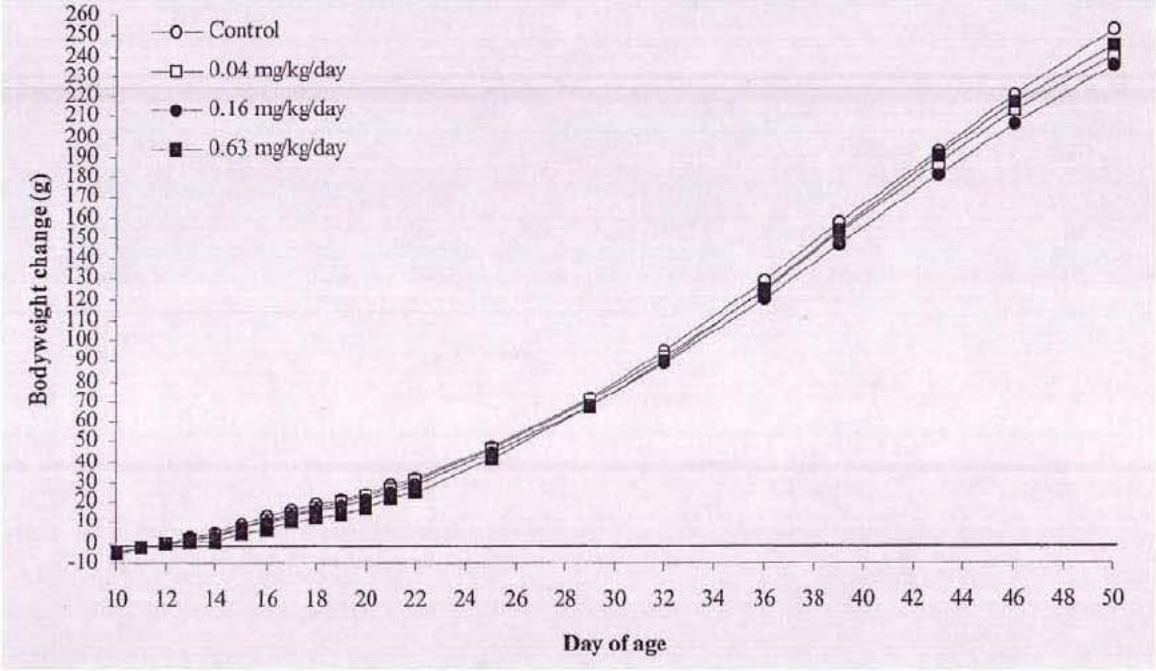


Table 2 - Group mean male bodyweights (g) - Subset I

(Page 1 of 1)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
10#	21.8 ± 0.6 (8)	22.4 ± 1.1 (8)	22.3 ± 1.0 (8)	23.1 ± 2.0 (8)
11#	24.3 ± 1.1	24.0 ± 1.6	25.0 ± 1.5	25.9 ± 1.8*
12#	26.4 ± 1.0	26.5 ± 1.6	27.3 ± 1.2	28.5 ± 2.1**
13	29.0 ± 1.3	28.0 ± 2.0	28.9 ± 1.4	28.9 ± 2.0
14	31.4 ± 1.8	30.2 ± 1.6	30.3 ± 1.7	29.3 ± 2.3
15	36.1 ± 2.0	34.3 ± 2.1	34.9 ± 2.7	33.0 ± 2.3
16	39.7 ± 2.4	37.7 ± 1.9	37.4 ± 2.5	35.5 ± 2.4
17	42.7 ± 2.0	41.2 ± 2.2	40.8 ± 2.5	38.6 ± 3.3
18	45.6 ± 2.0	43.6 ± 2.8	43.2 ± 2.9	40.7 ± 4.1
19	47.6 ± 2.2	46.9 ± 2.7	45.2 ± 3.5	42.9 ± 4.7
20	50.7 ± 2.6	49.5 ± 3.0	48.4 ± 4.5	46.0 ± 5.0
21	55.3 ± 2.7	54.0 ± 3.0	52.5 ± 5.1	50.4 ± 5.5
22	58 ± 3	57 ± 4	56 ± 4	54 ± 6
25	74 ± 3	73 ± 5	72 ± 5	70 ± 6
29	98 ± 4	97 ± 7	95 ± 5	96 ± 8
32	122 ± 6	119 ± 9	117 ± 5	119 ± 11
36	156 ± 9	151 ± 12	148 ± 6	154 ± 14
39	184 ± 11	179 ± 16	174 ± 6	182 ± 16
43	219 ± 13	213 ± 22	208 ± 8	219 ± 21
46#	247 ± 13	240 ± 25	234 ± 9	246 ± 22
50#	280 ± 15	267 ± 31	263 ± 9	274 ± 25

N = number of animals in mean
() = N, where different from the original
* = significantly different from the control, p<0.05
** = significantly different from the control, p<0.01
# = statistically analysed

Figure 2 - Group mean male bodyweight change (g) - Subset II

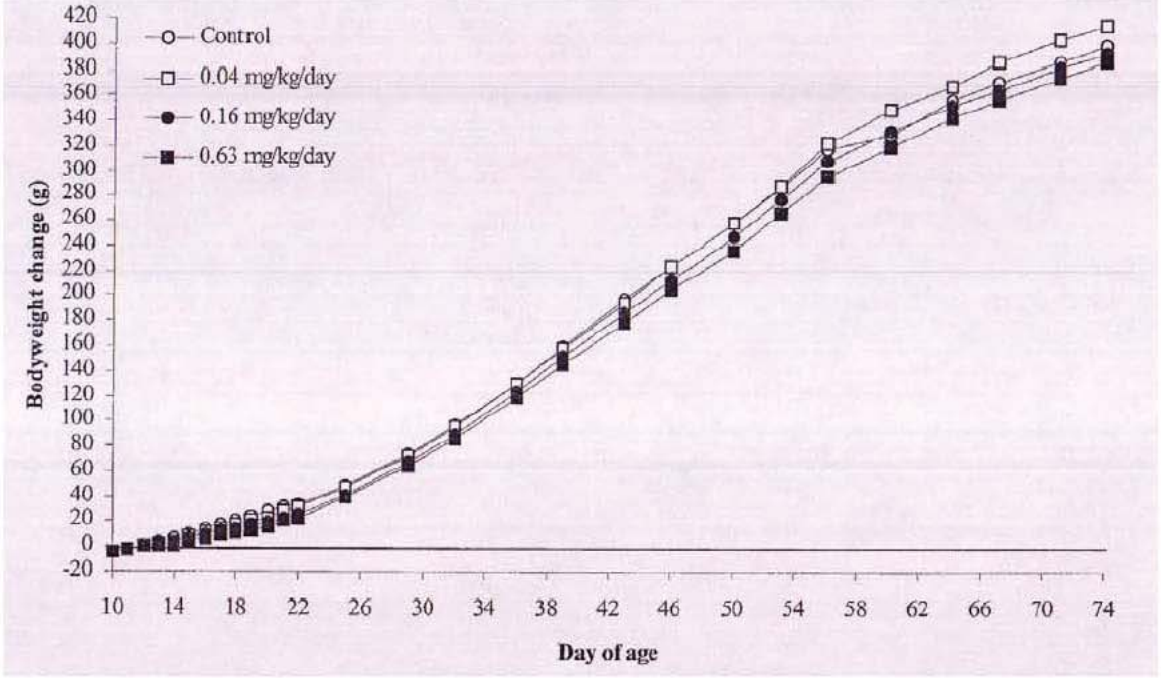


Table 3 - Group mean male bodyweights (g) - Subset II

(Page 1 of 1)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
10#	21.7 ± 2.2 (8)	22.9 ± 0.9 (8)	22.7 ± 1.2 (8)	22.9 ± 1.1 (8)
11#	24.1 ± 2.3	24.5 ± 1.5	25.1 ± 1.3	25.2 ± 1.1
12#	26.7 ± 2.4	27.0 ± 1.4	27.8 ± 1.3	27.8 ± 1.0
13	29.8 ± 2.4	28.7 ± 1.4	29.1 ± 1.7	28.3 ± 1.3
14	32.2 ± 2.2	30.8 ± 1.6	30.5 ± 1.7	29.1 ± 1.3
15	36.6 ± 2.4	35.2 ± 2.1	34.6 ± 1.5 ↓5%	33.1 ± 1.4 ↓10%
16	40.2 ± 2.9	38.3 ± 2.1	36.8 ± 1.7	34.5 ± 1.8
17	43.9 ± 3.6	42.2 ± 2.2	40.3 ± 2.2	37.8 ± 2.3
18	47.1 ± 3.9	45.0 ± 2.6	42.4 ± 2.3 ↓10%	39.8 ± 2.2 ↓15%
19	50.7 ± 4.5	47.1 ± 3.2	44.3 ± 3.1	41.1 ± 2.5
20	54.2 ± 4.3	50.4 ± 3.7	47.0 ± 3.0	43.7 ± 4.0
21	58.6 ± 5.0	54.7 ± 4.2	50.9 ± 2.9 ↓13%	47.6 ± 5.6 ↓19%
22	60 ± 5	58 ± 4	53 ± 3	51 ± 6
25	76 ± 6	74 ± 6	69 ± 4 ↓9%	68 ± 3 (11) ↓11%
29	101 ± 8	100 ± 8	95 ± 6	92 ± 5 (11)
32	124 ± 10	123 ± 10	117 ± 7	114 ± 7 (11)
36	158 ± 12	157 ± 14	152 ± 8 ↓4%	147 ± 11 (11) ↓7%
39	187 ± 15	185 ± 17	180 ± 9	174 ± 13 (11)
43	224 ± 18	222 ± 20	214 ± 11	207 ± 14 (11)
46#	251 ± 17	251 ± 23	242 ± 14	233 ± 16 (11)* ↓7%
50#	285 ± 19	285 ± 24	275 ± 16	265 ± 17 (11)* ↓7%
53	314 ± 21	316 ± 27	305 ± 20	294 ± 18 (11)
57	345 ± 23	350 ± 32	337 ± 19	325 ± 18 (11) ↓6%
60	356 ± 17	376 ± 36	361 ± 23	348 ± 19 (11) ↓2%
64	384 ± 24	395 ± 39	381 ± 19	371 ± 21 (11)
67	399 ± 26	414 ± 40	393 ± 22	386 ± 20 (11)
71	414 ± 29	431 ± 44	410 ± 23	403 ± 22 (11)
74#	426 ± 28	442 ± 49	421 ± 24	415 ± 22 (11)

N = number of animals in mean
() = N, where different from the original
* = significantly different from the control, p<0.05
# = statistically analysed

Figure 3 - Group mean male bodyweight change (g) - Subset III

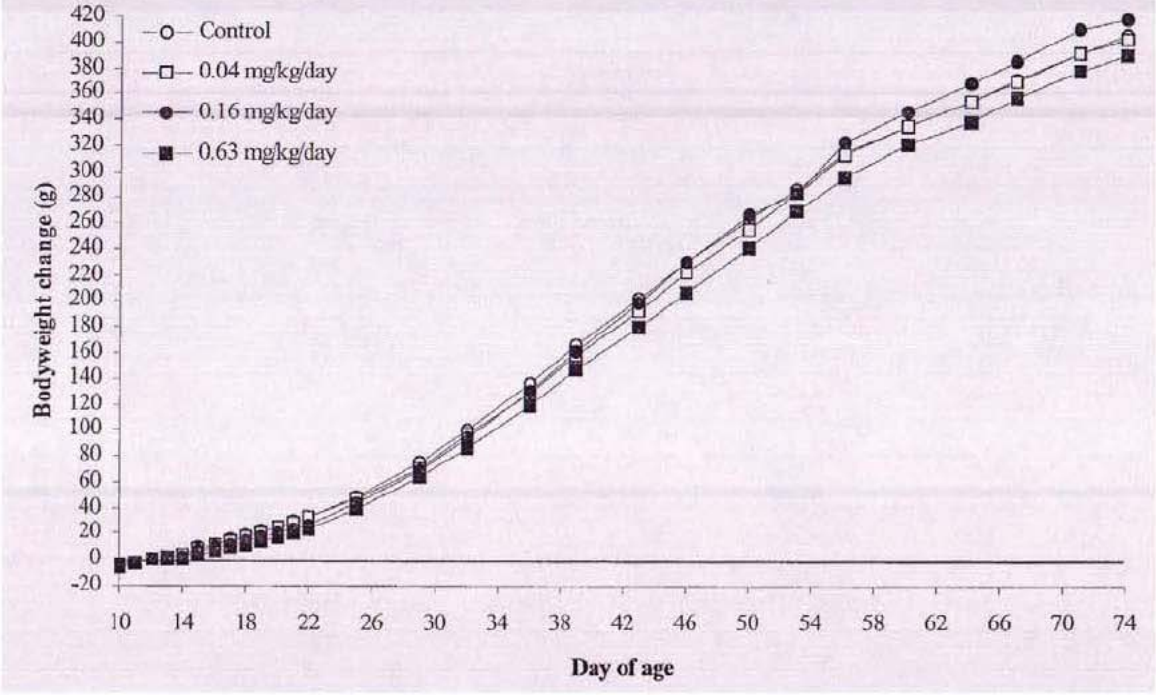


Table 4 - Group mean male bodyweights (g) - Subset III

(Page 1 of 2)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
10#	23.0 ± 1.2 (8)	22.7 ± 1.6 (8)	22.9 ± 2.1 (8)	22.2 ± 2.2 (8)
11#	25.8 ± 1.1	25.6 ± 1.4	26.1 ± 2.6	24.4 ± 2.5
12#	28.4 ± 1.4	28.3 ± 2.1	29.1 ± 3.1	26.8 ± 2.9
13	30.5 ± 1.5	30.1 ± 2.2	30.2 ± 3.6	27.0 ± 3.1
14	32.7 ± 1.9	32.4 ± 2.8	31.3 ± 4.0	27.5 ± 3.2
15	37.1 ± 2.5	36.2 ± 2.7	35.1 ± 4.4	31.1 ± 3.2
16	40.7 ± 2.6	40.0 ± 3.7	37.6 ± 4.3	33.4 ± 3.8
17	44.0 ± 2.5	43.7 ± 4.3	41.1 ± 4.1	36.5 ± 4.2
18	47.2 ± 2.5	46.3 ± 4.7	43.8 ± 4.4	38.8 ± 4.0
19	49.9 ± 2.6	49.3 ± 5.5	45.8 ± 4.6	40.8 ± 4.7
20	53.7 ± 2.9	53.1 ± 5.9	49.3 ± 4.9	43.5 ± 5.2
21	58.4 ± 3.3	57.4 ± 6.5	52.9 ± 4.4	47.3 ± 5.8
22	61 ± 4	61 ± 7	56 ± 4	51 ± 6
25	77 ± 5	76 ± 8	73 ± 4	67 ± 7
29	104 ± 5	99 ± 14	99 ± 6	92 ± 10
32	128 ± 6	125 ± 14 (11)	124 ± 6	114 ± 13
36	165 ± 8	157 ± 17 (11)	160 ± 9	147 ± 17
39	194 ± 10	186 ± 20 (11)	190 ± 11	175 ± 21
43	231 ± 12	221 ± 22 (11)	228 ± 15	208 ± 25
46#	258 ± 14	250 ± 23 (11)	259 ± 16	234 ± 27*
50#	291 ± 18	283 ± 27 (11)	295 ± 17	268 ± 32*
53	315 ± 22	311 ± 24 (11)	312 ± 14	297 ± 38
57	343 ± 24	341 ± 27 (11)	352 ± 15	324 ± 41
60	363 ± 27	364 ± 28 (11)	376 ± 13	348 ± 43
64	383 ± 27	382 ± 30 (11)	397 ± 12	366 ± 46
67	398 ± 32	398 ± 31 (11)	415 ± 14	385 ± 50
71	420 ± 33	420 ± 36 (11)	439 ± 16	405 ± 56
74	434 ± 30	430 ± 32 (11)	448 ± 17	417 ± 55

N = number of animals in mean
* = significantly different from the control, p<0.05
() = N, where different from the original
= statistically analysed

Table 4 - Group mean male bodyweights (g) - Subset III

(Page 2 of 2)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
78	450 ± 30	446 ± 36 (11)	467 ± 18	429 ± 58
81	462 ± 28	461 ± 37 (11)	481 ± 18	442 ± 60
85	472 ± 32	474 ± 37 (11)	497 ± 19	455 ± 65
89#	489 ± 28	487 ± 39 (11)	507 ± 20	468 ± 65
92#	504 ± 30 (8)	501 ± 21 (7)	523 ± 18 (8)	473 ± 42 (8)
95#	517 ± 35 (8)	508 ± 23 (7)	536 ± 19 (8)	486 ± 45 (8)

N = number of animals in mean
() = N, where different from the original
= statistically analysed

Females

Figure 4 - Group mean female bodyweight change (g) - Subset I

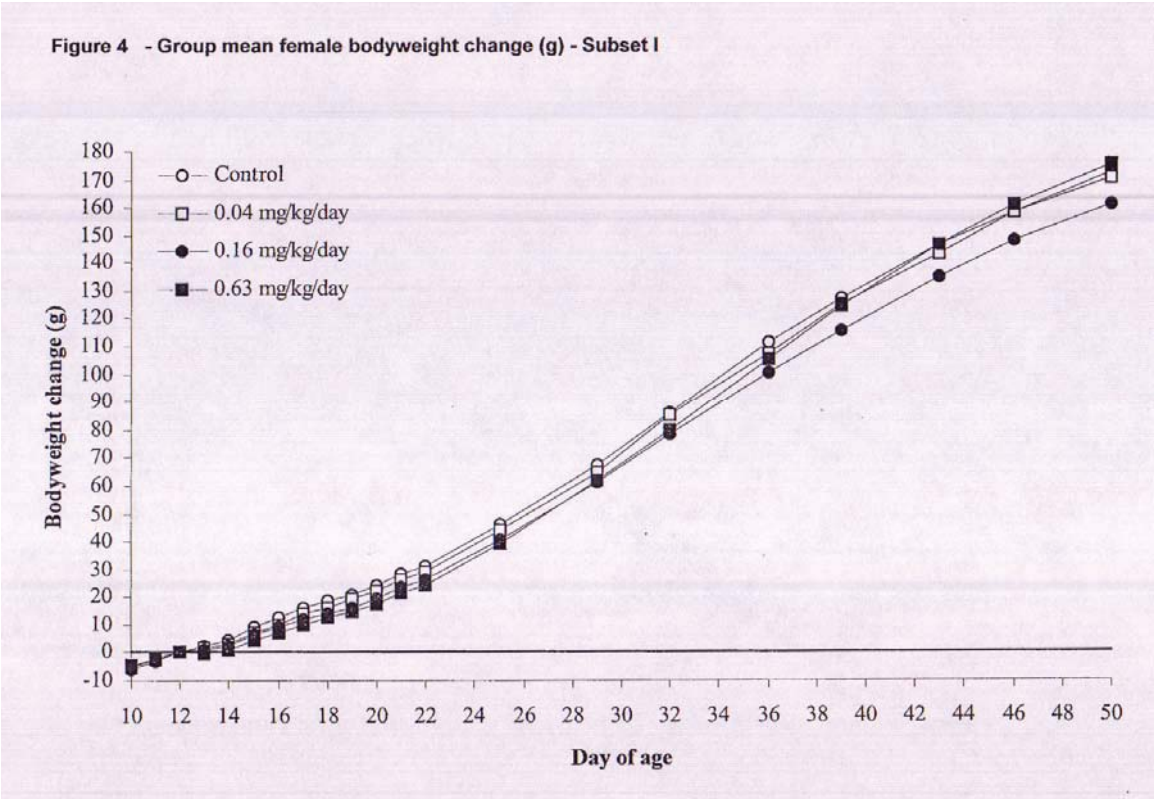


Table 5 - Group mean female bodyweights (g) - Subset I

(Page 1 of 1)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
10#	20.6 ± 1.3 (8)	21.4 ± 0.6 (8)	21.7 ± 0.8 (8)	21.8 ± 2.8 (8)
11#	23.6 ± 1.7	23.4 ± 1.0	24.6 ± 1.0 (11)	24.2 ± 2.9
12#	25.7 ± 1.6	25.9 ± 0.7	27.4 ± 1.3	26.9 ± 3.2
13	28.1 ± 2.2	27.3 ± 1.0	28.6 ± 1.3	26.8 ± 3.1
14	30.3 ± 2.3	29.2 ± 1.1	30.0 ± 1.2	27.6 ± 2.8
15	35.2 ± 2.4	33.0 ± 1.2	34.1 ± 2.5	31.5 ± 2.8
16	38.5 ± 2.6	36.0 ± 1.2	36.6 ± 1.9	34.2 ± 2.7
17	41.5 ± 2.3	39.8 ± 1.8	39.5 ± 1.7	37.1 ± 3.7
18	44.4 ± 2.8	42.0 ± 2.1	41.5 ± 2.4	39.3 ± 4.1
19	46.9 ± 3.0	45.3 ± 2.6	43.7 ± 3.0	41.4 ± 4.6
20	50.0 ± 3.3	48.1 ± 2.7	47.2 ± 3.9	44.5 ± 4.9
21	54.1 ± 3.9	52.5 ± 3.1	51.3 ± 4.2	48.5 ± 4.9
22	57 ± 3	55 ± 3	54 ± 4	51 ± 5
25	72 ± 3	70 ± 4	68 ± 4	66 ± 6
29	93 ± 5	91 ± 7	89 ± 6	89 ± 6
32	112 ± 7	111 ± 10	106 ± 6	107 ± 8
36	137 ± 9	133 ± 12	128 ± 6	132 ± 10
39	153 ± 10	151 ± 15	143 ± 6	151 ± 12
43	172 ± 12	169 ± 19	162 ± 6	173 ± 15
46#	184 ± 15	184 ± 20	175 ± 7	188 ± 15
50#	198 ± 16	196 ± 23	188 ± 9	202 ± 17

N = number of animals in mean
() = N, where different from the original
= statistically analysed

Figure 5 - Group mean female bodyweight change (g) - Subset II

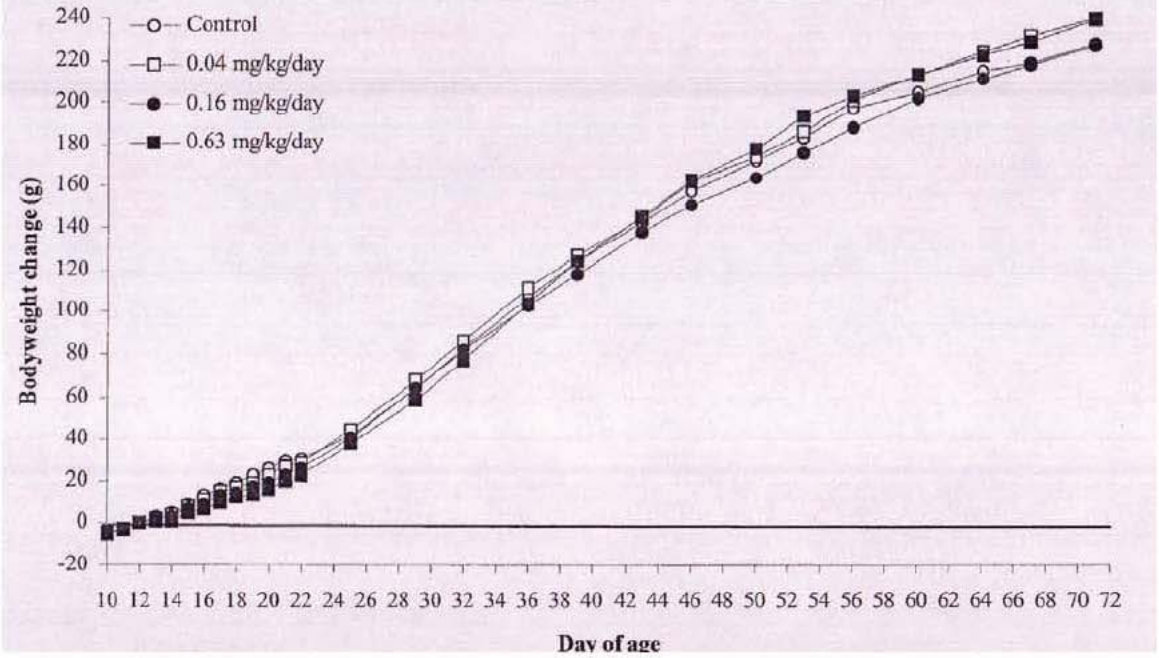


Table 6 - Group mean female bodyweights (g) - Subset II

(Page 1 of 1)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
10#	21.6 ± 1.9 (8)	22.4 ± 2.3 (8)	21.5 ± 0.7 (8)	21.8 ± 2.2 (8)
11#	24.1 ± 2.1	24.5 ± 2.3	24.0 ± 0.8	24.3 ± 1.8
12#	26.8 ± 2.3	26.8 ± 2.3	26.3 ± 1.1	26.9 ± 2.0
13	29.3 ± 2.2	28.5 ± 2.4	27.8 ± 1.7	27.4 ± 2.1
14	31.7 ± 2.7	30.7 ± 2.6	29.4 ± 1.8	28.0 ± 2.4
15	35.9 ± 2.6	35.0 ± 2.9	33.5 ± 1.7	32.1 ± 2.4
16	39.6 ± 3.1	38.1 ± 2.8	35.5 ± 2.0	33.9 ± 2.1 ↓10%
17	42.9 ± 3.3	41.5 ± 3.7	38.8 ± 2.3	36.7 ± 2.7
18	46.0 ± 3.8	43.9 ± 3.6	40.7 ± 2.4	38.8 ± 3.0
19	49.4 ± 4.1	45.9 ± 3.9	43.0 ± 2.7 ↓12%	40.0 ± 3.4 ↓20%
20	52.9 ± 4.5	49.6 ± 4.9	45.7 ± 3.4	43.0 ± 3.7
21	56.6 ± 4.7	54.2 ± 5.0	49.6 ± 3.5 ↓12%	47.1 ± 3.8 ↓17%
22	58 ± 4	56 ± 4	52 ± 3	50 ± 3 ↓14%
25	69 ± 5	72 ± 6	67 ± 4	65 ± 4
29	91 ± 6	95 ± 8	90 ± 5	86 ± 6 (11)
32	110 ± 7	113 ± 10	108 ± 5	104 ± 7 (11)
36	134 ± 9	138 ± 12	129 ± 6	131 ± 7 (11)
39	151 ± 11	154 ± 12	144 ± 7	151 ± 9 (11)
43	170 ± 12	172 ± 13	164 ± 7	173 ± 10 (11)
46#	185 ± 12	189 ± 15	177 ± 7	190 ± 11 (11)
50#	199 ± 15	201 ± 14	190 ± 12	205 ± 12 (11)
53	211 ± 16	213 ± 13	202 ± 13	221 ± 15 (11) ↑5%
57	224 ± 18	228 ± 13	214 ± 15	230 ± 13 (11)
60	232 ± 18	240 ± 12	228 ± 15	240 ± 13 (11)
64	242 ± 18	251 ± 14	237 ± 16	249 ± 12 (11)
67	246 ± 19	259 ± 14	244 ± 20	256 ± 13 (11)
71#	255 ± 19	267 ± 16	253 ± 17	266 ± 13 (11)

N = number of animals in mean
() = N, where different from the original
= statistically analysed

Figure 6 - Group mean female bodyweight change (g) - Subset III

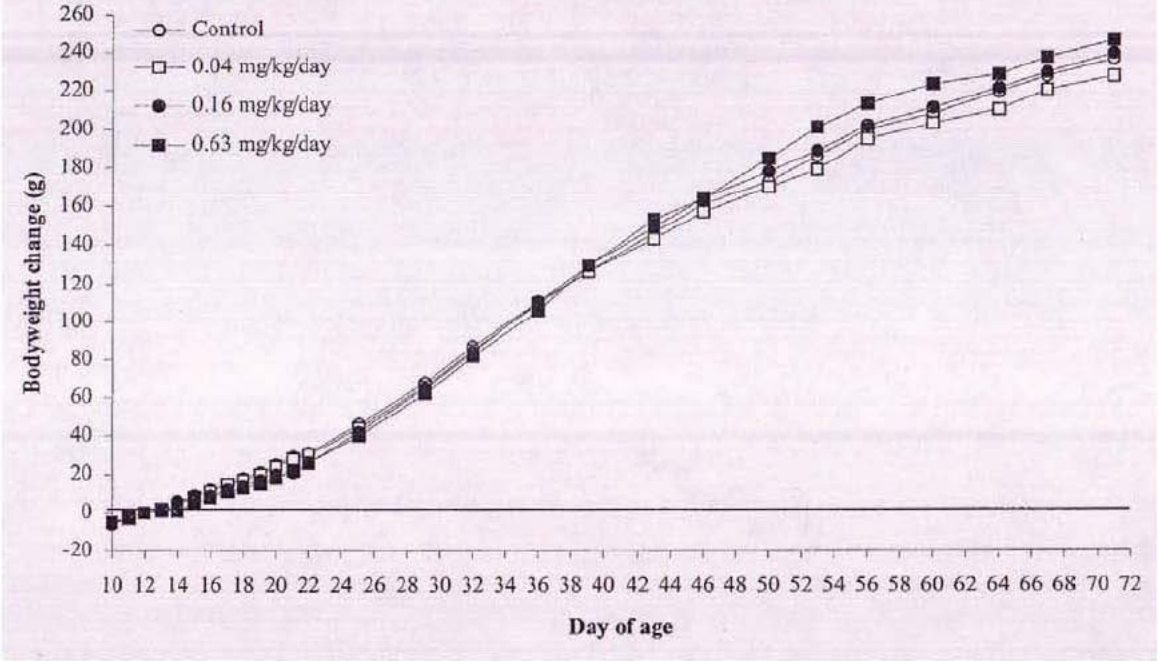


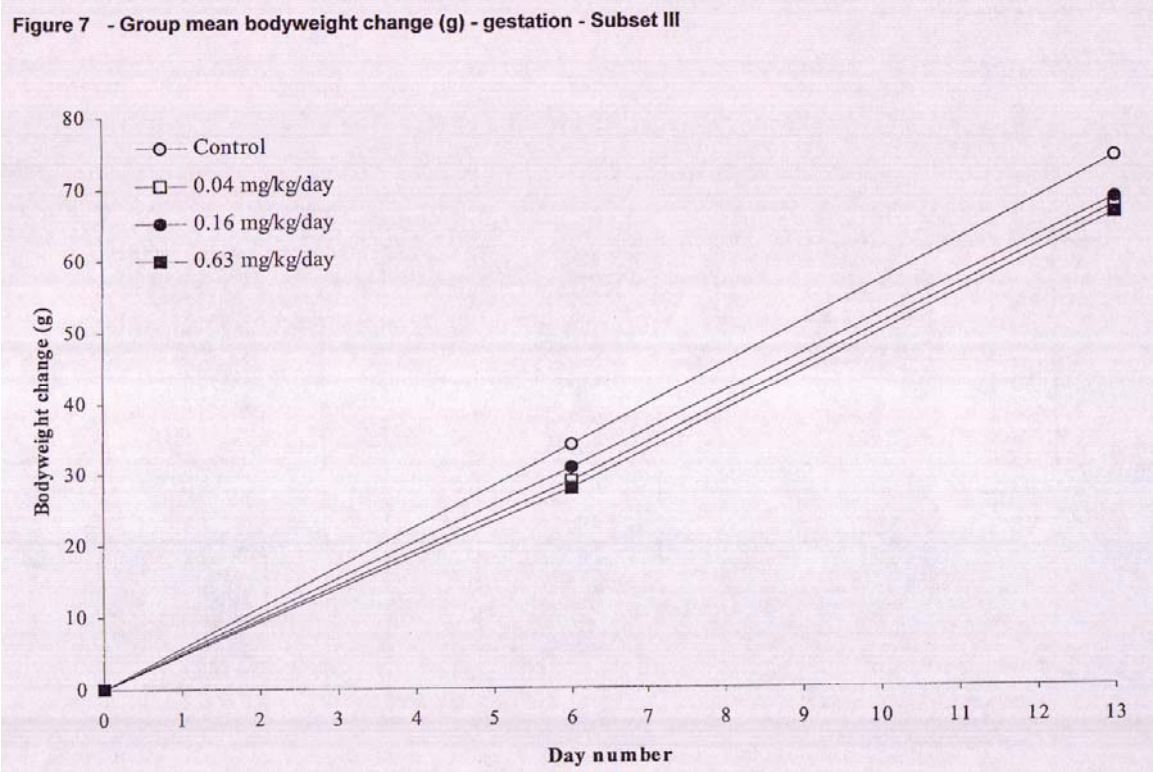
Table 7 - Group mean female bodyweights (g) - Subset III

(Page 1 of 1)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Day of age	Group 1	2	3	4
N	12	12	12	12
10#	22.1 ± 1.6 (8)	22.5 ± 1.7 (8)	22.1 ± 1.1 (8)	21.8 ± 0.9 (8)
11#	24.7 ± 1.7	24.6 ± 1.4	25.1 ± 2.3	24.0 ± 1.1
12#	27.2 ± 1.8	27.2 ± 1.8	28.0 ± 3.0	26.4 ± 1.6
13	29.4 ± 2.3	28.8 ± 2.0	29.4 ± 3.7	26.9 ± 2.2
14	31.8 ± 2.7	30.9 ± 2.4	30.5 ± 4.0	27.4 ± 2.1 ↓14%
15	35.7 ± 3.5	34.7 ± 2.3	34.1 ± 4.8	31.4 ± 2.2
16	39.2 ± 3.8	38.5 ± 3.6	36.9 ± 4.6	34.1 ± 2.5
17	42.4 ± 4.0	41.7 ± 4.1	40.1 ± 3.7	37.0 ± 2.8 ↓9%
18	45.6 ± 4.0	44.0 ± 4.4	42.3 ± 3.5	39.0 ± 2.8
19	48.6 ± 5.1	46.7 ± 5.1	44.6 ± 3.8	41.7 ± 2.8
20	52.2 ± 5.4	51.0 ± 5.6	47.9 ± 3.7	44.2 ± 3.3
21	56.2 ± 5.7	54.8 ± 5.7	51.4 ± 3.8 ↓9%	48.0 ± 3.6 ↓15%
22	58 ± 5	57 ± 6	54 ± 4	52 ± 3
25	73 ± 6	71 ± 6	70 ± 5	66 ± 3
29	95 ± 7	93 ± 8	93 ± 7	88 ± 5
32	114 ± 7	112 ± 10	112 ± 8	108 ± 7
36	138 ± 9	137 ± 12	139 ± 12	132 ± 8
39	153 ± 9	153 ± 14	157 ± 15	155 ± 12
43	173 ± 10	170 ± 14	177 ± 17	179 ± 17
46#	188 ± 11	184 ± 16	192 ± 22	190 ± 19
50#	200 ± 13	197 ± 18	206 ± 23	211 ± 22
53	213 ± 13	206 ± 18	217 ± 26	227 ± 24
57	227 ± 12	222 ± 21	230 ± 27	239 ± 29
60	235 ± 14	230 ± 22	239 ± 29	249 ± 28
64	246 ± 13	237 ± 22	249 ± 30	254 ± 26
67	254 ± 14	247 ± 23	257 ± 30	263 ± 26
71#	263 ± 13	254 ± 23	267 ± 30	272 ± 28

N = number of animals in mean
() = N, where different from the original
= statistically analysed



Food consumption:

Food consumption was not affected by treatment.

Pup Development (Subsets I, II, and III):

Pup development as assessed by timing of eye opening and papillary light response was comparable in all groups.

Long bone growth (Subsets II and III):

There was no difference between the control and the treated groups.

Locomotor activity:

There appeared to be no drug effect on locomotor activity as assessed by the rotarod test in both M and F on Day 29 of age (Subset I) and Day 64 (Subset II). All animals generally showed an improved duration on the rotarod with repeated runs. A wide variation in performance was seen but no consistent clear drug effect was observed.

Preyer Reflex:

When animals from Subset I were tested (Day 36 ± 2), two M from HD group and 1 F from MD group failed the test on two consecutive days. All animals in subset II (Day 65 ± 2) passed the test.

Figure Eight Maze:

Motor activity as assessed by Figure 8 test did not indicate a drug effect in F in subset III (Day 64 ± 1); however, mean group activity counts for M in HD in Subset III appeared to be higher than those for the control group especially after the second time interval (it was also noted that the number of animals with increased activity was higher in this group compared to the other groups).

Table 54 - Group mean motor activity counts - Day 64 ± 1 of age : Males - Subset III

(Page 1 of 1)

Group :	1	2	3	4
Treatment :	Control		Risperidone	
Dosage (mg/kg/day) :	0	0.04	0.16	0.63

Time interval	Group 1	2	3	4
N	12	11	12	12
1	172 ± 33	185 ± 29	163 ± 36	170 ± 26
2	101 ± 33	99 ± 45	95 ± 42	101 ± 38
3	36 ± 30	44 ± 39	39 ± 32	55 ± 37
4	12 ± 24	23 ± 28	10 ± 16	35 ± 44
5	11 ± 23	14 ± 32	11 ± 21	21 ± 29
6	8 ± 19	1 ± 4	5 ± 7	18 ± 23

N = number of animals in mean
Analysis of motor activity was performed using repeated measures ANOVA.
There was no evidence of a difference in the counts between groups for either the repeated time analysis (P=0.3035) or the individual analysis at any of the time points.

Table 55 - Group mean motor activity counts - Day 64 ± 1 of age : Females - Subset III

(Page 1 of 1)

Group	:	1	2	3	4
Treatment	:	Control		Risperidone	
Dosage (mg/kg/day)	:	0	0.04	0.16	0.63

Time interval	Group 1	2	3	4
N	12	12	12	12
1	218 ± 20	227 ± 27	222 ± 24	235 ± 34
2	152 ± 42	164 ± 27	147 ± 37	168 ± 35
3	115 ± 42	116 ± 53	105 ± 53	126 ± 57
4	69 ± 59	69 ± 54	95 ± 57	108 ± 63
5	50 ± 60	46 ± 44	52 ± 50	67 ± 61
6	34 ± 39	21 ± 29	36 ± 51	33 ± 46

N = number of animals in mean
Analysis of motor activity was performed using repeated measures ANOVA.
There was no evidence of a difference in the counts between groups for either the repeated time analysis (P=0.3035) or the individual analysis at any of the time points.

Learning test (Morris Water Maze):

The time it took to complete the exercise was generally shortened for all groups including the control over the four days. This improvement seemed to be seen by the third run on Day 1 (session 1). By day 4 most of the animals finished the exercise in less than 10 seconds.

There was no effect on the number of animals successfully finding the platform in either Subset I or II. The % of animals finding the platform successfully generally showed an increase by run 3 of Day 1. Further increases were observed on the following days and by Day 4, during runs 2 and 3, the number of animals finding the plat form reached 100% in almost all of the groups (the % of animals in the other groups was > 90%) The % of animals completing the exercise did not indicate a drug effect and there was no dose relationship.

The numbers of the quadrants entered by the control and the treated groups did not indicate a drug effect. However, after Day 3 animals seemed to enter quadrant # 4 (where the platform was placed) more times than any other quadrant, indicating successful learning.

The overall effect of treatment with the test article at the doses used did not indicate an effect on learning or memory at either of days tested (Day 46 or Day 68).

Sexual Development:

Vaginal perforation in F in both Subset I and II was not different between control and treated groups.

Balanoperputial separation in M of Subset I was statistically significantly delayed in the HD treated group compared to control (occurred on 44.7 in HD compared to day 42.8 in control group). However, in Subset II balanoperputial separation occurred earlier in M treated with MD and HD compared to control group (on Day 42.1 at MD and Day 42.2 at HD compared to Day 44.4 in control). The sponsor stated that the differences were not dose-related (in severity) and the inter-group differences were not considered to be associated with treatment.

Hormone Assessment:

At preputial separation in M pups, plasma prolactin levels were increased ~2 fold at MD and HD with statistical significance achieved at HD.

In F pups, prolactin levels at the time of vaginal perforation was increased in all test article treated groups compared to control with increases from 2.7-4 fold and the increases were dose-related and achieved statistical significance. See the following tables as provided by the sponsor (pages 1144-1145):

Johnson & Johnson Pharmaceutical Research & Development,
a division of Janssen Pharmaceutica N.V.

ENDO 1

EXPERIMENT : TOX - 6569
Oral Juvenile Toxicity Study in the Rat
R064766 - OR/GAV - RAT

ENDOCRINOLOGY
Mean values per dosage group
Preputial separation

Parameter	Unit	Dosage Groups (mg/kg) MALES Group 1	Group 2 0.04	Group 3 0.16	Group 4 0.63
Prolactine	ng/ml	21.13 (4.06)	18.67 (5.07)	40.09 (6.45)	44.08 (7.62) *

Standard Error is shown between brackets if more than 2 animals
Significance versus Group 1 computed by Mann-Whitney U test (two-tailed): * P<.05 ** P<.01 *** P<.001

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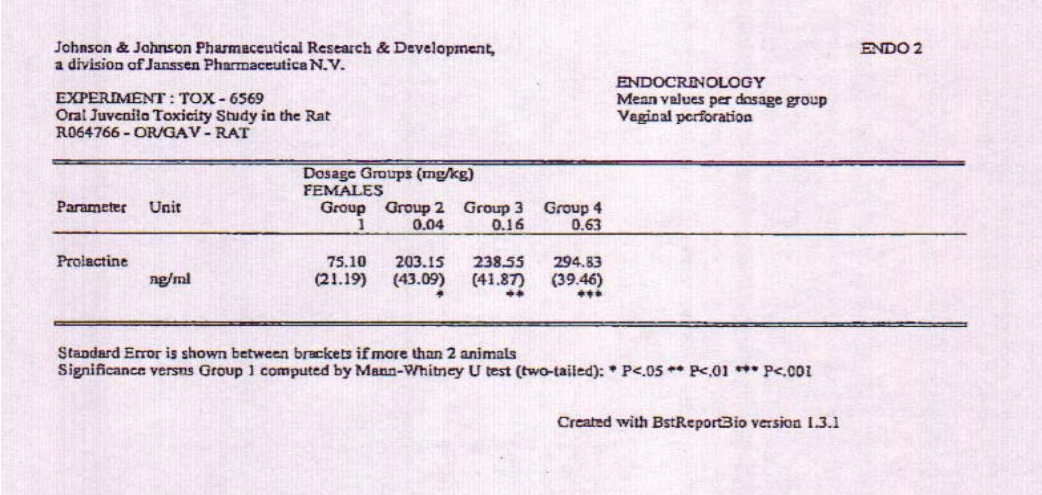

Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen Pharmaceutica N.V.

ENDO 2

EXPERIMENT : TOX - 6569
Oral Juvenile Toxicity Study in the Rat
R064766 - OR/GAV - RAT

ENDOCRINOLOGY
Mean values per dosage group
Vaginal perforation

Parameter	Unit	Dosage Groups (mg/kg) FEMALES Group 1	Group 2 0.04	Group 3 0.16	Group 4 0.63
Prolactine	ng/ml	75.10 (21.19)	203.15 (43.09) *	238.55 (41.87) **	294.83 (39.46) ***

Standard Error is shown between brackets if more than 2 animals
Significance versus Group 1 computed by Mann-Whitney U test (two-tailed): * P<.05 ** P<.01 *** P<.001

Created with BstReportBio version 1.3.1

Time course of mating-Subset III:

There was no difference between test article treated groups and control group as for the time taken by the Subset III animals to mate. The majority of animals in all groups mated within one estrous cycle.

Fertility and Mating Performance (Subset III):

There were no differences between control and test article-treated groups on copulation and fertility indices (the number of copulation plugs observed, the number of F with copulation plugs or the number of M that resulted in the formation of copulation plugs).

Pregnancy Data (Subset III):

Pregnancy parameters as assessed by the number of corpora lutea, implantations and live embryos and the extent of pre- and post-implantation losses were not different between control and animals treated with 0.04 or 0.16 mg/kg risperidone. However, in the group treated with 0.63 mg/kg/day, a slight increase in the number of implants and live embryos, which achieved statistical significance, was observed. The sponsor considered this finding as incidental since dosing of the animals stopped three weeks before the animals were paired.

Macroscopic findings:

Abnormal color was reported in the thymus of M in subset I (4/12 in control, 6/12 at LD, 7/12 at MD, and 7/12 at HD). Similar findings were not observed in M in other subsets nor in F of any of the other subsets. Abnormal size of the ovaries was reported for F in subset II (3/12 control, 6/12 LD, 7/12 MD, and 6/12 HD) and subset III (6/12 control, 8/12 LD, 8/12 MD, and 10/12 HD). There were no histopathological findings associated

with the gross findings in the ovaries, however, agonal changes/congestion was reported in animals with macroscopic changes in the thymus. The sponsor considered all these gross findings irrelevant.

Organ Weights:

In subset I a decrease in the absolute wt of the spleen was seen in both M and F at all doses (~15% compared to control in all groups, all reached statistical significance). This was reflected on the relative wt to body wt only in M (~12% for all groups). The sponsor considered this finding as irrelevant to treatment since there were no indications for effects on haematopoiesis. There was a decrease in absolute wt of the uterus of F (11% at LD, 15% at MD and 18% at HD with only HD reaching statistical significance). A decrease in the relative wt to body wt was seen only at HD (29%). The sponsor considered this change in the uterus in line with the histopathological changes observed in the ovaries and vagina and thus considered them to be treatment related.

In Subset II, there was a slight increase in absolute wt of the spleen in M at HD (12%, not statistically significance) with a comparable increase in the relative wt to body wt which was statistically significant.

In Subset III, the absolute weight of the thymus was increased in M at MD (33%) and HD (16%) which was also seen in the relative wt (21% at MD and 28% at HD). A decrease in the absolute wt of the prostate was seen in M at HD (20% not statistically significant). The absolute wt of the gravid uterus at HD was increased compared to control (19%) which was also seen in the relative wt (25%). The sponsor related the increase in the gravid uterus to the increased number of corpora lutea, implants and live embryos in this group, which was considered incidental and not drug related (see the Pregnancy Data section).

Bone marrow smears:

Individual variations were observed; however, these findings did not indicate a treatment related effect.

Microscopic findings:

In Subset I (animals sacrificed on Day 51-53 of age): changes in the vagina (disturbed oestrus cycling) were observed indicating a condition of pseudopregnancy in treated groups only (3/12 at LD, 4/12 at MD, and 10/12 at HD). In other animals where the vagina did appear to be cycling normally, there was an increased epithelial mucification of the vagina and cervix (4/12 at MD and 1/12 at HD) which is a condition that is not normally seen in rats of this age but is the normal status of the epithelium during pregnancy and pseudopregnancy.

In addition, other changes in the ovaries (active corpora lutea) were seen in treated animals only (1/12 at LD, 7/12 at MD, and 12/12 at HD).

In the uterus resting appearance was observed at MD and HD only (2/12 at MD and 10/12 at HD).

Changes in the mammary tissue (increased secretory activity) was also observed in F and M treated with the test article. The following table was prepared by the reviewer from data obtained from histopathology tables:

observation	sex	severity	control	0.04 mg/kg/day	0.16 mg/kg/day	0.63 mg/kg/day
Acinar proliferation/secretory activity	M	minimal	--	--	--	--
		slight	0	1	1	3
		moderate	--	--	--	--
	F	minimal	0	2	2	2
		slight	1	0	1	5
		moderate	0	0	0	2

In the spleen a slight increase in extramedullary haemopoiesis was observe in F at HD compared to control (5/12 in control group and 9/12 at HD described as slight); however the moderate findings were more in the control compared to the HD (2/12 controls and 0/12 at HD).

In Subset II (animals sacrificed approximately Day 97 of age):

Changes in the mammary tissue were observed in 1M and 2F from HD but not in the other groups.

In the ovaries, there was a slight increase in corpora lutea in HD group compared to the control group (slight 4/12 in control and 5/12 at HD, moderate 1/12 at HD).

In the spleen, extramedullary haemopoiesis was observed at higher incidence in the HD group in both M (2/12 in control and 8/12 at HD) and F (2/12 in control and 5/12 at HD).

In the liver there was a slightly higher incidence of focal hepatocyte degeneration/inflammation at HD compared to control in M (1/12 in control and 3/12 at HD) and F (1/12 in control and 3/12 at HD), all were described as minimal.

Subset III (animals sacrificed approximately Day 97 of age):

No treatment related findings in this subset.

Toxicokinetics:

The increase in concentration (for all the measured parameters) was almost dose proportional. There was no clear gender difference; however, a slightly higher levels were seen sometimes in F compared to M at some dosages but not a consistent finding. The maximum 9-OH-risperidone concentrations were 1.1 to 2.6 times higher than those of risperidone at all dose levels, while the AUC values for 9-OH-risperidone was between 2 and 3-fold higher than that of risperidone at all dose levels. The following tables summarize the mean plasma concentrations of all the parameters measured as reported by the sponsor (pages 130-132).

TABLE 2

Table 2A: Mean Plasma Concentrations (ng/mL) and Some Basic Pharmacokinetic Parameters of Risperidone in Rats on Day 16 of Age after Repeated Oral Dosing of 0.04, 0.16 or 0.63 mg/kg/day Risperidone from Day 12 to Day 16 of Age of a Juvenile Toxicity Study in the Rat.

	Day 16 of Age					
Time (h) Dose Group Gender	0.04 mg/kg/day 2		0.16 mg/kg/day 3		0.63 mg/kg/day 4	
	Male	Female	Male	Female	Male	Female
0	<0.500	<2.50	<0.500[1]	<0.500	1.06	<0.500[1]
1	1.36	2.24	11.6	10.7	35.6	52.0
4	0.719	0.875[1]	4.39	9.79	12.8	12.9
8	<0.500[1]	<0.500[1]	3.01	2.35	4.60	6.75
C_{max} (ng/mL)	1.36	2.24	11.6	10.7	35.6	52.0
T_{max} (h)	1	1	1	1	1	1
$t_{½\ (4\text{-}24h)}$ (h)	-[7]	-[7]	-[7]	1.9[5]	6.0	2.4[6]
$AUC_{0\text{-}8h}$ (ng.h.mL)	5.63	7.48	42.7	56.8	117	148
$AUC_{0\text{-}24h}$ (ng.h.mL)	-[4]	-[4]	-[4]	63.4	156	171
Male to Female ratios (C_{max})	0.6		1.1		0.7	
Male to Female ratios ($AUC_{0\text{-}8h}$)	0.8		0.8		0.8	
Male to Female ratios ($AUC_{0\text{-}24h}$)	-[3]		-[3]		0.9	
Dose-proportionality Ratios[2] (C_{max})			8.5	4.8	3.1	4.9
Dose-proportionality Ratios[2] ($AUC0_{.8h}$)			7.6	7.6	2.7	2.6
Dose-proportionality Ratios[2] ($AUC_{0\text{-}24h}$)			-[3]	-[3]	-[3]	2.7

[1] - Median calculated.
[2] - Dose proportionality versus lower dose.
[3] - Not appropriate or not calculable due to lack of enough data points.
[4] - Not appropriate as extrapolation value >25 %.
[5] - Timepoints used in $t_{½}$ - 4 and 8 hours.
[6] - Timepoints used in $t_{½}$ - 1 to 8 hours.
[7] - Values could not be reliably calculated.

Table 2B: Mean Plasma Concentrations (ng/mL) and Some Basic Pharmacokinetic Parameters of 9-OH Risperidone in Rats on Day 16 of Age after Repeated Oral Dosing of 0.04, 0.16 or 0.63 mg/kg/day Risperidone from Day 12 to Day 16 of Age of a Juvenile Toxicity Study in the Rat.

	Day 16 of Age					
Time (h) Dose Group Gender	0.04 mg/kg/day 2		0.16 mg/kg/day 3		0.63 mg/kg/day 4	
	Male	Female	Male	Female	Male	Female
0	<0.500[1]	<2.50[1]	2.82	1.12[1]	6.91	8.62
1	1.17	1.78	8.77	9.83	32.6	43.6
4	2.21	2.84	15.4	21.7	51.7	56.7
8	3.50	2.60	13.3	11.9	34.2	38.3
C_{max} (ng/mL)	3.50	2.84	15.4	21.7	51.7	56.7
T_{max} (h)	8	4	4	4	4	4
$t_{½ (4-24h)}$ (h)	-[2]	-[5]	7.9	4.7	6.9	7.4
AUC_{0-8h} (ng.h.mL)	17.1	18.7	99.3	118	316	364
AUC_{0-24h} (ng.h.mL)	-[2]	-[4]	208	191	589	682
Male to Female Ratios (C_{max})	1.2		0.7		0.9	
Male to Female Ratios (AUC_{0-8h})	0.9		0.8		0.9	
Male to Female Ratios (AUC_{0-24h})	-[2]		1.1		0.9	
Dose proportionality Ratios[3] (C_{max})			4.4	7.6	3.4	2.6
Dose proportionality Ratios[3] (AUC_{0-8h})			5.8	6.3	3.2	3.1
Dose proportionality Ratios[3] (AUC_{0-24h})			-[2]	-[2]	2.8	3.6
9-OH-risperidone/ risperidone Ratios (C_{max})	2.6	1.3	1.3	2.0	1.5	1.1
9-OH-risperidone/ risperidone Ratios (AUC_{0-8h})	3.0	2.5	2.3	2.1	2.7	2.5
9-OH-risperidone/ risperidone Ratios (AUC_{0-24h})	-[2]	-[2]	-[2]	3.0	3.8	4.0

[1] - Median calculated.
[2] - Not appropriate or not calculable due to lack of enough data points.
[3] - Dose proportionality versus lower dose.
[4] - Not appropriate as extrapolation value >25 %.
[5] - Values could not be reliably calculated.

Table 2C: Mean Plasma Concentrations (ng/mL) and Some Basic Pharmacokinetic Parameters of the Active Moiety (Risperidone + 9OH-Risperidone) in Rats on Day 16 of Age after Repeated Oral Dosing of 0.04, 0.16 or 0.63 mg/kg/day Risperidone from Day 12 to Day 16 of Age of a Juvenile Toxicity Study in the Rat.

	Day 16 of Age					
Time (h) Dose Group Gender	0.04 mg/kg/day 2		0.16 mg/kg/day 3		0.63 mg/kg/day 4	
	Male	Female	Male	Female	Male	Female
0	<1.00[1]	<1.00[1]	3.01	1.12[1]	7.97	9.42
1	2.52	4.02	20.4	20.5	68.2	95.5
4	2.93	3.46	19.8	31.4	64.5	69.6
8	3.82	2.78	16.3	14.2	38.8	45.0
C_{max} (ng/mL)	3.82	4.02	20.4	31.4	68.2	95.5
T_{max} (h)	8	1	1	4	1	1
$t_{½\ (4-24h)}$ (h)	-[2]	-[5]	7.1	4.2	6.7	7.0
AUC_{0-8h} (ng.h.mL)	22.9	25.6	144	176	439	524
AUC_{0-24h} (ng.h.mL)	-[2]	-[4]	270	258	751	888
Male to Female Ratios (C_{max})	1.0		0.6		0.7	
Male to Female Ratios (AUC_{0-8h})	0.9		0.8		0.8	
Male to Female Ratios (AUC_{0-24h})	-[2]		1.0		0.8	
Dose proportionality Ratios[3] (C_{max})			5.3	7.8	3.3	3.0
Dose proportionality Ratios[3] (AUC_{0-8h})			6.3	6.9	3.0	3.0
Dose proportionality Ratios[3] (AUC_{0-24h})			-[2]	-[2]	2.8	3.4

[1] - Median calculated.
[2] - Not appropriate or not calculable due to lack of enough data points.
[3] - Dose proportionality versus lower dose.
[4] - Not appropriate as extrapolation value >25 %.
[5] - Values could not be reliably calculated.

2.6.6.2 Discussion and Conclusions:

The death that was observed in one F in the HD group was probably not drug related based on the fact that a higher dose (2.5 mg/kg/day) used in the range finding study until PND 25 was not associated with death. In addition, the fact that it was the only death at this dose with no associated histopathological findings adds to the argument that this death is not drug related. The observation of convulsions in this animal during treatment before death could have been incidental and not drug related since it was an isolated finding in this animal.

The animals treated with 0.63 mg/kg/day presented periodic decreases in activity at certain times during the day after treatment. However, these signs were intermittent and seemed to dissipate by the end of the day and towards the end of the study they were no longer observed.

The effects on body wt in the main study using 0.63 mg/kg/day as the HD were variable among the different subsets of animals that were treated in a similar way with the compound up to PND 50. While there was a consistent effect on body wt between the different subsets up to PND 21 (time of weaning) this effect was seen in a less dramatic trend and with a variable magnitude from that point onwards to the end of the study in M and was not seen in F. It is not clear why an effect was not seen in F at the end of the study even though there was no significant difference in plasma levels between M and F.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Dose finding study (R064766):

Methods and observations:

Range finding study in juvenile rats	
# animals	8M/dose and 7-8F/dose
Test article	Risperidone Batch #ZR064766PUA373
Dose levels (oral by gavage)	0, 0.04, 0.16, 0.63 and 2.5 mg/kg/day A dose volume of 10 ml/kg
Administration period	PND 12 to 25 inclusive
TK	Day 25, 2/sex/group, at pre-dose, 1, 4, & 8 h post dose
Clinical observations	Daily for any abnormalities and/or change in behavior and for clinical signs of toxicity after dosing. Mortality twice daily
Body wt	Daily from PND 12 through PND 25
Necropsy	No necropsy (except if sacrificed prematurely)

Results:

Range finding study in juvenile rats	
Mortality	No drug-related mortalities
Clinical signs	1st or 2nd day M pups treated with 2.5 mg/kg/day were cold all over (only one was described in individual data, see review for more details), the next few days only extremities were described as being cold and appearing dark. These signs were not observed beyond day 17. One M treated with 2.5 mg/kg was dehydrated, had labored breathing and was cold on Day 14. Was not dosed on that day. Decreased activity and partially closed eyes at ~ 3h post dosing, from day 19-22 in all pups treated with 0.63 mg/kg and F treated with 2.5 mg/kg. No sings observed after these signs were finished. Rapid breathing and intermittently closed and partially closed eyes in all pups treated with 0.63 mg/kg/day and all F pups treated with 2.5 mg/kg on Day 24 and/or 25 from 2.5-7h post dosing. Rapid breathing was also observed in pups treated with 0.16 mg/kg/day. Observed 3h post dose to the end of the day. Unsteady gait at ≥ 0.63 mg/kg/day on day 24 and/or day 25 lasted from 0.5-1h post dosing. 1F treated with 0.63 mg/kg/day had splayed hindlimbs and decreased activity on PND 25. *Some of the previous signs were not observed in M at 0.25 mg/kg/day even though they were observed at the lower dose of 0.63 mg/kg/day*
Body wt	↓ in bd wt gain ~21% in M treated with 0.63 and 2.5 mg/kg/day mostly seen during the first 2 days. ↓ in absolute body wt ~14% compared to control in M treated with 0.63 and 2.5 mg/kg/day. In F treated with 2.5 mg/kg/day, Bd wt gain was less than the control for the first two days (2 g vs. 7 g in control). Absolute bd wt was ↓ in F treated with 2.5 mg/kg/day by 8% compared to control and by 13-15% in F treated with 0.63 mg/kg compared to control
NOAEL	0.04 mg/kg/day

Definitive study (R06466 of TOX6569):

Methods and observations:

Definitive study in juvenile rats	
# animals	36/sex/group: 3 subsets (I, II, or III of 12 rats/sex/subset) and12 animals/sex/group for a TK satellite group
Test article	Risperidone

	Batch #ZR064766PUA373
Dose levels (oral by gavage)	0, 0.04, 0.16, and 0.63 mg/kg/day
Treatment period	PND 12-50 inclusive (all subsets)
TK	PND 12 & 16 at pre-dose, 1, 4, and 8 h after dosing.
Clinical observations	Daily for changes in behavior and/or appearance and for signs of toxicity after treatment (all subsets)
Body wt	Daily from PND 11 until PND 21 and then twice weekly thereafter. F of subset III were also weighed on Days 0, 6, and 13 of gestation
Development and behavior	
Long bone growth	every two days during lactation then weekly thereafter (10 M and 10 F/group, subsets II & III)
Locomotor activity (rotarod)	PND 29 (subset I) & PND 64 (subset II)
Eye opening	Daily from PND 11 till occurrence (all subsets)
Papillary light reflex	PND 21 (all subsets)
Static right reflex	PND 5 (all subsets),
Preyer reflex (hearing test)	PND 36 (subset I) & PND 65 (subset II)
Motor activity (figure 8-activity maze with photobeam mountings)	PND 64 (subset III)
Learning and memory (Water Maze)	Day 46 (subset I) & day 68 (subset II)
Vaginal opening	PND 30 until occurrence (subset II)
Balanopreputial seperation	PND 40 until occurrence (subset II)
Hormone assessment	Prolactin levels. On the day that vaginal opening or balanopreputial separation occurred.
Reproductive capacity	At 10 weeks of age (PND 70, subset III) animals of subset III were paired up to 7 days. Vaginal smears were taken daily until sperm was found in smear. Stage of estrous cycle was determined, mating activity assessed by # of copulation plugs. Pregnant F were necropsied on gestation day 13 and pregnancy status was determined, # of corpora lutea, # of implantations, resporptions, live embryos.
Necropsy	All pups sacrificed or found dead
Organ wts and histopathology	See review for organs weighed and tissues and organs used for histopathology.

Results:

Definitive study in juvenile rats	
Mortality	1F from HD (0.63 mg/kg/day) died on PND 25 that was described as "convulsing during treatment" which might not be drug related *(no findings to indicate the cause of death in this animal besides the unexplained convulsions, no deaths were observed at a 2.5 mg/kg/day in the preliminary study up to PND 25).* Three deaths (1M from HD, 1F from MD, and 1 M from LD) were all due to gavage accidents.
Clinical signs	Partially closed eyes in all treated pups at HD starting on PND 18 onwards from 2-3 h after dosing until the end of the day and at MD between Day 20-25. Periodic decreases in activity in all pups at HD (from PND 18-44) with decreased incidence towards the end of the study. At MD decreased activity was observed in all pups on PND 24 only observed only once during the day.
Body wt	Body wt gain compared to control: for both M & F a ↓ ranged from 90% on PND 12 to 25% on PND 21 at HD, at MD ↓ ranged from 50% on PND 12 to 10% on PND 21, and ≤ 40% at LD the first few days. There was no effect beyond PND 21. Absolute body wt compared to control: in **M** ↓ at HD on PND 21 (10% in subset I, 20% in subsets II and III), and from 7-8% on PND 50 in subsets II & III and no effect in subset I. In mostly pups of subset III during the recovery period up to PND 90 there was a ↓ 4% that was occasionally statistically significant. At MD ↓ of 5% in subset I, 13% in subset II and 9% in subset III up to PND 25. No effect on PND 50. In **F** ↓ at HD (10% subset I, 17% in subset II, and 15% in subset III) on PND 21. No effect on PND 50. At MD ↓ of 5% in subset I, 12% in subset II and 9% in subset III on PND 21 and no effect on PND 50.
Development and behavior	No drug effect on several parameters (eye opening, papillary light reflex, long bone growth, locomotor activity as assessed by rotarod, sexual maturation, and learning and memory). Motor activity as assessed by Figure 8 test indicated an increase in M of subset III on PND 64 especially after the second time interval of testing. No effect was seen in subset I (PND 36) and no effect in F. In the Preyer Reflex test 2/10 M from HD and 1 F from MD all from subset I (tested on PND 36) failed the test on two consecutive days. All animals in subset II (PND 65) passed the test.
Hormone assessment	Prolactin levels were ↑ 2X in M treated with MD & HD compared to control (significant achieved at HD) at the time of preputial separation. In F an increase in prolactin was seen in all treatment groups (from

	2.7-4 fold) compared to control.
Reproductive assessment	No difference between control and treated groups for time to mate, fertility indices (# of copulation plugs, # of F with copulation plugs and # of M that resulted in copulation plugs) and in pregnancy parameters (# of corpora lutea, implantations and live embryos, pre and post-implantation losses). However, it should be noted that in HD group a slight increase in # of implants and live embryos was observed. The sponsor considered it incidental since dosing of animals stopped 3 weeks before animals were paired.
Gross findings	Abnormal size of the ovaries of some treated animals compared to control (no histopathological findings with this observation)
Organ wts	↓ in absolute wt of the uterus of treated F compared to control (11% at LD, 15% at MD, 18% at HD only HD reached statistical significance), and ↓ relative wt (29% at HD only). ↓ in absolute wt of prostate in M of subset III at HD (20%, not statist sign). ↑ in the absolute wt of the gravid uterus of F of subset III at HD (19%) and the relative wt (25%).
Histopathological findings	Changes in the vagina (disturbed oestrus cycle) indicating pseudopregnancy in treated animals only (3/12 at LD, 4/12 at MD, and 10/12 at HD). ↑ epithelial mucification of the vagina and cervix (not usually seen in rats of this age.) of treated animal that showed normal cycling (4/12 at MD, and 1/12 at HD). Active corpora lutea in treated animals only (1/12 at LD, 7/12 at MD, 12/12 at HD). Resting appearance in the uterus (2/12 at MD and 10/12 at HD). Acinar proliferation and secretory activity in mammary tissue in M & F (see table in review for incidence and severity).

Safety factors (animal plasma levels/human plasma levels):

Rat	**Dose**	**AUC** (ng.h/ml) **Active moiety**
(range finding study)	2.5 mg/kg/day (*F only*) @	1350
(Main study)	0.63 mg/kg/day @	820
Human		
Children **(Study RIS-USA-160)***	1 mg bid	316
Adolescent **(Study RIS-USA-160)***	1 mg bid	254

* values were obtained from Clinical Pharmacology and Biopharmaceutical Review of NDAs 20-272/SE1-036, 20-588/SE1-024, and 21-444/SE1-008 by Dr. John Duan. Human plasma levels were measured up to 12h post dosing and the AUC values presented here in the table were designated as AUCτ, ss.
@ AUC0-24h, values were calculated since blood samples were collected up to 8h post treatment

It should be noted that the (b) (4) and there were no data available for plasma levels at that dose. The human plasma levels presented in the previous table should be doubled assuming a linear dose relationship as suggested in the labeling for the compound. Comparing the animal to human data indicate that there is no adequate human coverage.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The conducted rat juvenile studies were submitted to support the long term use of risperidone in children and adolescents ages 5-16 years for the treatment of irritability associated with autism. The conducted studies consisted of a range finding study in which animals were treated from PND 12-25 orally by gavage and the main study in which animals were treated with doses chosen based on the range finding study from PND 12-50 with a recovery period of 2 weeks after the cessation of treatment in some animals in which neurobehavioral and reproductive parameters were evaluated after this recovery period.

From reviewing the data of the range finding study the reviewer was not comfortable with the doses chosen by the sponsor for the main study as reflected by the conclusion at the end of review of the range finding study. It appears that the main factor in deciding the dose limiting toxicity in the range finding study was the effect on body wt and body wt gain in animals treated with risperidone from PND 12-25. In that study the effect on body wt in M treated with a dose of 0.63 mg/kg/day was similar to that with a dose of 2.5 mg/kg/day and the effect in F was slightly higher at a dose of 0.63 mg/kg/day than that observed at a dose of 2.5 mg/kg/day. Therefore, it appears that the effect of the drug on body wt is not dose dependent and the effect seems to be seen at both doses (0.63 mg/kg/day and 2.5 mg/kg/day). Some clinical signs were observed at 2.5 mg/kg/day; however, they did not appear to last longer than the first few days of treatment at the beginning of the study and then were not observed and the animals appeared to do well after that. It is the view of the reviewer that the doses chosen for the main study based on the body wt effect are not based on a consistent dose effect since both the dose of 0.63 mg/kg/day and a dose of 2.5 mg/kg/day had similar effects on body wt and in such a situation the higher dose of the two (i.e. 2.5 mg/kg/day) should have been picked for the main study. As mentioned earlier some clinical signs were observed at a dose of 2.5 mg/kg/day and even though they were not long lasting and were not observed after the first few days this might add support to the conclusion that the dose of 2.5 mg/kg/day is the more appropriate as a HD for the main study since it was also associated with clinical signs of toxicity in addition to the effect on body wt. It is not clear why the sponsor chose a dose of 0.63 mg/kg/day and not 2.5 mg/kg/day for the main study even though

they had similar effects on body wt if that was the main determining factor. The sponsor stated that the dose of 2.5 mg/kg/day will be "too high of a dose level" in the main study mainly for its effect on body wt and body wt gain. If the sponsor was choosing the dose based on the body wt effect then the 2.5 mg/kg/day should have been picked because it resulted in similar effects to those seen at 0.63 mg/kg/day but if the sponsor avoided the 2.5 mg/kg/day due to the clinical signs observed with this dose then this decision might not have been optimal since these signs were not long lasting and the animals appeared to do well after that. If the sponsor thought the 2.5 mg/kg/day is too high for the main study, it was probably more logical to use a dose higher than 0.63 mg/kg/day which is only 1/4th of the HD used in range finding study.

The findings in the main study did not indicate a drug effect on a variety of the parameters that were evaluated except for the effect on prolactin levels which were elevated in both M (MD & HD) and F (all groups) compared to the control. There were some histopathological findings that might be associated with the increase in prolactin (mainly in the mammary tissues but also in the uterus, ovary and vagina). These effects on prolactin levels and the mammary tissue were also seen with risperidone treatment in adult rats.

It should be emphasized that that doses at which these effects produced by risperidone are not providing a large safety factor in humans (see human and animal plasma levels previously presented).

The reviewer is concerned about the validity of the HD used in the study and its acceptance as the MTD. The reviewer believes that the dose could have been higher than 0.63 mg/kg/day to be satisfactory as an MTD especially that this dose was only 1/4th of a dose that was considered as too high to be used for the main study in the range finding study. The reviewer is concerned that the lack of effects with treatment could be due to the low level of the HD used in the study especially in view of the low levels of human safety factors obtained from using this dose.

In previous communication with the sponsor, the sponsor was told that both a rodent and non-rodent juvenile animal studies will be needed for risperidone to be approved for the use in children of the proposed age (see correspondence to and from the sponsor to the division as summarized in review in DFS dated 6/4/04). Later on the sponsor was told that a rat juvenile study will be accepted and based on the findings of the rat study a dog juvenile study might be needed as a phase IV commitment (see meeting minutes dated 12/20/05). The reviewer still believes that a study in juvenile beagle dogs is needed regardless of the findings in the rat study and even as a Phase IV commitment to look into the effect of risperidone on sexual development in view of some findings in adult dogs in the prostate (increase of clear basal cells, fibrotic interstitial tissue and immature aspect of the prostate in dogs treated with 1.25 and 5 mg/kg/day for 3 months) and testes (incomplete spermatogenesis in M treated with 1.25 and 5 mg/kg/day for three months and degeneration of testicular tubules in M treated with 0.31, 1.25, and 5 mg/kg/day for 12 months) as was reported in the original NDA review (see the review by Dr. Lois Freed for the original NDA dated 4/30/93).

Conclusions:

Unresolved toxicology issues (if any):

The reviewer is not fully satisfied with the doses used in the definitive juvenile rat study based on the fact that a higher dose (2.5 mg/kg/day) that was used in the range finding study could have been a better dose than the dose used (0.63 mg/kg/day) in this study. Therefore, the doses used in the definitive rat study are not considered optimal. The concern is that the lack of effects seen in many aspects in this study might not be comforting because it is not clear if this lack of effect is a true finding for the effect of the drug or because the dose was not optimal especially in view of the small human safety factor. However, it should be pointed out that there were some effects observed with this dose that are commonly seen with risperidone treatment (the effect on prolactin) indicating that the dose used is effective even though it was not optimal (i.e. the MTD). The reviewer feels that even though the current rat study was not optimal in the doses used it can be used to conclude that no major concern can be expected at the coverage observed. However, the reviewer still believes that the sponsor should conduct another study in the rat as soon as possible after approval to investigate whether different findings might be seen at higher and more optimal doses with higher safety factors in humans.

In our original correspondence with the sponsor both a rodent and non-rodent studies were recommended for approval of the NDA. However, the sponsor submitted only the rodent study and the decision on the non-rodent study was apparently negotiated to be dealt with after the review of the rodent study. In addition, the reviewer believes that a juvenile animal study in dogs is to be conducted also as phase IV commitment as soon as possible regardless of the findings from the rat study since some findings were observed in adult dogs with risperidone treatment especially in the male reproductive system.

Recommendations: The submitted rat juvenile study will be considered satisfactory but not optimal and will be accepted for approval, however, another study with more optimal doses and higher human safety factors is to be conducted as soon as possible after approval as a Phase IV commitment. In addition, a dog juvenile study is to be conducted as soon as possible as phase IV commitment based on the findings in adult dogs in the male reproductive system (See Dr. Freed's review).

Suggested labeling:

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Appears this way on the original

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/s/

Ikram Elayan
6/22/2006 04:14:09 PM
PHARMACOLOGIST

Barry Rosloff
6/22/2006 06:24:35 PM
PHARMACOLOGIST

NDA#: 21444
Reviewer: Ikram Elayan
Date review completed: 25 May 2004
Division: DNDP
Sponsor: Johnson & Johnson
Drug: Risperdal® (risperidone)
Submission: sNDA 21444 S-008 submitted December 19th 2003 supporting the use of Risperdal in the treatment of Autism (cross reference to sNDA 20-272/S-036 and 20-588/S-024).

Background:
The sponsor is proposing to market the drug for (b) (4) in a population of an age range of 5-16 years. In a response from the Division dated February 25th 2004 the following recommendations were conveyed to the sponsor:

"*Since you intend to market Risperdal for* (b) (4) *young children as well as in adolescents, two studies in juvenile animals (rodent and non rodent) need to be conducted. We recommend that you start these studies as soon as possible.*"

In response to this recommendation J&J responded on 2 April 2004 acknowledging the Division's request and committing to conduct a rodent study only. However, the Division responded to this proposal on May 4th 2004 as follows:

"*In your submission dated April 2, 2004 you propose to conduct a juvenile toxicity study in only one animal species (i.e., rat), based on the extent of previous clinical (pediatric and adult) and nonclinical experience. However, we continue to believe that juvenile studies in rodent and nonrodent are needed to support the use of risperidone for autism, based on the age of the intended patient population (≥5 years) and the adverse effects on male reproductive organs (testis, prostate) observed in the oral toxicity studies of risperidone in dogs (NDA 20-272).*"

The sponsor responded to the Division's recommendation on May 10th 2004 by committing to completion of both rodent and rodent studies as a Phase IV commitment.

Proposed Draft Protocols for rodent study:

Proposed Design Outline

J&JPRD has begun to design a juvenile toxicity study in rats and a draft outline for your input follows.

Description	Details
Test article	Risperidone
Study type	Juvenile Toxicity Study
Species	Crl. CD rat
Number / sex / group	Main - 30 /sex/group Subset I - 15 /sex/group Subset II - 15 /sex/group Satellites (TK)- as required
Number of groups	4 : Control and three treated
Dose levels	3: low, intermediate, high
Allocation	All group in a litter
Route of administration	Oral gavage
Commencement of dosing	Day 10/12 post-partum
Duration of dosing	Subset I – Day 10 – 50 of age Subset II – Day 10 – 50 of age
Dose volume	10 ml/kg
Age at initiation	Observations to commence Day 7 post-partum Post-coital age to be evenly distributed through groups
Culling	Litters culled Day 4 post-partum to appropriate even numbers of males and females
Weaning	Day 21 post-partum
Observations	
Routine clinical observation	Daily
Bodyweight	Daily during lactation and twice weekly thereafter
Food consumption	Twice weekly from weaning
Long bone growth	Every two days during lactation weekly thereafter
Reflex ontogeny	At least two measures assessed pre-weaning
Eyes open	From Day 12
Vaginal opening	From Day 30
Preputial separation	From Day 40

Sensory function	According to standard procedures, at least once post-weaning and again post-treatment in Subset II
Motor function (including habituation)	Assessed post-treatment in Subset II
Learning and memory	Assessed post-treatment in Subset II
Hormone assessment	Onset of puberty; prolactin
Toxicokinetics	During lactation (between days 14 and 17)
Mating Phase	Commencing when animals are at least 10 weeks old and after completion of the neurobehavioural assessments- Subset II only
Necropsy	Subset I - At the end of treatment (Day 50) Subset II - Males once fertility is confirmed, Females Day 13/14 of pregnancy
Histopathology	Full histopathology and including detailed examination of brain, peripheral nerves, testes and ovaries

Reviewer's Comments on the proposed draft rodent protocol:

The draft protocol appears generally adequate; however, the following recommendations are to be conveyed to the sponsor:

1- for all the neurobehavioral studies, the tests should be conducted both during the treatment period and at the end to the treatment after an appropriate washout period. Different subsets of animals should be used for the "during" and "after" treatment tests. For example of the proposed subsets (I and II), subset I is to be tested for all the neurobehavioral tests during treatment and subset II is to be tested at the end of treatment after an appropriate washout period. In addition, subset II can be used for fertility studies after being tested in the neurobehavioral tests after the appropriate washout period at the end of the treatment period.

Proposed Draft Protocol for non-rodent study:

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PROPOSED STUDY OUTLINE

Juvenile toxicity study in the dog: Proposed Study Design

Description	Details
Test article	Risperidone
Study type	Juvenile Toxicity Study
Species	Beagle dog (male only)
Number males/ group	Subset I - 6/group (C, L, M, H dose groups) Subset II - 4/group (C and H dose recovery groups) (in total 32 animals)
Number of groups	4 : Control and three treated
Proposed dose levels	0.31 – 1.25 – 5 mg/kg/day
Route of administration	Oral gavage
Commencement of dosing	~ 2 weeks post-weaning (approximately 10 weeks of age)
Duration of dosing	9 months (subset I-II)
Duration recovery period	Up to 3 months (C and H dose animals in subset II)
Dose volume	5 ml/kg
Allocation	Litter mates to be evenly distributed between groups
Observations	
Routine clinical observation	Daily
Body weight	Weekly
Food consumption	Weekly
Clinical pathology	Timepoints (to be decided)
Hormone assessment	Testosterone and prolactin Timepoints (to be decided)
Sperm assessment	Sperm count, morphology and motility (CASA) Timepoints (to be decided)
Toxicokinetics	at start and end of dosing period
Necropsy	Subset I - At the end of treatment (at the age of 11 m) Subset II - At the end of recovery (at the age of 14 m), once sperm analysis and histopathology of target organs of Subset I animals are completed
Histopathology	Full histopathology of male genital organs

Reviewer's comments on the non-rodent draft protocol:

The following recommendations are to be conveyed to the sponsor to address of some of the deficiencies that were recognized in the proposed draft protocol:

1- both male and female dogs are to be included in the studies and not only males as proposed.

2- Neurological examinations including evaluation of gait, head posture and coordination such nerve reflexes, papillary light reflex, palpebral reflex, pain perception, gag reflex, and evaluation of the neck, forelimbs, and hind limbs including placing, spinal reflexes, and flexor reflex are to be performed during treatment predose and after dosing and during the recovery period.

3- The hormonal and sperm assessment are to be conducted during treatment, during the recovery period, and after the recovery period to evaluate sexual maturation.

4- A full histopathology examination is to be conducted with emphasis on the brain and the reproductive organs of both males and females.

Recommendations:

I generally agree with the proposed draft protocols with the provided previous recommendations; however, I believe that these studies should be done as soon as possible and not as a phase IV commitment.

The following information should be relayed to the sponsor:

1. Regarding the protocol for the rat juvenile study, the protocol appears to be adequate except that assessment of neurobehavioral development (i.e., motor and sensory function, learning and memory) needs to be conducted during treatment and after an appropriate washout period following the cessation of treatment (in order to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals need to be used at the two assessment times. Therefore, neurobehavioral testing could be conducted in subset I during treatment and in subset II following cessation of treatment (after an appropriate washout period). As you have planned, reproductive effects should be evaluated after cessation of treatment following completion of the neurobehavioral assessment (i.e., in subset II).

2. The protocol for the dog juvenile study needs to be revised as follows:

(a) the study should be conducted in both males and females, not only in males as proposed.

(b) a detailed neurological examination needs to be conducted at the end of the treatment period (prior to the last dose) and at the end of the recovery period.

(c) evaluation of cardiovascular parameters should be conducted.

(d) hormonal and sperm assessment should be conducted at the end of the treatment and recovery periods.

(e) the histopathological evaluation needs to include examination of a full battery of tissues, in addition to a thorough evaluation of male reproductive organs.

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/s/

Ikram Elayan
6/1/04 08:35:45 AM
PHARMACOLOGIST

Lois Freed
6/1/04 09:03:53 AM
PHARMACOLOGIST
I agree with Dr. Elayan’s recommendation that the juvenile animal studies be completed (and reviewed) prior to approval.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-272/S-036
Drug Name:	Risperdal ® Risperidone
Indication:	Autistic Disorder
Applicant:	Johnson & Johnson
Date:	12/19/2003
Review Priority:	Priority
Biometrics Division:	I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader James Hung, Ph.D., Acting Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	June Cai, M.D., Clinical Reviewer Paul Andreason, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Melina Griffis, R. Ph.

Keywords: ANCOVA

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Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The current submission is for indication of (b) (4) . The primary analyses from (b) (4) studies, RIS-CAN-23, RIS-USA-150 Part 1, (b) (4) provide statically significant evidence that risperidone treated subjects were better than placebo treated subjects in the corresponding primary endpoints of each study.

1.2 Brief Overview of Clinical Studies

There are (b) (4) studies in the current submission. Studies RIS-CAN-23, RIS-USA-150 Part 1, (b) (4)

Study RIS-CAN-23 was a randomized, 8-week double-blind, parallel-group, multicenter study to assess the safety and efficacy of risperidone versus placebo in the treatment of symptoms of Autistic Disorder and other PDDs in children aged 5 to 12 years inclusive. Eighty subjects (41 and 39 subjects in the risperidone and placebo groups, respectively) were randomized in the study with 38 in placebo and 37 in risperidone groups, respectively, included in the ITT population. The dose was oral solution 0.02 to 0.06 mg/kg/day. The primary efficacy parameter was the change from baseline to end point in the Irritability subscale of the Aberrant Behavior Checklist (ABC). Clinical Global Impression of Change (CGI-C) was one of secondary endpoints. The primary analysis was ANCOVA. It was conducted in Canada.

Study RIS-USA-150 Part 1 was a multicenter, randomized, 8-week double-blind, placebo-controlled, parallel group, flexible-dose study in children and adolescents between the ages 5 and 17 years 2 months with Autistic Disorder. Risperidone was dosed twice daily and flexibly according to weight (up to 2.5 mg/day for subjects weighing <45 kg and up to 3.5 mg/day for subjects weighing ≥45 kg). One hundred and one subjects (49 and 52 subjects in the risperidone and placebo groups, respectively) were randomized and treated in the study for the ITT population. The co-primary efficacy parameters for this study were the change from baseline in Irritability subscale scores of ABC and CGI-C at end point. The primary analyses were ANCOVA for the change from baseline in Irritability subscale scores of ABC, and CMH for CGI-C. It was conducted in USA.

(b) (4)

(b) (4)

The following table lists p-values for the primary analyses of (b) (4) studies.

Study	Variable	Placebo	Risperidone	R - P	p-value
RIS-CAN-23	Mean change of ABC_Irritability Week 8 LOCF	38 -6.5	37 -12.1	-5.6	.0001
RIS-USA-150 Part 1	Mean change of ABC_Irritability Week 8 LOCF	52 -3.5	49 -14.9	-11.4	.0001
	CGI-I Responders Week 8 LOCF	11.5% 6/52	75.5% 37/49	60%	.0001

(b) (4)

For Study RIS-CAN-23, one secondary analysis of CMH for CGI-C gives p-value .0001. (b) (4) The p-value for final analysis presented in the above table didn't adjust interim analyses.

1.3 Statistical Issues and Findings

Although RIS-USA-150 was sponsored by National Institute of Mental Health, the primary analyses presented in this submission either adopted or modified (discussed with the Agency) from the original protocol specified analyses. This reviewer thinks that the primary analyses presented in this submission for RIS-USA-150 are appropriate.

2. Introduction

2.1 Overview

There are (b) (4) studies in the current submission. Studies RIS-CAN-23, RIS-USA-150 Part 1, (b) (4)

Study RIS-CAN-23 was a randomized, 8-week double-blind, parallel-group, multicenter study to assess the safety and efficacy of risperidone versus placebo in the treatment of symptoms of Autistic Disorder and other PDDs in children aged 5 to 12 years inclusive. Eighty subjects (41 and 39 subjects in the risperidone and placebo groups, respectively) were randomized in the study with 38 in placebo and 37 in risperidone groups, respectively, included in the ITT population. The dose was oral solution 0.02 to 0.06 mg/kg/day. The primary efficacy parameter was the change from baseline to end point in the Irritability subscale of the Aberrant Behavior Checklist (ABC). CGI-C – change in clinical global impression of severity was one of secondary endpoints. The primary analysis was ANCOVA. It was conducted in Canada.

Study RIS-USA-150 Part 1 was a multicenter, randomized, 8-week double-blind, placebo-controlled, parallel group, flexible-dose study in children and adolescents between the ages 5 and 17 years 2 months with Autistic Disorder. Risperidone was dosed twice daily and flexibly according to weight (up to 2.5 mg/day for subjects weighing <45 kg and up to 3.5 mg/day for subjects weighing ≥45 kg). One hundred and one subjects (49 and 52 subjects in the risperidone and placebo groups, respectively) were randomized and treated in the study for the ITT population. The co-primary efficacy parameters for this study were the change from baseline in Irritability subscale scores of ABC and CGI-C at end point. The primary analyses were ANCOVA for the change from baseline in Irritability subscale scores of ABC, and CMH for CGI-C. It was conducted in USA.

(b) (4)

(b) (4)

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

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3. Statistical Evaluation

3.1 Evaluation of Efficacy

Text, tables and figures presented in Section 3.1.1 to 3.1.3 are mainly from the applicant's submission.

3.1.1 Study RIS-CAN-23

3.1.1.1 Objective

The primary objective of the study was to assess the superiority over placebo of risperidone oral solution 0.02 to 0.06 mg/kg/day in the treatment of behavioral symptoms, as measured by the primary efficacy variable, in children aged 5 to 12 years inclusive with Autistic Disorder and other PDDs.

3.1.1.2 Study Design

RIS-CAN-23 was a randomized, double-blind, parallel-group, multicenter 8-week study to assess the safety and efficacy of risperidone oral solution 0.02 to 0.06 mg/kg/day versus placebo in the treatment of symptoms of Autistic Disorder and other PDDs in children aged 5 to 12 years inclusive. The choice of the dose range and duration of treatment with study medication was selected on data from small open-label pilot studies in children with Autistic Disorder.

The total study duration was 8 weeks. Study medication was started at a dose of 0.01 mg/kg/day and increased to 0.02 mg/kg/day on Day 3. Depending upon the response on Day 8, the dose could be increased by a maximal dose increment of 0.02 mg/kg/day. Thereafter the dosage was raised or lowered at weekly intervals as judged necessary by the clinician. However, increments were not allowed to exceed 0.02 mg/kg/day and the maximal permitted dose was 0.06 mg/kg/day.

3.1.1.3 Efficacy Measures

The primary efficacy variable was the change from baseline at end point on the Irritability subscale of the Aberrant Behavior Checklist score (ABC). The ABC was measured at screening/baseline and at all subsequent visits, weeks 1, 2, 3, 5, 7, and 8.

The ABC consisted of 58 items and was scored by the parent or caregiver, under the guidance of the investigator. The scores for each of the items ranged from 0 to 3; lower scores indicated a better condition: 0 = no problem, 1 = slight problem, 2 =moderate problem, 3 = severe problem. The ABC consisted of 5 subscales viz., Irritability, Lethargy and social withdrawal, Stereotypic behavior, Hyperactivity/non compliance and Inappropriate speech. The primary efficacy endpoint is the change from baseline at endpoint in the irritability sub-scale of the ABC. Irritability (range 0-45) subscale is the total of the 15 items listed below.

Injures self on purpose	Mood changes quickly
Aggressive to others (verb/phys)	Cries over minor annoyances and hurts
Screams inappropriately	Stamps feet or bangs objects or slams doors
Temper tantrums	Deliberately hurts himself/herself
Irritable and whiny	Does physical violence to self
Yells at inappropriate times	Tantrums when does not get own way
Depressed mood	Cries and screams inappropriately
Demands must be met immediately	

Clinical Global Impression of Change (CGI-C) was one of secondary endpoint.

3.1.1.4 Statistical Analysis Plan

The primary efficacy variable will be analyzed by using an analysis of covariance (ANCOVA) model with treatment and center as factor and the baseline score as covariate based on ITT population using LOCF.

3.1.1.5 Study Population

Table 3.1.1.5.1 shows the disposition of subjects by treatment group and reasons for discontinuation.

Table 3.1.1.5.1 Subject Completion/Discontinuation Information (Study RIS-CAN-23; ITT Analysis Set)

Termination Type Termination reason	Placebo (N=39)	Risperidone (N=40)
Completed	34 (87.2)	38 (95.0)
Withdrawn	5 (12.8)	2 (5.0)
Adverse event	1 (2.6)	1 (2.5)
Insufficient response	2 (5.1)	1 (2.5)
Subject withdrew consent	2 (5.1)	0

Table 3.1.1.5.2 presents demographic baseline data in the ITT analysis set.

Table 3.1.1.5.2 Demographics
(Study RIS-CAN-23; ITT Analysis Set)

Characteristic	Placebo (N=39)	Risperidone (N=40)	Total (N=79)
Age (years)			
Mean (SD)	7.3 (2.32)	7.6 (2.33)	7.5 (2.31)
Median	7.0	7.0	7.0
Range	5 - 12	5 - 12	5 - 12
Sex; No. (%)			
Female	7 (17.9)	11 (27.5)	18 (22.8)
Male	32 (82.1)	29 (72.5)	61 (77.2)
Race; No. (%)			
Black	6 (15.4)	6 (15.0)	12 (15.2)
Caucasian	28 (71.8)	27 (67.5)	55 (69.6)
Oriental	1 (2.6)	0	1 (1.3)
Other	4 (10.3)	7 (17.5)	11 (13.9)
Weight (kg)			
Mean (SD)	27.59 (8.620)	31.23 (14.459)	29.43 (12.003)
Median	24.00	27.50	26.00
Range	17.0 - 52.0	16.0 - 91.3	16.0 - 91.3
DSM-IV Axis I; No. (%)			
Autistic disorder	28 (71.8)	27 (67.5)	55 (69.6)
Asperger's disorder	7 (17.9)	5 (12.5)	12 (15.2)
Childhood disintegrative disorder	0	1 (2.5)	1 (1.3)
PDD-NOS	4 (10.3)	7 (17.5)	11 (13.9)
Domiciliary Status; No. (%)			
Other	6 (15.4)	3 (7.5)	9 (11.4)
Parents	33 (84.6)	37 (92.5)	70 (88.6)
Vineland Adaptive Behavior Score			
N	38	40	78
Mean (SD)	52.2 (19.84)	46.6 (13.07)	49.3 (16.85)
Median	54.5	46.0	51.0
Range	19 - 96	22 - 76	19 - 96

PDD-NOS = pervasive developmental disorders – not otherwise specified

The 2 treatment groups were comparable with respect to age, sex, race, baseline weight and domiciliary status. The majority of subjects were male (77.2%) and Caucasian (69.6%).

The most frequent DSM-IV Axis I diagnosis of PDD was Autistic Disorder (67.5% and 71.8% for risperidone and placebo groups, respectively) followed by Asperger's disorder (12.5% and 17.9% for risperidone and placebo groups, respectively).

The Vineland Adaptive Behavior Score (VABS) was used to characterize adaptability of subjects. The mean score was comparable between the 2 groups with mean ± SD of 46.6 ± 13.07 and 52.2 ± 19.84 in the risperidone and placebo groups, respectively.

The mean total score on the Childhood Autism Rating Scale (CARS) was similar in the risperidone and placebo groups (3.1.1.5.3). In the risperidone group 23 (57.5%) subjects had severe, and 17 (42.5%) had mild/moderate CARS Scores. In the placebo group 21 (53.8%) had CARS scores that were severe and 18 (46.2%) subjects had mild/moderate CARS scores.

Table 3.1.1.5.3 Childhood Autism Rating Scale (CARS)
(Study RIS-CAN-23; ITT Analysis Set)

	Placebo (N=39)	Risperidone (N=40)
Total Score		
Mean ± SD	39.1 ± 6.7	38.9 ± 5.3
Median	38.0	38.5
Min-Max	31-53	31-51
Classification of Rating Scale, N (%)		
Mild/moderate (31 - 36)	18 (46.2)	17 (42.5)
Severe (≥ 37)	21 (53.8)	23 (57.5)

Cross-reference: Attachment 1.2

3.1.1.6 Applicant's Efficacy Results

All randomized subjects who received at least 1 dose of study medication were included in the intent-to-treat analysis set, which was used for all efficacy analyses presented in this report. Seventy-nine subjects, 39 in the placebo group and 40 in the risperidone group, were included in this analysis set. Two risperidone subjects (4153, 4173) did not have any baseline score of the Irritability subscale. Also, 1 subject (4150) in the risperidone group and 1 subject (2105) in the placebo group did not have any postbaseline values (and hence no values for end point) although the subjects had a nonmissing baseline value. Change from baseline could not be calculated for these 4 subjects, so the analysis of change from baseline to end point in Irritability subscale included 38 placebo subjects and 37 risperidone subjects.

A summary of the results from the analysis of the Irritability subscale of ABC at end point is presented in Table 3.1.1.6.1 for LOCF data. The mean changes from baseline at end point in the Irritability subscale were -6.5 (SD = 8.41) and -12.1 (SD = 5.81) in the placebo and risperidone treatment groups, respectively. Treatment with risperidone was significantly ($p < 0.001$) more effective than placebo as measured by the change from baseline in the Irritability subscale of ABC. The least squares mean difference in the change from baseline in the risperidone group compared with that in the placebo group was -6.3 points with corresponding 95% confidence interval (-9.4, -3.2).

Table 3.1.1.6.1 Irritability Subscale of the ABC at End Point (Study RIS-CAN-23; ITT Analysis Set – Restricted to Subjects with End Point Data Only)

	Placebo		Risperidone	
	N	Mean (SD)	N	Mean (SD)
Baseline	38	21.2 (9.74)	37	18.9 (8.84)
End point	38	14.7 (11.46)	39	6.9 (5.52)
Change from baseline at end point:				
Mean (SD)	38	-6.5 (8.41)	37	-12.1 (5.81)
Least squares mean[a] (SD[b])		-4.8 (6.62)		-11.2 (6.62)
Between-group difference in LS means (95% CI)[a]		—		-6.3 (-9.4, -3.2)
p value[a]		—		<0.001

[a] Between-treatment group comparison based on ANCOVA model including treatment, investigator as factors, and baseline value as covariate.
[b] Pooled SD based on ANCOVA model

Clinical Global Impression - Change was secondary endpoint. Results from the analysis of the CGI-C score at end point are provided in Table 3.1.1.6.2. There was a higher percentage of subjects in the risperidone treatment group (54%) than in the placebo group (18%) who had CGI-C scores in the "very much improved" or "much improved" categories at the 8-week end point. The overall distributions of the CGI-C score in the placebo and risperidone groups were significantly ($p < 0.001$) different based on the modified ridit scores (i.e., the Van Elteren test derived from rank scores) controlling for center effect.

Table 3.1.1.6.2 Clinical Global Impression of Change (CGI-C) of Subject's Condition Rating at End Point (Study RIS-CAN-23; ITT Analysis Set)

Category of change	Placebo (N=38) n (%)	Risperidone (N=39) n (%)
Very much improved	1(2.6)	3(7.7)
Much improved	6(15.8)	18(46.2)
Minimally improved	8(21.1)	13(33.3)
Unchanged	17(44.7)	4(10.3)
Minimally worse	3(7.9)	0
Much worse	2(5.3)	1(2.6)
Very much worse	1(2.6)	0

p <0.001 based on Van Elteren test controlling for center.

3.1.2 Study RIS-USA-150 PART 1

3.1.2.1 Objective

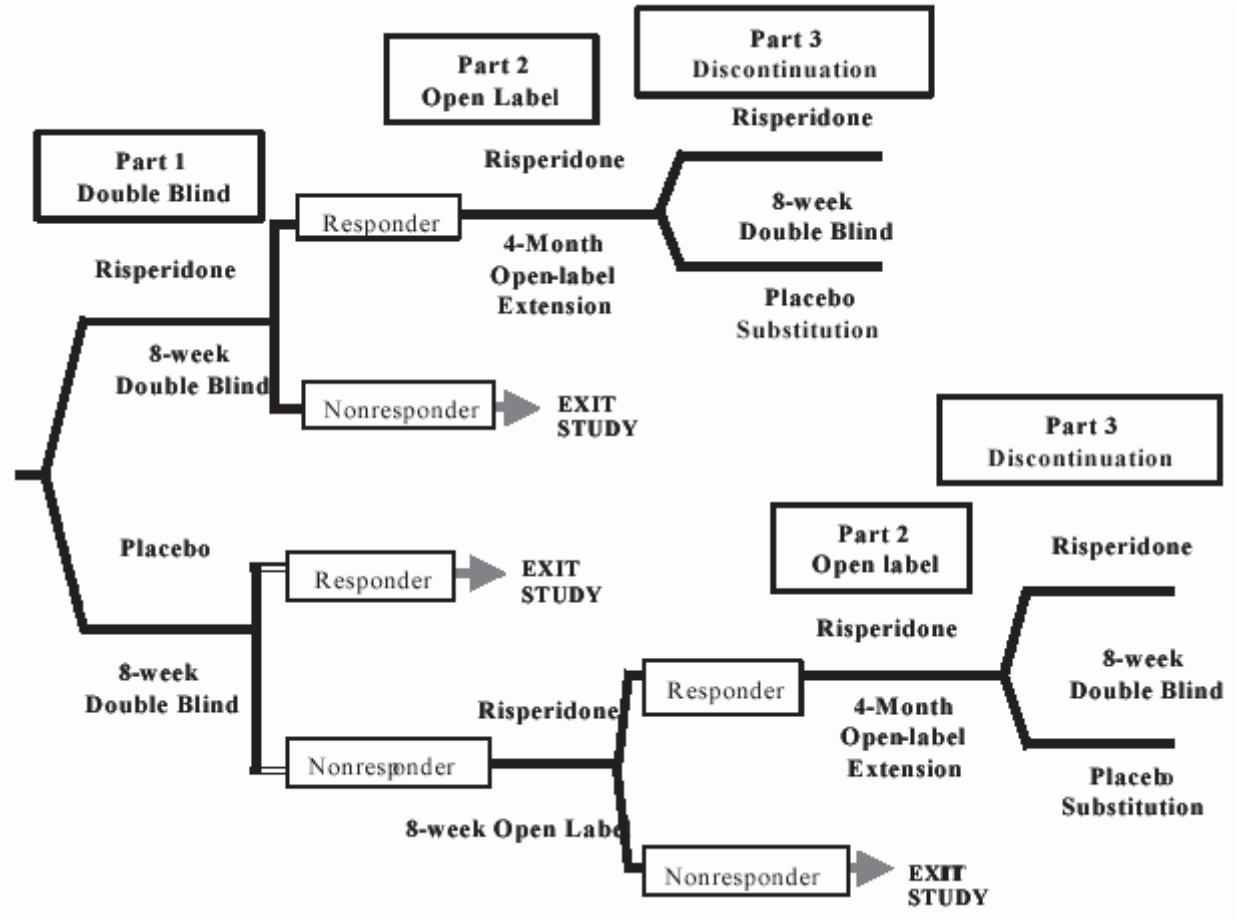
The primary purpose of this study was to compare the relative safety and efficacy of risperidone and placebo in the treatment of children and adolescents with Autistic Disorder. The hypotheses tested were risperidone will be more effective than placebo in reducing impulsive aggression, agitation, self-injurious behavior, and troublesome repetitive behavior associated with autism; and risperidone will result in more sedation (transient) and weight gain than placebo.

3.1.2.2 Study Design

RIS-USA-150 Part 1 was a randomized, 8-week double-blind, placebo-controlled, parallel group, flexible-dose study to assess the efficacy and safety of risperidone in children and adolescents with Autistic Disorder that was conducted in the United States at 5 centers. Each center enrolled 20-25 subjects for a total sample size of 100-120 subjects. The dose range and duration of treatment were based on small, open-label pilot studies in children with Autistic Disorder.

At the end of double-blind treatment, subjects were categorized as responders or nonresponders. Responders in the risperidone group could enter a 4-month, open-label risperidone treatment period. Nonresponders in the placebo group (subjects randomized to placebo who did not meet response criteria) entered an 8-week open-label treatment period with risperidone. Responders from this treatment period entered an additional 4 months of open-label risperidone treatment. Those subjects who responded to placebo and those subjects who did not respond to risperidone were discontinued from the study. Results from only the first 8-week double-blind part of the study are summarized in this report (See Figure 3.1.2.2.1). Results from the open label treatment periods and the subsequent double-blind randomized withdrawal period are summarized in a separate document.

Figure 3.1.2.2.1 Study Design



3.1.2.3 Efficacy Measures

The co-primary efficacy variables are the change from baseline in irritability sub-scale scores of Aberrant Behavior Checklist (ABC) and Clinical Global Impression of Change (CGI-C) response ("much" or "very much improved") at endpoint. The CGI-C was measured on the following 7-point scale: very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse.

3.1.2.4 Statistical Analysis Plan

For ABC, to assess the change in Irritability subscale from baseline to the endpoint, the primary analysis model will be a repeated measures analysis model.

For CGI-C, the percentage of responders in the risperidone group at endpoint was compared to the percentage of responders in the placebo group with a chi-square test.

RIS-USA-150 Part 1 was conducted by RUPP Autism Network with sponsorship from the National Institutes of Mental Health (NIMH). The analyses presented in this report are re-analysis of data from RIS-USA-150 according to J&JPRD standards. This re-analysis is based on the pre-planned statistical analyses that were specified in the protocol for Part 1 of RIS-USA-150.

The protocol-specified primary analysis method for the Irritability subscale of the ABC was a repeated measures model. As a result of the request by the United States Food and Drug Administration that took place prior to performing the analyses presented in this filing, the ANCOVA model was used as the primary analysis method. The repeated measures model was used as a secondary analysis method.

3.1.2.5 Study Population

Table 3.1.2.5.1 shows the disposition of subjects by treatment group and reasons for discontinuation.

Table 3.1.2.5.1 Subject Completion/Discontinuation Information (Study RIS-USA-150; ITT Analysis Set)

Termination Type Termination reason	PLACEBO (N=52) n (%)	RISPERIDONE (N=49) n (%)
Completed	34 (65.4)	46 (93.9)
Discontinued	18 (34.6)	3 (6.1)
Adverse event	1 (1.9)	1 (2.0)
Insufficient response	12 (23.1)	2 (4.1)
Subject lost to follow-up	2 (3.8)	0
Subject noncompliant	1 (1.9)	0
Subject withdrew consent	1 (1.9)	0
Subject ineligible to continue the trial	1 (1.9)	0

Note: Percentages calculated with the no. of subjects in each group as denominator.

As shown in Table 3.1.2.5.1, subjects in the placebo group began discontinuing from treatment sooner (i.e. during the .11-day time interval) than those in the risperidone group (during the 33-39 day time interval).

At baseline, there were no clinically meaningful differences between treatment groups in demographic variables. Table 3.1.2.5.2 presents demographic baseline data in the ITT analysis set.

Table 3.1.2.5.2 Demographics
(Study RIS-USA-150; ITT Analysis Set)

	PLACEBO (N=52)	RISPERIDONE (N=49)	TOTAL (N=101)
Age, years			
N	52	49	101
Category, n (%)			
5-12 years	49 (94.2)	46 (93.9)	95 (94.1)
>12 years	3 (5.8)	3 (6.1)	6 (5.9)
Mean (SD)	8.5 (2.45)	8.1 (2.88)	8.3 (2.66)
Median	8.0	7.0	8.0
Range	5 – 14	5 - 16	5 – 16
Sex, n (%)			
N	52	49	101
Female	9 (17.3)	10 (20.4)	19 (18.8)
Male	43 (82.7)	39 (79.6)	82 (81.2)
Race, n (%)			
N	52	49	101
Black	6 (11.5)	4 (8.2)	10 (9.9)
Caucasian	33 (63.5)	34 (69.4)	67 (66.3)
Hispanic	5 (9.6)	2 (4.1)	7 (6.9)
Oriental	4 (7.7)	5 (10.2)	9 (8.9)
Other	4 (7.7)	4 (8.2)	8 (7.9)
Weight, kg			
N	51	45	96
Mean (SD)	38.55 (25.480)	33.32 (17.537)	36.10 (22.159)
Median	31.70	26.20	29.80
Range	16.0 - 163.1[a]	18.4 - 104.3	16.0 - 163.1
Height, cm			
N	48	45	93
Mean (SD)	133.49 (15.726)	131.10 (17.498)	132.34 (16.559)
Median	132.00	127.00	128.00
Range	102.0 - 174.0	104.0 - 178.7	102.0 - 178.7
Body mass index			
N	48	44	92
Mean (SD)	20.49 (10.072)	18.79 (5.249)	19.68 (8.133)
Median	18.05	17.30	17.55
Range	13.0 - 78.7[a]	13.7 - 36.1	13.0 - 78.7
Domiciliary status: lives with, n (%)			
N	52	49	101
Other	4 (7.7)	5 (10.2)	9 (8.9)
Parents	48 (92.3)	44 (89.8)	92 (91.1)
Vineland adaptive behavior score			
N	52	48	100
Mean (SD)	39.2 (14.60)	41.1 (15.19)	40.1 (14.84)
Median	36.5	41.0	38.5
Range	21 – 109	20 - 75	20 – 109

[a] The maximum body weight and body mass index in the placebo group are a result of a data entry error for weight.

Cognitive testing was used to assess the subjects intellectual functioning. The Mullen test was given to 40.2% of subjects, the Leiter international scale was used for 32.0% of subjects, the Wechsler scale was used for 24.7% of subjects, and the WPPSI-R scale was used for 3.1% of subjects (Table 3.1.2.5.3).

Table 3.1.2.5.3 Cognitive Test Scores
(Study RIS-USA-150: ITT Analysis Set)

	PLACEBO (N=52)	RISPERIDONE (N=49)	TOTAL (N=101)
Cognitive test performed, n (%)			
N	49	48	97
Leiter international performance scale	18 (36.7)	13 (27.1)	31 (32.0)
Mullen[a]	19 (38.8)	20 (41.7)	39 (40.2)
Wechsler	11 (22.4)	13 (27.1)	24 (24.7)
WPPSI-R	1 (2.0)	2 (4.2)	3 (3.1)
Intelligence quotient			
N	29	26	55
Category, n (%)			
<=49	9 (31.0)	5 (19.2)	14 (25.5)
50-70	12 (41.4)	13 (50.0)	25 (45.5)
71-84	4 (13.8)	5 (19.2)	9 (16.4)
>84	4 (13.8)	3 (11.5)	7 (12.7)
Mean (SD)	82.4 (127.44)	65.8 (16.12)	74.6 (92.80)
Median	58.0	66.0	63.0
Range	1 – 736[b]	38 - 102	1 - 736[b]

[a] Composite scaled scores were recorded for each test except for the Mullen test
[b] The numbers 1 and 736 are not possible scores. The investigator wrote ">36" as the IQ for Subject Y9023 and 1%(IQ of 64) as the IQ for Subject L6022. This information was incorrectly entered into the database as 1 and 736; these errors cannot be corrected

3.1.2.6 Applicant's Efficacy Results

All randomized subjects who received at least one study medication were included in the intent-to-treat analysis set. All 101 randomized subjects provided post-baseline efficacy data and were included in the efficacy analysis.

The change from baseline to end point in the Irritability subscale of the ABC was one of the 2 co-primary efficacy variables in this study. A summary of the results from the analysis of the Irritability subscale of ABC at end point is presented in Table 3.1.2.6.1. The mean changes from baseline at end point in the Irritability subscale were –3.5 (SD = 8.12) and –14.9 (SD = 10.42) in the placebo and

risperidone treatment groups, respectively. Treatment with risperidone was significantly ($p<0.001$) more effective than placebo as measured by the change from baseline in the Irritability subscale of ABC.

Table 3.1.2.6.1 Irritability Subscale of the Aberrant Behavior Checklist at End Point (Study RIS-USA-150; ITT Analysis Set)

	Placebo		Risperidone	
	N	Mean (SD)	N	Mean (SD)
Baseline	52	25.0 (7.00)	49	26.1 (8.35)
End point	52	21.6 (9.52)	49	11.3 (7.39)
Change from baseline at end point:				
Mean (SD)	52	-3.5 (8.12)	49	-14.9 (10.42)
Least squares mean[a](SD[b])		-4.0 (7.99)		-14.6 (7.99)
Between-group difference in LS means (95% CI)[a]		—		-10.6 (-13.8, -7.5)
p value[a]		—		<0.001

[a] Between-treatment group comparison based on ANCOVA model including treatment, investigator as factors, and baseline value as covariate.
[b] Pooled SD (= square root of Mean Square Error (MSE)) based on ANCOVA model

CGI-C response was the other co-primary efficacy variable. A subject was defined as a responder if he/she had a rating of "much improved" or "very much improved" on the CGI-C scale. Subjects with other ratings on the CGI-C scale were defined as non-responder.

Table 3.1.2.6.2 presents results from the analysis of responders at endpoint based on the CGI-C scale. There was a higher percentage of subjects in the risperidone treatment group (75.5%) than in the placebo group (11.5%) who had CGI-C scores in the "very much improved" or "much improved"
categories at the 8-week end point. The difference of 64% between risperidone and placebo was significant ($p<0.001$).

Table 3.1.2.6.2 Analysis of Responders at End Point Based on CGI-C Scale (RIS-USA-150 Part 1: ITT Analysis Set)

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	Placebo		Risperidone	
	N	n (%)	N	n (%)
Number and % Responder	52	6 (11.5)	49	37 (75.5)
Between-Group Difference in Percentages (95% CI)		—		64.0 (49, 79)
p-Value				<0.001

p-Value: CMH test for association between risperidone treatment and CGI-C response controlling for investigator.

The original protocol specified primary analysis is repeated measures analysis. P-value from the repeated measures analysis is .0001

(b) (4)

[redacted]

11 Pages Immediately Following Withheld - b(4)

(b) (4)

[redacted]

3.1.5 Reviewer's Analysis

The reviewer validated the applicant's results according to the protocol for all (b) (4) studies.

Study RIS-CAN-23:

For change from baseline to endpoint of the Irritability subscale of ABC Week 8 LOCF, there were 38 in placebo, and 37 in risperidone groups, respectively, with mean change from baseline at Week 8 LOCF were -6.5 in placebo, and -12.1 in risperidone. P-value from the ANCOVA is .0001. Risperidone was numerically better than placebo across all sites. Wilcoxon rank sum test gives p-value .0015.

For change from baseline to endpoint of the Irritability subscale of ABC Week 8 OC, there were 31 in placebo, and 32 in risperidone groups, respectively, with mean change from baseline at Week 8 were -7.5 in placebo, and -12.1 in risperidone. P-value from the ANCOVA is .0036. Wilcoxon rank sum test gives p-value .0117.

For CGI-C Week 8 LOCF, there were 38 in placebo and 39 in risperidone groups, respectively. P-value from CMH is .0001.

For CGI-C Week 8 OC, there were 32 in placebo and 35 in risperidone groups, respectively. P-value

from CMH is .0001.

Study RIS-USA-150 Part 1:

The original protocol-specified primary analysis method for the Irritability subscale of ABC was a repeated measures model, whose p-value is .0001. After discussion with the Agency, the primary analysis was changed to ANCOVA. Both analyses are statistically significant.

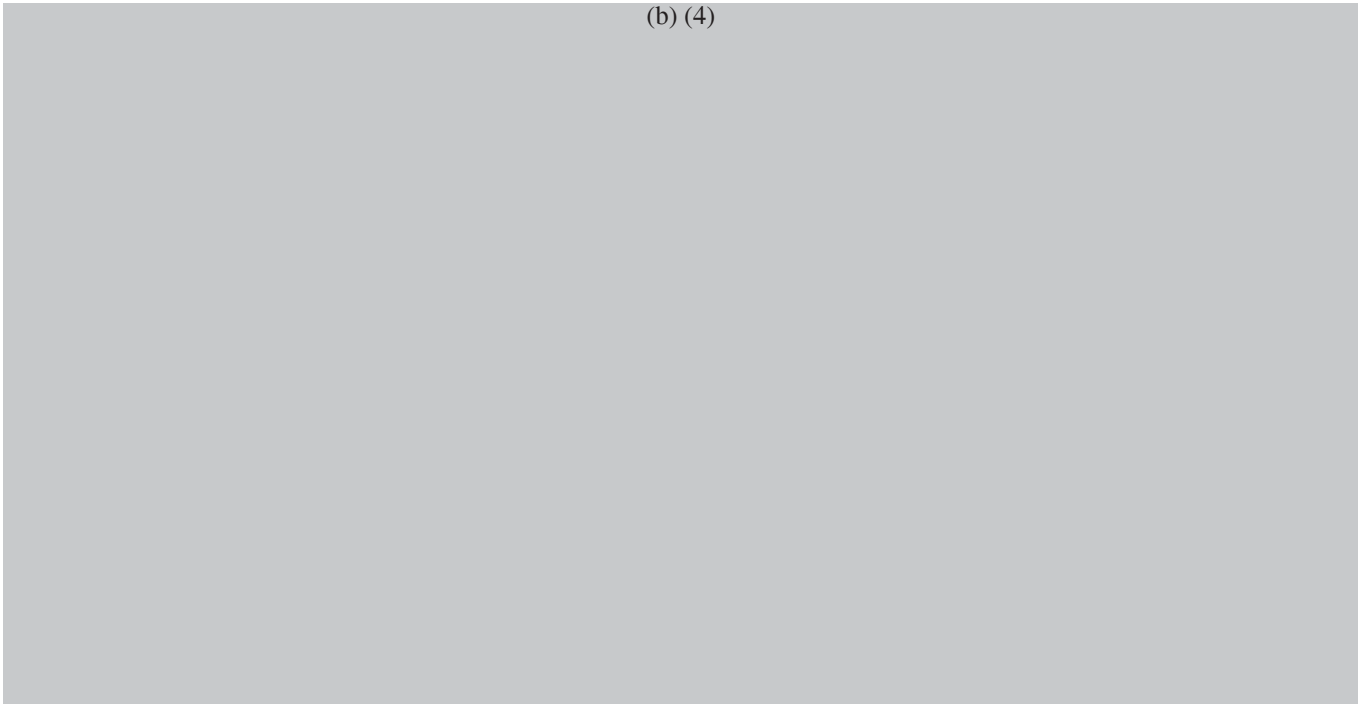
For change from baseline to endpoint of the Irritability subscale of ABC Week 8 LOCF, there were 52 in placebo, and 49 in risperidone groups, respectively, with mean change from baseline at Week 8 LOCF were -3.5 in placebo, and -14.9 in risperidone. P-value from the ANCOVA is .0001. Risperidone was numerically better than placebo across all sites. Wilcoxon rank sum test gives p-value .0001.

For change from baseline to endpoint of the Irritability subscale of ABC Week 8 OC, there were 34 in placebo, and 45 in risperidone groups, respectively, with mean change from baseline at Week 8 were -4.8 in placebo, and -15.8 in risperidone. P-value from the ANCOVA is .0001. Wilcoxon rank sum test gives p-value .0001.

For CGI-C Week 8 LOCF, there were 11.5% (6/52) responders in placebo and 75.5% (37/49) responders in risperidone groups, respectively. P-value from CMH is .0001.

For CGI-C Week 8 OC, there were 17.6 (6/34) responders in placebo and 80.4% responders (37/46) responders in risperidone groups, respectively. P-value from CMH is .0001.

(b) (4)



(b) (4)

3.2 Evaluation of Safety

See Clinical Review by Dr. June Cai.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Table 4.1.1 and 4.1.2 give the primary endpoints by gender. Since majority subjects are white and age between 5-12, no descriptive statistics are calculated for race and age.

"X" indicates a direction where placebo is numerically better than ropinirole.

Table 4.1.1 Primary Endpoints by Gender

Study	Variable	Gender	Placebo N	Risperidone N	
RIS-CAN-23	Mean ABC_change Week 8 LOCF	Male	31 -5.19	26 -12.85	
		Female	7 -12.29	11 -10.45	**X**
RIS-USA-150 Part 1	Mean ABC_change Week 8 LOCF	Male	43 -3.81	39 -14.23	
		Female	9 -1.89	10 -17.3	
	CGI-I Responders Week 8 LOCF	Male	14% (6/43)	72% (28/39)	
		Female	0% (0/9)	90% (9/10)	

(b) (4)

4.2 Other Special/Subgroup Populations

Since RIS-CAN-23 was conducted in Canada only, and RIS-USA-150 was conducted in USA only, no descriptive statistics are calculated for country.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary analyses in (b) (4) studies are all statistically significant. The following table lists p-values for the primary analyses of (b) (4) studies.

Study	Variable	Placebo	Risperidone	R - P	p-value
RIS-CAN-23	Mean change of ABC_Irritability Week 8 LOCF	38 -6.5	37 -12.1	-5.6	.0001
RIS-USA-150 Part 1	Mean change of ABC_Irritability Week 8 LOCF	52 -3.5	49 -14.9	-11.4	.0001
	CGI-I Responders Week 8 LOCF	11.5% 6/52	75.5% 37/49	60%	.0001

(b) (4)

For Study RIS-CAN-23, one secondary analysis of CMH for CGI-C gives p-value .0001. (b) (4)

Although RIS-USA-150 was sponsored by National Institute of Mental Health, the primary analyses presented in this submission either adopted or modified (discussed with the Agency) from the original protocol specified analyses. This reviewer thinks that the primary analyses presented in this submission for RIS-USA-150 are appropriate.

5.2 Conclusions and Recommendations

The primary analyses from (b) (4) studies, RIS-CAN-23, RIS-USA-150 Part 1, (b) (4) provide statically significant evidence that risperidone treated subjects were better than placebo treated subjects in the corresponding primary endpoints of each study.

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/s/

Kun He
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Kun Jin
5/3/04 11:52:04 AM
BIOMETRICS

James Hung
5/3/04 12:04:06 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-272/ S-036 SUBMISSION DATA: January 16, 2006
NDA 20-588/ S-024 February 10, 2006
NDA 21-444/ S-008

DRUG NAME: RISPERDAL (RISPERIDONE)
DOSAGE STRENGTHS: 0.25, 0.5,1,2,3, and 4 mg tablets, 1 mg/ml oral solution, orally disintegrating tablets
APPLICANT: Johnson& Johnson
Reviewer: Andre Jackson
Team Leader: Raman Baweja
Type of Submission: Supplemental complete Response

TABLE OF CONTENTS

BACKGROUND:

The firm has submitted a Complete Response to the 19 May 2005 Not Approvable Letter, with requirements amended as agreed at the 7 December 2005 End of Review Conference. This amendment is to support an indication for the use of oral RISPERDAL® in the treatment of irritability associated with autism in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums and quickly changing moods.

REVIEW HISTORY:

On 19 December 2003, the Company submitted a supplemental application (NDA 20-272/S-036) for RISPERDAL which had an indication for the treatment of schizophrenia and for the short-term treatment of acute manic episodes associated with Bipolar I disorder. In the 2003 application, the applicant sought approval for use of risperidone in children and adolescents (5-16 years of age) (b) (4) The indication was supported by two short-term (8 weeks), placebo-controlled trials with the irritability subscale as the primary end point. Treatment was initiated at about 0.5 mg with a maximum allowed dose of 3.5 mg. Limited PK in children and adolescents with autistic disorder were provided. Pharmacokinetic information collected from studies of

other unapproved indications in children and adolescents were submitted. Body weight accounted for variability in PK. Comments from the OCPB reviewer raised the following concerns.
1) The dose-irritability subscale relationship was flat probably due to the use of too high doses or titration to effect.
2) The evidence of the need for dose titration was weak and the rationale is not clear.
3) Dose-adverse event (AE) analyses conducted by the reviewer showed that the probabilities of AEs such as somnolence, fatigue and dizziness are higher in autism patients than patients with other disorders.

Based upon these findings the reviewer recommended to the Medical Officer that the firm has not convincingly shown that lower fixed doses (perhaps even lower than 0.5 mg) was not as effective as the higher doses. The other major concern was that despite the lower per kg doses compared to adults, higher incidences of AEs are observed in the autism patients. The rate of AEs in pediatrics with other disorders seems to be considerably less than that for the autism patients. Dose adjustment in several patients resolved the AEs to some extent. It was suggested that the dose titration scheme used in the trial is not optimal and that the benefit risk ratio should be carefully assessed.

The second major point made by the reviewer was that (b) (4) Several patients in the placebo group continue to show changes in the desired direction to up to 2 weeks at which point a plateau is reached. The same dose given once or twice daily seems to be effective, increasing the uncertainty in the proposed doses. It was recommended that the applicant should study lower fixed doses to allow meaningful dosing instructions in the labeling.

In a submission dated November 2004, the firm submitted a response to the previous FDA comments.

(b) (4)

The major comment from the OCP review was that the new proposal still suffered from a lack of clear rationale for the starting dose (given the high AE rate and dose-independent

desired effect) and titration scheme, and importantly there was no empirical evidence to substantiate the new choice.

On 19 May 2005, J&JPRD received a Not Approvable Letter from the Agency. The major reasons cited for this action were lack of identification of a minimally effective dose, unacceptably high risk of adverse events at the lowest dose tested, and continuing concerns over long-term safety. The Company disagreed with the conclusions of the Not Approvable Letter and submitted a Briefing Document on 16 August 2005, to outline the Company's position on the issues raised and request a meeting with the Agency to further discuss the file.
At the meeting held on 7 December 2005, the FDA indicated that they were persuaded by the arguments made in the 16 August 2005 Briefing Document, particularly regarding the safety findings. It was recommended that the Company conduct additional analyses to improve understanding of the dose response and explore the need for an increase in dose beyond Week 3. The FDA indicated that they could potentially approve the file without the conduct of any additional clinical studies following their review of a Complete Response containing the additional information as discussed at the meeting. During the meeting, Dr. Laughren provided copies of a manuscript by Dr. Lewis Sheiner *et al*, (Study Designs for Dose-Ranging. *Clin. Pharmacol. Ther.* 1989; 46:63-77) and referenced a methodology applied in the paper to combine dose response data from individual subject dose-response curves. FDA suggested that the Company use the existing dose data from the trials and apply this methodology to determine the dose-response curves. The FDA acknowledged this methodology may or may not provide the answer they are seeking through a post-hoc analysis given the limits of the autism trial design. (b) (4)

This current submission is the firm's Complete Response to the 19 May 2005 Not Approvable Letter and provides all of the required elements of the Complete Response, as amended by the FDA at the 7 December 2005 meeting with the Sheiner analysis and dosing recommendations.

COMPLETE RESPONSE

Commentary on Sheiner paper

The basis of this response is the application of the information in the following reference (Lewis Sheiner *et al*, (Study Designs for Dose-Ranging. *Clin. Pharmacol. Ther.* 1989; 46:63-77) in determining an appropriate starting dose for RISPERDAL. The main point of the paper was to recommend that all subjects should be started on a placebo dose. After a period of time responses are measured in all subjects and each subject is given the lowest active dose. After another predefined period if the response fails to satisfy the clinical endpoint and if unacceptable toxicity is not present the dose is escalated. This process is repeated until either the clinical endpoint is reached or the highest dose is atttained. Once this data is obtained an Emax model is used to describe the population response. Many advantages over crossover and parallel designed studies are discussed in the article. The main advantage is the ability to define the population since several doses can be studied in the same person which provides upper and lower limits for the parameteric dose response curve.

Firm's Dose Over Time Analysis

Table 1 summarizes daily dose by week in studies RIS-USA-150 and RISCAN-23 (autistic disorder subset); the daily doses summarized in this table are those from the day before a subject's visit for the given week (RIS-CAN-23 did not have Week 4 or 6 visits). To compare dosing trends between the placebo and risperidone groups, the 'risperidone-equivalent' dose is summarized for placebo subjects based on the number of tablets (RIS-USA-150) or volume of solution (RIS-CAN-23) that was administered. Mean dose by week is also plotted in Figure 1 overlayed on mean ABC Irritability subscale scores (ABC-I; ABC assessments were not made at every visit in RIS-USA-150.

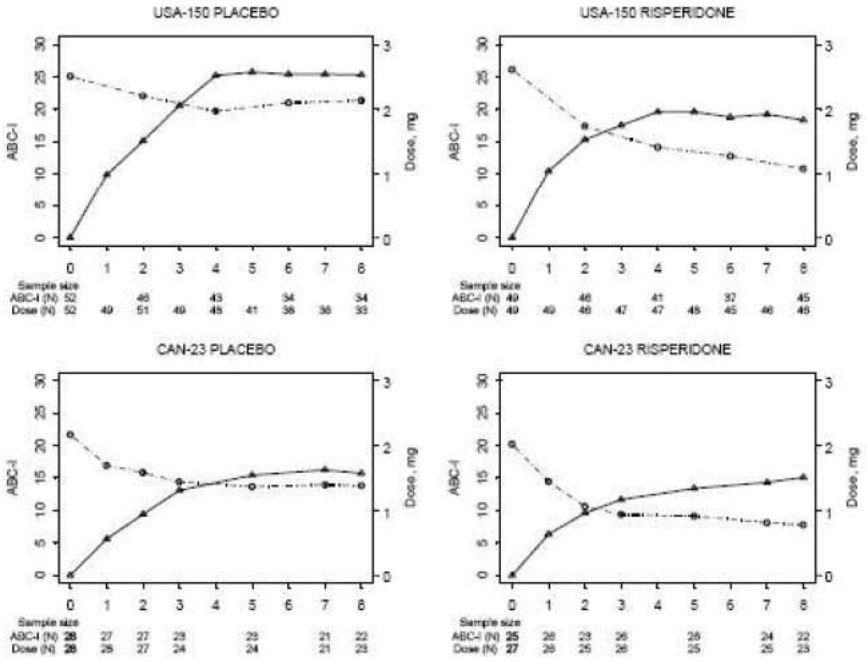
In RIS-USA-150, dose in the risperidone group increased through Week 3 (Week 3 mean: 1.76 mg, median: 2 mg) and was stable from Week 4 to Week 8 (means: 1.96 mg to 1.84 mg, medians: 2 mg). Mean ABC-I scores improved throughout the 8-week treatment period, but the rate of improvement was greater from Baseline to Week 4 than from Week 4 to Week 8. Risperidone-equivalent doses in the placebo group suggest continued increasing of the dose through Week 4, when a plateau of approximately 2.5 mg was reached. This seemed to have been in response to the lack of effect evidenced by the relatively flat mean ABC-I curve.

In RIS-CAN-23, dosing patterns in the two treatment groups were similar. In the risperidone group, mean dose increased throughout the study, although at a greater rate from Baseline to Week 3 than from Week 3 to Week 8. This correlates well with the pattern of improvement demonstrated by mean ABC-I scores over time.

Table 1: Dose by Week – RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)

Study	Placebo[a]			Risperidone		
Time point	N	Mean (SD)	Med (Min, Max)	N	Mean (SD)	Med (Min, Max)
RIS-USA-150						
Week 1	49	0.99 (0.22)	1 (0.5, 1.5)	49	1.05 (0.19)	1 (0.5, 1.5)
Week 2	51	1.51 (0.34)	1.5 (0.5, 2.5)	46	1.53 (0.32)	1.5 (1, 2.5)
Week 3	49	2.06 (0.44)	2 (1, 3)	47	1.76 (0.54)	2 (0.5, 3)
Week 4	48	2.52 (0.50)	2.5 (1, 3.5)	47	1.96 (0.63)	2 (0.5, 3.5)
Week 5	41	2.57 (0.44)	2.5 (1.5, 3.5)	48	1.96 (0.62)	2 (0.5, 3.5)
Week 6	38	2.54 (0.54)	2.5 (1, 3.5)	45	1.88 (0.75)	2 (0, 3.5)
Week 7	36	2.54 (0.54)	2.5 (1, 3.5)	46	1.92 (0.65)	2 (0.5, 3.5)
Week 8	33	2.53 (0.53)	2.5 (1, 3.5)	46	1.84 (0.71)	2 (0, 3.5)
RIS-CAN-23						
Week 1	28	0.56 (0.19)	0.5 (0.4, 1.1)	26	0.63 (0.25)	0.6 (0.3, 1.4)
Week 2	27	0.94 (0.32)	0.8 (0.5, 1.7)	25	0.96 (0.36)	0.9 (0.4, 2.1)
Week 3	24	1.31 (0.41)	1.2 (0.8, 2.4)	26	1.17 (0.54)	1 (0.4, 2.8)
Week 5	24	1.54 (0.49)	1.4 (0.8, 2.9)	25	1.34 (0.72)	1.2 (0.5, 4.2)
Week 7	21	1.62 (0.60)	1.4 (0, 3.4)	25	1.43 (0.71)	1.2 (0.5, 4.2)
Week 8	23	1.57 (0.69)	1.4 (0, 3.4)	23	1.51 (0.70)	1.3 (0.7, 4.2)

Figure 1: Mean Dose (Triangles) and Mean ABC-I Score (Circles) by Week - RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)



Maximum Dose by Response

The distribution of maximum daily dose of risperidone subjects by response status at end point is summarized in Table 3. Overall, 89.6% of responders

were treated with a maximum daily dose ≤ 2.5 mg.

Table 3: Distribution of Maximum Daily Dose by Response Status at End Point - RIS-USA-150 and RIS-CAN-23 (Risperidone Subjects With Autism)

	Nonresponder			Responder			Total		
	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%
Max. daily dose, mg									
>0.5, <=1.0	2	7.4	7.4	2	4.2	4.2	4	5.3	5.3
>1.0, <=1.5	7	25.9	33.3	13	27.1	31.3	20	26.7	32.0
>1.5, <=2.0	8	29.6	63.0	12	25.0	56.3	20	26.7	58.7
>2.0, <=2.5	10	37.0	100.0	16	33.3	89.6	26	34.7	93.3
>2.5, <=3.0	0	0.0	100.0	2	4.2	93.8	2	2.7	96.0
>3.0, <=3.5	0	0.0	100.0	2	4.2	97.9	2	2.7	98.7
>3.5	0	0.0	100.0	1	2.1	100.0	1	1.3	100.0
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Total	27			48			75		

STUDY DESIGN DIFFERENCES FROM SHEINER METHOD

The designs of the autism studies, RIS-USA-150 and RIS-CAN-23, differ from the dose escalation study design in several respects:
• Subjects were not exposed to each dose for a fixed period of time.
• Dose increases were not determined as rigorously as in a dose escalation study. Subjects had increases in dose at times when ABC assessments were not made and increases in dose occurred for some subjects even after having met predefined response criteria for ABC-I (≥25% improvement from baseline).
• The autism studies had a concurrent placebo control, unlike the dose escalation study design described by Sheiner, et al.

The firm suggests that although these differences in study design may limit the feasibility of applying the statistical model suggested by Sheiner, et. al. to the data from the autism pivotal trials, the pattern of dosing in the studies resembles a dose escalation, as seen in Figure 1. Dose increased over approximately 3 weeks and was maintained for the rest of the subject's participation in the study. The dose at around Week 3 was presumably based on the subject's response. Therefore, the autism studies do provide ABC-I assessments made at different doses for individual subjects and the nonlinear mixed effect model approach suggested by Sheiner, et. al., can theoretically be applied.

There were two other differences which the firm did not point out. These were that there were several subjects whose dose was decreased during the dosing (Study #23-1171,4121, etc) and for the other study (US 150-K8020, K0819K8020,L6015, 5133,O7010, O7018,Y9012 etc).

FIRM'S ANALYSIS

The firm used the following model I to initially analyze their data:

(b) (4)

Table 4: Fixed Effect Estimates From Model 1: Placebo Subjects

Study (N)	Fixed Effect	Estimate (SE)	p-value
RIS-USA-150	β_0	25.1 (0.97)	<0.001
(N=52)	β_1	4.5 (1.00)	<0.001
	k	0.16 (0.09)	0.101
RIS-CAN-23	β_0	21.3 (1.84)	<0.001
(N=28)	β_1	7.7 (1.31)	<0.001
	k	0.11 (0.03)	0.002

Source: Attachment A3
SE: Standard error

The firm then employed Model II

(b) (4)

(b) (4)

Table 5: Fixed Effect Estimates From Model 2: Autistic Disorder Subjects

Study	Fixed Effect	Estimate (SE)	p-value
RIS-USA-150	β_0	25.7 (0.78)	<0.001
Placebo, N=52	β_1	6.4 (1.16)	<0.001
Risperidone, N=49	k	0.08 (0.01)	<0.001
	Emax	6.6 (1.83)	<0.001
	ED50	-0.06 (0.26)	0.825
RIS-CAN-23	β_0	20.9 (1.24)	<0.001
Placebo, N=28	β_1	7.6 (1.09)	<0.001
Risperidone, N=27	k	0.11 (0.02)	<0.001
	Emax	5.8 (2.17)	0.008
	ED50	0.08 (0.38)	0.827

Source: Attachment A4
SE: Standard error

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In current clinical practice, substantially higher doses than those recommended by J&JPRD in the proposed labeling (b) (4) are often being used off-label; therefore, providing well-defined dosing guidance that is based on data from controlled studies to treat children and adolescents with autism is important. Although physicians are familiar with recognizing the adverse events associated with risperidone, there is a pressing need for communication and education about the use of safe and effective doses in children and adolescents.

The dosing recommendations below and presented in the proposed label (see Label) are based both on analyses of data from the pivotal trials and a prudent and cautious clinical approach to treatment, taking into account efficacy, and tolerability and safety. (b) (4)

(b) (4)

The key components of the dosing recommendations, as mentioned in the label, are outlined below:

a) The underlying clinical principle is to 'start low, and go slow'.

(b) (4)

c) The recommended dose should be tried for at least 14 days, if tolerable.

(b) (4)

FDA COMMENTS:

1.The firm's design has subjects that increase in dose but then later (i.e., for the same subject) decrease in dose which raises questions related to possible carryover to the next lower dose in terms of PD response and why was the dose decreased since the method is designed specifically to maintain at a specified dose. There is no reason to decrease the dose if it is effective and it should be increased only if ineffective. Therefore it is difficult to understand the firm's rationale for decreasing and increasing doses.

2.The results from the firm's analysis using model II are problematic for two reasons. First a negative ED50 is not interpretable and the ED50 value for study RIS-CAN-23 is

so small and with such a large SE that the 90% CI contains zero which is also an uninterpretable result. The meaning of this result is that in the region of 0.25 mg/day, the dose response is flat (i.e., no dose response) which makes it difficult to define the lowest effective dose. The firm's conclusion " any risperidone dose is more effective than placebo" does not answer the question of what is the lowest efffective dose. Therefore, the firm's current explanation for the lowest effective dose is not supported by the analysis using the Sheiner method.

3. In the 2003 OCP review of this product it was proposed that :

"In one of the 2 double-blind, placebo-controlled studies in autism (RIS-USA-150), most of the patients used b.i.d. dose and the somnolence rate is 63% in the treatment group. In another study (RIS-CAN-23), the recommended dose schedule was once daily in the morning. In the risperidone group, some subjects had changes in the dose schedule from a.m. to b.i.d. or to p.m. during reports of somnolence. Somnolence resolved in 18 of these 20 subjects after the change of dose schedule. Although twice daily dosing did not consistently result in the lack of somnolence, it may be helpful for some patients to switch from once daily to twice daily dosing or to the evening dosing. Labeling recommendations on this issue need medical judgment regarding effectiveness and safety." (b) (4)

4.The starting dose (or lowest effective dose) and need for titration are not justified for this indication. The concerns about the lack of good justification for the proposed dosing strategy that were raised in our previous 2003 review still hold. The exposure-response analysis conducted by the sponsor corroborates this fact. That is, the response across the lowest to highest doses are not different.

5.The dose titration interval is not justified._The placebo response reaches its maximal change from baseline in about 4 weeks. Further, the active metabolite reaches steady-state in about a week. (b) (4) . It is important to note that the PK of risperidone are quite variable due to metabolic differences among patients. These recommendations are incorporated in the Dosage and Administration section of the pediatrics labeling (see end of this review).

(b) (4)

(b) (4)

7. OCP edits to the Dosage and Administration section (b) (4) (Children and Adolescents) are being provided in this review.

PROPOSED OCP PHASE IV STUDY FOR THE FIRM

OCP believes that a Phase IV fixed dose placebo parallel controlled trial would be the best way to determine the lowest effective dose. For instance, such a trial would consist of three arms (i.e., placebo, 0.125 mg and 1 mg) studied for 6 weeks. RIS-CAN-23 included 25 patients per group. The 0.125 mg could be dosed using the 1 mg/ml solution. The Agency would be willing to discuss the details of this design further with the sponsor.

SIGNATURES

Andre Jackson_____
Reviewer, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

RD/FT initialized by Raman Baweja , Ph.D._____
Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

Mehul Mehta, Ph.D._____
Division Director, DCP I
Office of Clinical Pharmacology

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/s/

Andre Jackson
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Raman Baweja
5/22/2006 01:55:53 PM
BIOPHARMACEUTICS
Common review for NDAs 20272/SE 1 36, 20588/SE1 24, 21444/SE1 8

Mehul Mehta
5/22/2006 02:12:45 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-272/SE1-036 20-588/SE1-024 21-444/SE1-008	**SUBMISSION DATES:** November18, 2004
DRUG NAME:	RISPERDAL® (risperidone)	
DOSAGE STRENGTH:	0.25, 0.5, 1, 2, 3, and 4 mg tablets, 1 mg/mL oral solution, orally disintegrating tablets	
APPLICANT:	Johnson & Johnson	
REVIEWER:	John Duan, Ph.D.	
TEAM LEADERS:	Ramana Uppoor, Ph.D, Joga Gobburu, Ph.D.	
TYPE OF SUBMISSION:	Responses to Approvable Letter for sNDA	

I. Executive Summary

RISPERDAL® (risperidone) is a benzisoxazole derivative with serotonin 5-HT_{2A} and dopamine D_2 receptor-blocking properties. The current submission includes the responses to the Approvable Letter issued on June 18, 2004 with regard to an application for use of risperidone in children and adolescents (5-16 years of age) with autistic disorder. The Approvable letter indicated poor dose choice as the major deficiency, and requested the sponsor to submit the PK information collected in Study RIS-USA-150. As requested, pharmacokinetic information on Study RIS-USA-150 is provided, which shows that the pharmacokinetics of the active moiety and risperidone in the target population of children/adolescents with Autistic Disorder are essentially similar to those in a reference population of children and adolescents with Disruptive and Behavioral Disorders. Other than the PK information, the sponsor did not submit any additional evidence supporting the approval of the proposed dosing scheme. The sponsor still maintains the need for a starting dose of 0.25 or 0.5 mg and an increment to 0.5 or 1.0 mg on Day 4.

(b) (4)

The new proposal still suffers from a lack of clear rationale for the starting dose (given the high AE rate and dose-independent desired effect) and titration scheme, and importantly there is no empirical evidence to substantiate the new choice. The European labeling of risperidone for conduct and other disruptive behavior disorder indications (Australia, Belgium, Finland, Denmark, etc.) is noteworthy. The recommended dose is 0.5 mg once daily for most patients < 50 kg. Some

patients, however, may benefit from 0.25 mg once daily while others may require 0.75mg once daily. This may provide certain references regarding optimal dosing of risperidone in behavior disorders.

RECOMMENDATIONS

Overall, the sponsor has not submitted any new evidence to support the proposed dosing scheme. The uncertainties pertaining to the dosing instructions still remain. The starting dose is still under question, owing to the excessive toxicity observed in Studies 23 and 150. The recommendations from the previous OCPB review are still valid. A well designed fixed dose study should ideally be conducted. The medical officer should evaluate the risk-benefit of this proposal.

1. The applicant has not shown that lower starting doses (perhaps even lower than 0.25 or 0.5 mg) are not as effective as the higher doses.

2. (b) (4) Further, the sponsor has now shown that the steady-state concentrations in the responders are higher than in non-responders. If the lower exposures are the root cause of the lack of response, then it is not clear what the rationale is for adjusting doses based on the effectiveness and/or toxicity.

3. (b) (4)

4. The sponsor should employ modeling and simulation techniques to utilize the knowledge from the available data to explore design options for the future study(ies).

LABELING RECOMMENDATIONS

Additional evidence is necessary before accepting labeling proposals.

John Duan, Ph.D. Date
Reviewer
Division of Pharmaceutical Evaluation I

Ramana Uppoor, Ph.D. Date
Team Leader
Division of Pharmaceutical Evaluation I

Joga Gobburu, Ph.D. Date
Team Leader
Division of Pharmaceutical Evaluation I

cc: NDA 20-272 Original
NDA 20-588 Original
NDA 21-444 Original
HFD-860 M. Mehta, A. Rahman, R. Uppoor, J. Duan
CDR

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John Duan
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Ramana S. Uppoor
12/20/04 06:06:49 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-272/SE1-036	**SUBMISSION DATES:** December 19, 2003
	20-588/SE1-024	March 5, 2004
	21-444/SE1-008	MAY 3, 2004
DRUG NAME:	RISPERDAL® (risperidone)	
DOSAGE STRENGTH:	0.25, 0.5, 1, 2, 3, and 4 mg tablets, 1 mg/mL oral solution, orally disintegrating tablets	
APPLICANT:	Johnson & Johnson	
REVIEWER:	John Duan, Ph.D.	
TEAM LEADERS:	Ramana Uppoor, Ph.D, Joga Gobburu, Ph.D.	
TYPE OF SUBMISSION:	Supplemental New Drug Application (Priority review)	

I. Executive Summary

RISPERDAL® (risperidone), a benzisoxazole derivative with potent serotonin 5-HT_{2A} and dopamine D_2 receptor-blocking properties, is an atypical antipsychotic for the treatment of schizophrenia and for the short-term treatment of acute manic episodes associated with Bipolar I disorder. It is used either as monotherapy or as adjunctive therapy to mood stabilizers. In this sNDA, the applicant is seeking approval for use of risperidone in children and adolescents (5-16 years of age) with autistic disorder. The effectiveness of RISPERDAL was supported by two short-term (8 weeks), placebo-controlled trials with the irritability subscale as the primary end point. Treatment was initiated at about 0.5 mg with a maximum allowed dose of 3.5 mg. Limited PK in children and adolescents with autistic disorder were provided. Pharmacokinetic information collected from studies of other unapproved indications in children and adolescents were submitted. Body weight accounted for variability in PK. The dose-irritability subscale relationship is flat probably due to the use of too high doses or titration to effect. The evidence of the need for dose titration is weak and the rationale is not clear. Dose-adverse event (AE) analyses conducted by the reviewer showed that the probabilities of AEs such as somnolence, fatigue and dizziness are higher in autism patients than patients with other disorders. Taking the dose-response into consideration, the following are recommended.

RECOMMENDATIONS

Comments to the Medical Reviewer

1. The rationale for the dose selection is not clear. The applicant has not convincingly shown that lower fixed doses (b) (4) are not as effective as the higher doses. The maximum dose studied in pediatrics is about 0.06 mg/kg, which translates to 4.2 mg in a 70 kg adult. Doses of 4-16 mg have been used to treat schizophrenia in adults. In spite of the lower per kg doses compared to adults, higher incidences of AEs are observed in the autism patients. The rate of AEs in pediatrics with other disorders seems to be considerably less than that for the autism patients. Dose adjustment in several patients resolved the AEs to some extent. But then this implies that the dose titration scheme used in the trial is not optimal. The benefit risk ratio should be assessed carefully given the rather

high incidence of AEs such as somnolence and upper respiratory tract infections, and lack of evidence that the proposed dosing is optimal.

Table. Frequency of AEs in pediatrics with autism and adults with schizophrenia in the risperidone (placebo) groups, as reported in the proposed labeling

Adverse Event	Adults (Placebo)	Pediatrics (Placebo)
Somnolence	8% (1%)	67% (23%)
Upper respiratory infection	3% (1%)	34% (15%)
Fatigue	23% (5%)	42% (13%)

2. (b) (4)

Several patients in the placebo group continue to show changes in the desired direction to up to 2 weeks at which point a plateau is reached. The same dose given once or twice daily seems to be effective, increasing the uncertainty in the proposed doses. The applicant should study lower fixed doses to allow meaningful dosing instructions in the labeling. Per the protocols, patients were titrated to desired effect initially and subsequently dose reductions due to toxicity were made. If the division should decide on approving the current labeling, then the following recommendations should be considered.

3. (b) (4) Patients in the pivotal trials did not require more than these doses and clearly the AEs are dose related.

4. (b) (4) . Patients with body weights less than 15 kg were not studied. Patients with body weights between 20 to 50 kg received similar doses in the pivotal trials.

5. PK in only 6 pediatric patients with autistic disorder is provided. The PK in general seems to be consistent with that in adults. However, the applicant concluded that the relative bioavailability of the active moiety is 3.4-fold higher than that in adults and other pediatrics. It is noted that the applicant collected PK samples in the pivotal trial RIS-USA-150 and a population analysis was planned. Requests for submitting the PK data were sent to the applicant. However these data were not submitted to the Agency. The applicant should conduct and submit the analysis for review. We believe the population PK report will allow estimation of PK variability in the target population and to gain insights into the potential cause for the high AE rate. The availability of the analysis report will enable the Agency to assess the dosing recommendations better, before the approval.

6. In one of the 2 double-blind, placebo-controlled studies in autism (RIS-USA-150), most of the patients used b.i.d. dose and the somnolence rate is 63% in the treatment group. In another study (RIS-CAN-23), the recommended dose schedule was once daily in the morning. In the risperidone group, some subjects had changes in the dose schedule from a.m. to b.i.d. or to p.m. during reports of somnolence. Somnolence resolved in 18 of these 20 subjects after the change of dose schedule. Although twice daily dosing did not consistently result in the lack of somnolence, it may be helpful for some patients to switch from once daily to twice daily dosing or to the evening dosing. Labeling recommendations on this issue need medical judgment regarding effectiveness and safety.

Comments to the applicant

1. PK in only 6 pediatric patients with autistic disorder is provided. The PK in general seems to be consistent with that in adults. However, the applicant concluded that the relative bioavailability of the active moiety is 3.4-fold higher than that in adults and other pediatrics. It is noted that the applicant collected PK samples in the pivotal trial RIS-USA-150 and a population analysis was planned. Requests for submitting the PK data were sent to the applicant. However these data were not submitted to the Agency. The applicant should conduct and submit the analysis for review. We believe the population PK report will allow estimation of PK variability in the target population and to gain insights into the potential cause for the high AE rate. The availability of the analysis report will enable the Agency to better assess the dosing recommendations.

2. Comments on population pharmacokinetic analyses of the data collected in the 6 autistic patients and several DBD and PDD pediatric studies.

   - Majority of the samples are collected at trough. The half-life of the parent is 3 h and that of the metabolite is 21 h. These data might not allow reliable estimation of systemic clearance and definitely not ka, V2, V3 and Q.

   - The volume of distribution of the parent was reported to be higher for the extensive metabolizers. No physiological reasoning is provided in support of this result.

   - Comparing the estimates between the base model and the final model, the incorporation of covariates into the model did not considerably reduce the inter-individual variability as shown in the following table for the active moiety models.

Parameters	Inter-individual variability (RSE)	
Model	Base model	Final model
CLNR/F (L/h)	33.0 (27.0)	36.1 (26.3)
Vc/F (L)	145 (36.7)	133 (45.4)
Residual variability (% CV)	18.0 (30.4)	16.4 (26.7)

   The clearance of the active moiety is similar for the autistic and other pediatric patients, based on studies 021 and 160 with rich PK sampling. The conclusion of the population PK analysis that the PK in autism patients (study 021) is different from other studies is probably a result of model misspecification and/or over-parameterization.

3. If data allow, please evaluate the time course of important adverse events, such as somnolence.

4. Please make the requested changes before the labeling is finalized.

LABELING RECOMMENDATIONS

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(b) (4)

John Duan, Ph.D. Date
Reviewer
Division of Pharmaceutical Evaluation I

Sally Yasuda, Pharm.D. Date
Team Leader
Division of Pharmaceutical Evaluation I

Joga Gobburu, Ph.D. Date
Team Leader
Division of Pharmaceutical Evaluation I

cc: NDA 20-272 Original
NDA 20-588 Original
NDA 21-444 Original
HFD-860 M. Mehta, A. Rahman, R. Uppoor, J. Duan, S. Yasuda, V. Tandon
CDR

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/s/

John Duan
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Jogarao Gobburu
6/4/04 05:03:02 PM
BIOPHARMACEUTICS

Atiqur Rahman
6/8/04 09:20:16 AM
BIOPHARMACEUTICS

Sally Yasuda
6/8/04 09:42:06 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**N20-272/SE1-036 N20-588/SE1-024 N21-444/SE1-008**	**Brand Name**	**Risperdal**
OCPB Division (I, II, III)	**DPE-I**	**Generic Name**	**Risperidone**
Medical Division	**HFD-120**	**Drug Class**	
OCPB Reviewer	**John Duan**	**Indication(s)**	(b) (4)
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**Tablets/Oral solution/ Orally Disintegrating Tablets**
		Dosing Regimen	**QD or BID based on weight. starting with 0.25 or 0.5 mg/day, titrated to response** (b) (4)
Date of Submission	**December 19, 2003**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**5/1/04**	**Sponsor**	**Johnson & Johnson**
PDUFA Due Date	**6/19/04**	**Priority Classification**	**P**
Division Due Date	**5/1/04**		

Clin. Pharm. and Biopharm. Information

Summary: This NDA is for a new indication of risperidone for autism. Risperidone is currently approved for the treatment of schizophrenia and for the short-term treatment of acute manic episodes associated with Bipolar I disorder, either monotherapy or as adjunctive therapy to mood stabilizers. A table is attached which lists the studies in which information on the pharmacokinetics of risperidone in children and adolescents were obtained (see Page 4). A population pharmacokinetic analysis in children and adolescents is also submitted, in which the plasma concentration-time data of the active moiety and risperidone obtained in RIS-BEL-21, RIS-USA-160, RIS-CAN-19, RIS-USA-93 and RIS-INT-41 were combined and analyzed using NONMEM. In addition, an overview of relevant published literature is presented. In this submission, there are no new formulation development activities.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	

Plasma protein binding:	**-**	**-**	**-**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**-**	**-**	**-**	
multiple dose:	**-**	**-**	**-**	
Patients-				
single dose:	**X**	**1**	**-**	
multiple dose:	**X**	**8**	**-**	
Dose proportionality -				
fasting / non-fasting single dose:	**-**	**-**	**-**	
fasting / non-fasting multiple dose:	**-**	**-**	**-**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**-**	**-**		
In-vivo effects of primary drug:	**-**	-		
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	**-**	**-**	**-**	
gender:	**-**	**-**	**-**	
pediatrics:	**-**	**-**	**-**	
geriatrics:	**-**	**-**	**-**	
Renal impairment:	-	-	-	
Hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	**X**	**1**		
Data sparse:	**-**	**-**		
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	**-**	**-**		
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	**-**	**-**	-	
Dissolution:	**-**	**-**		
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	**-**	-	-	
BCS class	**-**	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	**X**			
Total Number of Studies		**10**		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward to sponsor : 1. It is noted that in some clinical studies including study RIS-USA-150 (the pivotal clinical trial), the formulation used is not the marketed formulation. It is claimed that bioequivalence studies in healthy volunteers and psychotic patients demonstrated that the risperidone research tablets are bioequivalent to the marketed tablets. Please provide the bioequivalence studies indicated or refer to their location. 2. Please provide the status of the pharmacokinetic analyses in study RIS-USA-150 Part 1.		
QBR questions (key issues to be considered)	Does the pharmacokinetic profile differ in the autism patient population and schizophrenia patient population? Are drug interactions with concomitant drugs that are I kely to be used in autism a concern? Is the dosing regimen reasonable from pk/pd point of view (if data allow)?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 20-272/NDA20-588/NDA21-444, HFD-850(Electronic Entry or Lee), HFD-120(Griffis), HFD-860 (R. Uppoor, C. Sahajwalla, M. Mehta)

Attachment. Study summary

Study	Design/Dosage/PK Objective	Number of subjects[a]
COMPLETED STUDIES IN CHILDREN AND ADOLESCENTS WITH AUTISTIC DISORDER		
RIS-BEL-21	Single dose, OL/ Single dose risperidone (0.015 or 0.03 mg/kg)/ Pharmacokinetic profile	6 children (aged 3-7 years) with Autistic Disorder
RIS-BEL-22	4 weeks, OL/ Flexible dose risperidone (0.01-0.12 mg/kg/day), b.i.d./ Plasma concentrations	7 children and adolescents (aged 3-14 years) with Autistic Disorder
COMPLETED STUDY IN CHILDREN AND ADOLESCENTS WITH PSYCHOTIC AND BEHAVIORAL DISORDERS		
RIS-USA-160	1 week, OL/ Flexible-dose risperidone (0.01-0.08 mg/kg/day), b.i.d./ Pharmacokinetics in children and adolescents	12 children (aged 6-11 years), 12 adolescents (aged 12-16 years) with Psychotic and Behavioral Disorders
COMPLETED STUDIES IN CHILDREN AND ADOLESCENTS WITH DISRUPTIVE BEHAVIOR DISORDERS		
RIS-NED-9	6 weeks, DB/ Flexible dose risperidone (1.5-10 mg/day) vs. placebo, b.i.d./ Plasma concentrations	38 children and adolescents (aged 11-18 years) with an IQ of 60 to 90 inclusive and a diagnosis of Conduct Disorder, ADHD, or ODD
RIS-CAN-19	6 weeks, DB/ Flexible dose risperidone (0.02-0.06 mg/kg/day) vs. placebo, o.d./ Plasma concentrations	110 children (aged 5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD
RIS-USA-93	6 weeks, DB/ Flexible dose risperidone (0.02-0.06 mg/kg/day) vs. placebo, o.d./ Plasma concentrations	118 children (aged 5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD
RIS-CAN-20	1 year, OL/ Flexible dose risperidone (0.02-0.06 mg/kg/day), o.d./ Plasma concentrations	77 children (aged 5-12 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD
RIS-INT-41	1 year, OL/ Flexible dose risperidone (0.02-0.06 mg/kg/day), o.d./ Plasma concentrations	504 children and adolescents (aged 4-14 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD
RIS-USA-97	1 year, OL/ Flexible dose risperidone (0.02-0.06 mg/kg/day), o.d./ Plasma concentrations	107 children and adolescents (aged 5-13 years) with borderline intellectual functioning or mild or moderate mental retardation and a diagnosis of Conduct Disorder or other DBD

DB: double-blind; OL: open-label
[a]: all subjects randomized who received at least 1 dose of study medication

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/s/

John Duan
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Ramana S. Uppoor
2/4/04 02:35:35 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

OTHER REVIEW(S)

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 20-272/S-036
Drug: risperidone
Route: oral
Indication: irritability associated with (b) (4) children and adolescents
Materials reviewed: August 10, 2006 response to July 14, 2006 approvable letter; September 22 and September 28, 2006 responses to queries from Division
Sponsor: Johnson & Johnson
Reviewer: Alice T.D. Hughes, M.D.

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1 Background

The safety team was asked to review the data and proposed labeling pertaining to hyperprolactinemia in the sponsor's response[1] to the most recent approvable letter[2] for the use of risperidone for the treatment of irritability associated with autistic disorder. Changes to the labeling to more adequately address the available data pertaining to risperidone and hyperprolactinemia had been discussed with the sponsor during a teleconference on July 26, 2006.

The submitted data and proposed labeling are described in detail in the primary safety review by Dr. Lourdes Villalba dated September 28, 2006. (b) (4)

In this memorandum, I will address selected issues that require additional discussion and make labeling recommendations for the *Precautions; Hyperprolactinemia* and *Pediatric Use; Hyperprolactinemia, Growth, and Sexual Maturation* sections.

2 Hyperprolactinemia

All dopamine antagonists are associated with elevations in prolactin levels; this is due to the inhibitory effect of pituitary D_2 receptors on prolactin secretion. Risperidone has been shown in controlled studies to increase prolactin levels to a greater extent than the other atypical antipsychotics.[3,4]

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[1] August 10, 2006
[2] July 14, 2006
[3] Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353(12):1209-1223.

The available data from the application under review support the association between risperidone and hyperprolactinemia and indicate that risperidone is associated with hyperprolactinemia in children and adolescents.

In the safety database for the application under review, 43.9% (36/82) of risperidone-treated patients in placebo-controlled trials in children and adolescents developed elevated prolactin levels compared to 2.1% (2/95) of placebo-treated patients.[5] These data were provided in a September 22, 2006 response to a query from the Division. In this response, the sponsor also provided the percentages of patients who were reported to have the adverse event of "hyperprolactinemia." These data are less helpful given that hyperprolactinemia is frequently asymptomatic and may not have been reported.

In one short-term placebo-controlled study in children and adolescents with autistic disorder (USA-150), mean changes from baseline in prolactin levels were 29.70 ng/mL among risperidone-treated patients and 0.79 ng/mL among placebo-treated patients. In (b) (4)

The sponsor provided data regarding the percentage of children and adolescents treated with risperidone in clinical trials who experienced adverse events potentially related to hyperprolactinemia. 0.8% (16/1885) of (male and female) patients experienced galactorrhea ("lactation nonpuerperal"), 2.3% (44/1885) of patients experienced gynecomastia, and 0.6% (12.1885) of all patients experienced amenorrhea. 2.7% (7/264) of girls older than 12 were reported to have amenorrhea.

The sponsor's proposed modifications to the *Precautions; Hyperprolactinemia* sections are generally adequate. This section conveys the key information that risperidone increases prolactin levels more than do other atypical antipsychotics, and also conveys information regarding the known and potential consequences of supraphysiologic prolactin levels.

I agree with Dr. Villalba's recommendations regarding modifications to this section, (b) (4)

I agree with Dr. Villalba that including data from placebo-controlled trials in children and adolescents regarding the percentages of risperidone- and placebo-treated patients (b) (4)

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[4] Stroup TS, Lieberman JA, McEvoy JP et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006; 163(4):611-622.

[5] These percentages reflect the percentage of patients levels for whom both baseline and on-treatment prolactin levels were available who developed prolactin levels above the upper limit of normal.

(b) (4)

I support adding data regarding the percentages of children and adolescents who experienced galactorrhea and gynecomastia in clinical trials to the *Pediatric Use; Hyperprolactinemia, Growth, and Sexual Maturation section* of prescribing information. These events are likely to be related to hyperprolactinemia. (b) (4)

Although the data from the child and adolescent safety database provide strong support for an association between risperidone and hyperprolactinemia in this population, they do not shed light on the long-term consequences of this association, a particularly important question for children and adolescents that warrants further study.

3 Growth Hormone

In the pediatric and adolescent safety database, 12 patients treated with risperidone were reported to have had an adverse event of "growth hormone excess." All of these patients were in open-label trials (the majority of patients who underwent growth hormone measurements were in open-label trials). It is not possible, however, to conclude that risperidone is associated with increases in growth hormone levels based on the available data due to its substantial limitations. Growth hormone levels were only measured in selected trials, and not consistently measured within those trials. Baseline growth hormone measurements are available for 815 of the 1923 risperidone-treated patients (and 139 placebo-treated patients). Only 317 risperidone-treated patients and 54 placebo-treated patients had on-therapy growth hormone measurements. Measurement collection methodologies were not standardized within or between trials, which make the data particularly difficult to interpret because growth hormone is secreted in a pulsatile fashion and levels normally fluctuate throughout the day. Growth hormone levels are expected to be highest during sleep. For this reason, random blood sampling for determination of growth hormone levels is not very informative.[6] (b) (4) measurement of insulin-like growth factor-1 (IGF-1) may be more stable and more informative. Moreover, the laboratory reference ranges used for growth hormone (which were presumably the basis for patients being considered to have "growth hormone excess") were not age-adjusted. Children and adolescents have higher growth hormone

[6] Strasburger CJ and Bidlingmaier M. How robust are laboratory measurements of growth hormone status? Horm Res 2005; 64 suppl 2: 1—5.

levels than adults. The growth hormone elevations reported for the 12 patients with "growth hormone excess" were modest and well below levels reported in children with gigantism.[7,8]

None of the patients reported to have "growth hormone excess" had adverse events that can be directly attributed to increased growth hormone levels.

Hyperprolactinemia was present in 10 of the patients reported to have growth hormone excess, a notable finding. A true association between these two events cannot, however, be established based on the available data. Further study is warranted to assess whether risperidone increases the risk for pituitary tumors, some of which may secrete both growth hormone and prolactin.

The data in the current application pertaining to risperidone and growth hormone do not provide sufficient evidence of an effect of risperidone on growth hormone levels for us to mandate further study of the effect of long-term risperidone treatment on growth hormone levels and on the growth and development of children and adolescents treated with risperidone.

In order to understand whether risperidone does affect growth hormone levels, we will ask the sponsor to add growth hormone and IGF-1 assessments to the 6-week, fixed-dose, parallel-group, placebo-controlled clinical study that they have agreed to perform as a phase 4 commitment in autistic children and adolescents to determine the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance. Careful attention will need to be paid to appropriately and consistently collecting these hormone measurements. I recommend that we obtain Endocrinology input when we review the study protocol submitted by the sponsor.

In addition, IGF-1 and growth hormone level assessments will be added to the non-clinical (rat and dog) studies that the sponsor has agreed to as phase 4 commitments. In the dog study, we will also ask the sponsor to assess long bone growth in dogs. Any abnormalities detected would provide evidence that further study on growth in humans may be warranted.

We should also recommend to the sponsor that they consider studying the effect of long-term risperidone treatment on the growth and development of children and adolescents.

4 Sexual Maturation

No cases of precocious puberty were reported during clinical trials of risperidone in children. (b) (4) , cases of precocious puberty have been

[7] Zimmerman D et al. Congenital gigantism due to growth hormone-releasing hormone excess and pituitary hyperplasia with adenomatous transformation. J Clin Endocrinol Metab 1993; 76(1): 216-22.
[8] Minagawa et al. Effects of octreotide infusion, surgery and estrogen on suppression of height increase and 20K growth hormone ratio in a girl with gigantism due to a growth hormone-secreting macroadenoma. Horm Res 2000; 53 (3):157-60.

reported in the post-marketing setting. In the two most recent pediatric safety updates (together covering the period March 1, 2005 through February 28, 2006), I identified four cases of precocious puberty (two eight year-old boys, one of whom had elevated prolactin levels, a 5 year-old girl, and a 9 year-old girl). (b) (4)

Information regarding all of these cases is limited. We do not have evidence that risperidone was the cause of delayed or precocious puberty in these children. Many other etiologies are possible. Hyperprolactinemia itself is not known to be associated with precocious puberty. I do not think that the data currently available provide support for an association between risperidone treatment and either precocious or delayed puberty. I recommend adding precocious puberty to the post-marketing section of the risperidone prescribing information.

5 Labeling Recommendations

Published research has consistently indicated that risperidone is associated with increased prolactin levels and that this effect is more prominent than the effect observed with other atypical antipsychotics. The data from this safety database indicate that risperidone is associated with elevated prolactin levels in children and adolescents as well as in adults. The data from the child and adolescent safety database do not provide convincing evidence that risperidone is associated with changes in growth hormone levels, although further study of this area is warranted and will be requested as a phase 4 commitment.

I recommend the following labeling for the *Precautions; Hyperprolactinemia* and *Pediatric Use; Hyperprolactinemia, Growth, and Sexual Maturation sections*. (b) (4)

Precautions

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone 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 PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). 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.

Hyperprolactinemia, Growth, and Sexual Maturation

Risperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS—Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) (b) (4)

(b) (4)

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(b) (4)

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/s/

Alice T. Hughes
10/5/2006 01:12:55 PM
MEDICAL OFFICER

OND Safety Review

Drugs:	Risperidone
NDAs:	20-272
Sponsor:	Janssen
Subject:	Labeling changes related to hyperprolactinemia and growth. Complete Response to AE of July 14, 2006 for Autistic Disorders, submitted August 9, 2006.
Date:	September 27, 2006
Reviewer:	Lourdes Villalba, M.D., Medical Officer, Safety Team, DPP
Team Leader:	Alice Hughes, M.D., Team Leader, Safety Team, DPP

1. Background

This is the fourth review cycle for NDA 20-272/s036 (Risperidone for the treatment of irritability associated with autistic disorders, originally submitted on December 19, 2003).

Among other requests, the most recent Approvable (AE) letter issued on July 14, 2006, by the Division of Psychiatric Products (DPP), requested changes to the PRECAUTIONS, Hyperprolactinemia, and Pediatric Use sections of the Risperidone labeling. FDA changes were intended to reflect that risperidone is associated with higher prolactin levels than other antipsychotic agents, to update the label regarding the mechanism for which prolactin may induce hypogonadism-related adverse reactions and to incorporate hyperprolactinemia-related data from pediatric studies submitted under s036 and from postmarketing safety reports. This labeling also incorporated changes related to postmarketing reports of pituitary (b) (4) which the Sponsor added to the Adverse Reactions, Postintroduction Reports subsection, as part of supplement 043, submitted October 25, 2005.

Labeling changes were preliminary discussed by the DPP and the Sponsor at a Post Action teleconference held on July 26, 2006. At the same teleconference, the DPP requested clarifications related to growth hormone (GH) levels reported in the original NDA submission.

This safety review focuses on the "PRECAUTIONS, Hyperprolactinemia", "PRECAUTIONS, Pediatric use, Hyperprolactinemia", and "Adverse Reactions, Postintroduction" subsections of the labeling, as well as the information (b) (4) Other clinical informational requests are being reviewed by Dr. June Cai.

2. Sponsor's current submission

The labeling proposal of August 6, 2006, related to hyperprolactinemia, is as follows (new Sponsor's language is underlined; FDA's language that has been rejected is stricken):

10 pages immediately following withheld - b(4) Draft Labeling

(b) (4)

4. Conclusions and recommendations.

4.1 Labeling changes related to PRECAUTIONS, Hyperprolactinemia and Pediatric Use, Hyperprolactinemia, proposed by the Sponsor on August 9, 2006 require further discussion. (The FDA proposal is being written in a separate document).

(b) (4)

(b) (4)

(b) (4)

As part of the Complete Response to the July 14, 2006 AE letter, submitted August 9, 2006, the Sponsor proposes to conduct two phase IV juvenile toxicology studies and one 6-week clinical phase IV study to evaluate glucose and insulin related parameters. The Sponsor should be asked to add laboratory evaluation of IGF-1 and long bone growth measurements to the juvenile toxicology studies, and to add IGF-1 measurements to the clinical study.

Consideration should be given to a postmarketing commitment study to address the issue of potential long-term effects of risperidone on growth.

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/s/

Maria Villalba
9/27/2006 01:55:20 PM
MEDICAL OFFICER

Alice T. Hughes
9/28/2006 02:29:14 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20855

CLINICAL INSPECTION SUMMARY

DATE: May 24, 2004

TO: Melina Griffis, R.Ph., Senior Regulatory Project Manager
June Cai, M.D., Medical Officer
Gregory Dubitsky, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: 20-272/SE1-036
20-588/SE1-024
21-444/SE1-008

APPLICANT: Johnson & Johnson Pharmaceutical Research & Development, LLC

DRUG: Risperdal Tablets, Oral Solutions and Oral Disintegrating Tablets

THERAPEUTIC CLASSIFICATION: Type P

PROPOSED INDICATION: Autistic Disorder

CONSULTATION REQUEST DATE: February 3, 2004

ACTION GOAL DATE: June 19, 2004

I. BACKGROUND:

Risperidone is an atypical antipsychotic agent and is approved for treatment of schizophrenia. In this application, the sponsor has requested the use of risperidone in treatment of Autistic Disorder. The application included the results from protocol RIS-USA-150 Part 1 entitled "A Double-Blind, Placebo-Controlled Study of Risperidone in Children and Adolescents with Autistic Disorder" and protocol RIS-USA-150 Part 2/3 entitled "An open-label continuation

study of risperidone in children and adolescents with Autistic Disorder followed by a double-bline, placebo-controlled discontinuation", and protocol RIS-CAN-23 entitled "Efficacy and Safety of Risperidone in Treatment of Children with Autistic Disorder and Other Pervasive Developmental Disorders: A Canadian, Multicenter, Double-Blind, Placebo-Controlled Study."

The Canadian protocol enrolled pediatric patients (ages 5-12 years) with pervasive developmental disorder (PDD) including Autistic Disorder while the pivotal U.S. study enrolled solely pediatric patients (ages 5-17 years) who met the DSM-IV criteria for Autistic Disorder. The studies were not conducted under an IND. The funding of the U.S. study was provided by the National Institute of Mental Health in 1999-2001 to Research Units on Pediatric Psychopharmacology (RUPP) led by the Yale University. The Ohio State University and the Indiana University were listed as part of the research group. Janssen provided the study drug.

According to the Diagnostic and Statistical Manual-IV (DSM-IV), Autistic Disorder is characterized by qualitative impairment in social interaction, qualitative impairment in communication and restricted repetitive and stereotyped patterns of behavior, interest and activities. The delay or abnormal functioning in at least one of the following areas with onset prior to age 3 years: social interaction, language as used in social communication or symbolic or imaginative play.

Protocol RIS-USA-150 Part 1

The part 1 of the study was an eight-week, randomized, double-blind, parallel-group, flexible-dose, multicenter study to assess the efficacy and safety of risperidone versus placebo in the treatment of symptoms of autistic disorder (age 5-17 years). In this study, subjects with a DSM-IV Axis I diagnosis of Autistic Disorder with a clinical global impression (CGI) score of at least 4 and a score of 18 or greater on the irritability scale of the Aberrant Behavior Scale (ABC) were enrolled.

Dosing throughout the study was flexible starting with a single oral dose of 0.25 mg or 0.5 mg tablet taken at bedtime depending on the weight of the subject. On the day 4, study medication was increased to a b.i.d dosing schedule. The subjects who weighed between 15 and 20 kg, had a starting dose of 0.25 mg/day and for those subjects who weighed equal or above 20 kg the starting dose was 0.5 mg/day. For subjects weighing between 20 and 45 kg, a maximum dose of 2.5 mg was administered, 1 mg in the morning and 1.5 mg at bedtime. For subjects weighing above 45 kg, the maximum dose was 3.5 mg daily, 1.5 mg in the morning and 2 mg at bedtime.

The co-primary efficacy measures of this study was the change from baseline to end point in

1) the irritability subscale of the Aberrant Behavior Checklist (ABC). The ABC consisted of 58 items and scored by the parent or caregiver, under the guidance of the investigator at all scheduled visits. The ABC, clinician-administered irritability subscale and target symptoms (range 0-45), listed 15 items such as injury to self, aggressive to others and temper tantrums (item 2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57). Each item was rated on 0 to 3 point scale; 0 = not at all a problem, 3 = the problem is severe in

degree.

2) a clinical global impression change (CGI-C) scores: much or very much improved.

Protocol RIS-USA-150 Part 2/3

At the end of part 1, risperidone responders could enter part 2. The part 2 of the study was a 4-month, open-label risperidone treatment period. Placebo nonresponders from part 1 could enter an 8-week, open-label, risperidone treatment period and responders from this period could then enter an additional 4-month, open-label, risperidone treatment period.

Risperidone responders who completed the part 2 were randomized to either continued risperidone treatment or to a placebo substitution treatment arm for additional 8 week, double-blind, withdrawal period. In the placebo-substitution arm, risperidone was tapered down during the first 3 weeks. In both parts of this study, risperidone was dose once or twice daily and flexibly according to weight (up to 4 mg/day for subjects weighing <45 kg and up to 6 mg/day for subjects weighing ≥45 kg. The primary efficacy parameter was the rate of relapse during the randomized withdrawal phase. Relapse was defined by the occurrence of both of the following events: Clinical Global Impression of Change (CGI-C) score of much worse or very much worse than baseline ratings (week 16) for 2 consecutive weeks and an increase of ≥25% from baseline defined as entry into the randomized withdrawal phase in the irritability subscale of the Aberrant Behavior Checklist (ABC) score.

Protocol RIS-CAN-23

The study was a 8-week, randomized, double-blind, parallel-group, multicenter study to assess the efficacy and safety of risperidone (0.02 to 0.06 mg/kg/day) versus placebo in the treatment of symptoms of autistic disorder and other PDD in children (age 5-12 years). In this study, subjects with a DSM-IV Axis I diagnosis of Pervasive Developmental Disorders with a total score of ≥30 on the Childhood Autism Rating Scale with or without mental retardation were enrolled. The primary efficacy parameter was the change from baseline to end point in the irritability subscale of the Aberrant Behavior Checklist (ABC). The ABC consisted of 58 items and scored by the parent or caregiver, under the guidance of the investigator at all scheduled visits. The ABC, clinician-administered irritability subscale and target symptoms (range 0-45), listed 15 items such as injury to self, aggressive to others and temper tantrums (item 2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57). Each item was rated on 0 to 3 point scale; 0 = not at all a problem, 3 = the problem is severe in degree.

An inspection assignment was issued in February 2004 per the Review Division's request (HFD-120). These investigators requested for inspection were the high enrollers and/or contributed significant results.

II. RESULTS (by site):

Protocol RIS-USA-150

NAME	Location	ASSIGNED DATE	DATE EIR RECEIVED	FINAL CLASSIFICATION
Christopher McDougle, M.D.	Indianapolis, Indiana	2/19/2004	4/12/2004	VAI
Michael Aman, Ph.D.	Columbus, Ohio	2/19/2004	pending	Pending*

*final classification pending; inspectional findings based on Form FDA-483.

Protocol RIS-CAN-23

NAME	Location	ASSIGNED DATE	DATE EIR RECEIVED	FINAL CLASSIFICATION
William Fleisher, M.D.	Winnipeg, Manitoba	2/10/2004	pending	Pending**
Sarah Shea, M.D.	Halifax, Nova Scotia	2/10/2004	pending	Pending**
Atilla Turgay, M.D.	Scarborough, Ontario	2/10/2004	pending	Pending**

**final classification pending; inspectional findings based on preliminary establishment inspection report (EIR).

1. Christopher McDougle, M.D. (Indiana University)

a. What was inspected: At this site, 20 subjects were enrolled and three withdrawals (subject N5069: trouble swallowing the tablet; subject N5089: behavioral problems; subject 5130: lack of efficacy) for part 1 of the protocol RIS-USA-150. There were seven placebo non-responders entered the eight-week open label trial. Nine subjects were enrolled in parts 2/3 and most subjects withdrew from the study mainly for relapse or requested to withdraw during the double-blind placebo-controlled discontinuation phase. An audit of 10 subjects' records from part 1 and 5 subjects' records from parts 2/3 was conducted.

b. Limitations of inspection: N/A

c. General observations/commentary:

Following a limited review of the source documents, the CRF and data listing (primary efficacy and safety), a Form FDA-483 was issued.

Inspectional findings included: there was adequate documentation to show the subjects existed; all concomitant medications were reported in the CRFs and records indicated subjects took the study medication; the subjects dropped out of the study were reported

accordingly and all adverse experiences documented in the clinic notes were reported in the CRFs.

The study site entered the data into a computer database and transmitted weekly to the (b) (4) Upon comparing the source documents, CRFs and data listing provided by the sponsor, it seemed the study site has made several data entry errors when entering study data into the database (see attached table, appendix).

As stated above, there were instances of inaccurate records. Most of the discrepancies appear minor. However, please note there were approximately 20 errors for subject's 5090 baseline ABC score. Given the fact that the co-primary efficacy variable is change from baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC items #2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57), I have conveyed this observation to the Review Division.

d. Recommendation: DSI suggests the review division to check the SAS data sets in comparison with correct ABC score for subject 5090 as noted in table below. If discrepancy exists, DSI would recommend the review division should contact the sponsor to conduct an audit to ensure accuracy of primary efficacy data provided for study RIS-USA-150. Otherwise, data appear acceptable.

2. Michael Aman, Ph.D. (Ohio State University)

a. What was inspected: 23 subjects were enrolled for part 1 of the study RISP-USA-150. 12 subjects were enrolled in parts 2/3.

b. Limitations of inspection: N/A

c. General observations/commentary:

Subject 07007 (b) (6) protocol part 2 at the 12 week follow up visit (3/21/00), the score for dyspepsia in the side effect review form is changed from 1, mild to 0, absent on 8/27/00 over five months after the visit without a basis/explanation for the change.

Subject 07017 (b) (6) protocol part 1 the week 8 follow up visit electrocardiogram CRF reported that the overall ECG results were 1 or normal, however, the cardiologist reading the source ECG indicates that the ECG was poor quality and uninterpretable and recommends a repeat ECG.

d. Recommendation: DSI suggests the review division to note above minor discrepancies in safety data for two subjects. Overall, data appear acceptable.

3. William Fleisher, M.D. (St. Boniface General Hospital, Winnipeg)

a. What was inspected: At this site, nine subjects were enrolled. An audit of all subjects' records was conducted. No Form FDA-483 was issued at the end of inspection.

b. Limitations of inspection: Inspection took place in the absence of the PI, Dr. Fleisher, who is out on medical leave. The subinvestigator, (b) (6) filled in for him.

c. General observations/commentary:

Subject's 07188 AE of "no menses" that began 10/15/01 was still unresolved while the final study visit occurred on 12/4/01. No follow-up to resolution of this AE was observed in the chart. The protocol did not require measurements of prolactin levels or follow up with prolactin levels in case of amenorrhea or galactorrhea although the hyperprolactinemic effect of antipsychotics could result in the side effects of amenorrhea or galactorrhea.

Dose discrepancy was observed in the dispensing records for two subjects #07185 and 07201. (b) (6), subinvestigator, recalculated the dosing and stated that subject 07185 received only half of the expected dose during Week 3 (Visit 4). From Week 3 through Week 7, it appears the subject was underdosed. For subject 07201, the parents most likely began the prescription risperidone that had been prescribed by the personal physician prior to final study visit when the study drug should have been given.

d. Recommendation: DSI suggests the review division to note above discrepancies. Overall, data appear acceptable.

4. Sarah Shea, M.D. (IWK Grace Hospital, Halifax)

a. What was inspected: At this site, 12 subjects were enrolled. An audit of all subjects' records was conducted. No Form FDA-483 was issued at the end of inspection.

b. Limitations of inspection: N/A

c. General observations/commentary:

Subject's 01172 parents were provided the study medication before lab results and EKG results had been received and reviewed to assure the results were within protocol limits.

d. Recommendation: Data appear acceptable.

5. Atilla Turgay, M.D. (Scarborough General Hospital, Scarborough)

a. What was inspected: At this site, 38 subjects were enrolled. An audit of all subjects' records was conducted.

b. Limitations of inspection: N/A

c. General observations/commentary: The following issues were discussed.

Subject #04109 was randomized as eligible and was seen through Visit 3 before the lab results were received and reviewed by the site. Labs were abnormal for anemia.

The protocol specified that IQ test if not performed within 1 year of trial entry, the Wechsler, Stanfor-Binet, Differential Abilities Scale or McCarthy Scales of Children Abilities may be performed. If it is not possible to perform a verbal cognitive assessment, the Leiter International Performance Scales or Raven's Progressive Matrices may be performed. Ten of the 38 enrolled subjects had no cognitive testing at screening as per protocol. These were: Subjects #04122, 04123, 04148, 04152, 04154, 04157, 04165, 04166, 04173, and 04190.

The following AEs were not reported as adverse events:

Subject #04158: a loss of appetite prior to Visit #3.
Subject #04149: increased appetite Visit #3.
Subject #04165: increased appetite Visit #4.
Subject #04174: a tooth extraction (b) (6) and underwent a general anesthesia for dental work on (b) (6). His dose of study med was held on (b) (6) The dental work/extraction, concomitant med (anesthesia) and held dose were not reported in the CRF.
Subject #04198: increased appetite Visit #5; tiredness the week prior to Visit #4.

We observed the summary of the 1/13/01 investigator meeting; noted there was concern about the effects of risperidone on diabetes. Dr. Turgay stated that he was involved in initiation and implementation of the study. Since they saw no change in blood glucose in the prior two Canadian studies, that might be why they did not include blood glucose level in this study. He stated, though, that they now see in schizophrenia studies that blood glucose is a concern.

We did not see weight gain reported as an adverse event since it was not defined in this study. Dr. Turgay responded that they try to look at height and weight changes over time. He added that the drug effect on height and weight is unique to this population. Dr. Turgay stated that it was difficult to determine if weight gain from the drug or from the "rewards" as schools use food as a reward. He said gaining weight is a normal growth process—it may be significant when compared to baseline; yet many subjects came into the study at weights that were too low. He added that he recalled one case where risperidone was discontinued post-study due to weight gain.

We observed in his progress notes references to prolactin level. Dr. Turgay said that in earlier global studies involving 600 patients they did not see much change in girls; but for boys the levels went down after 3-4 months. He said it is difficult with autistic kids at this age to determine the significance. The protocol did not require to measure prolactin levels or

follow up with prolactin measurements in case of amenorrhea or galactorrhea which are the side effects of hyperprolactinemia.

d. Recommendation: As stated, the site did not report adverse effects of risperidone on appetite of four pediatric study subjects with pervasive developmental disorder. DSI suggests the review division to include these AEs in safety data. DSI also suggests the review division to note the issues on weight gain, blood glucose and prolactin levels. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy data captured.

As stated above, there were instances of inaccurate records at Dr. McDougle's site for protocol RIS-USA-150. Most of the discrepancies appear minor. However, there were approximately 20 errors for subject's 5090 baseline ABC score. Given the fact that the co-primary efficacy variable is change from baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC items #2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57), I have conveyed this observation to the Review Division to check whether or not this subject's ABC score has any impact on study outcome. At Dr. Aman's site, subject 07017 protocol part 1 the week 8 follow up visit electrocardiogram CRF reported that the ECG results were 1 or normal, however, the cardiologist reading the source ECG indicates that the ECG was poor quality and uninterpretable and recommends a repeat ECG.

For protocol RIS-CAN-23, the inspection of Dr. Turgay's site revealed an instance of protocol violation in that subject #04109 was randomized as eligible and was seen through Visit 3 before the lab results were received and reviewed by the site. Labs were abnormal for anemia. Dr. Turgay did not capture all AEs reported by subjects in data listing as the site did not report four subjects' experience of change in appetite during the study. Dose discrepancy was observed in the dispensing records for two subjects #07185 and 07201 at Dr. Fleisher's site.

DSI has concern on adequacy of safety data in this pediatric population with Autistic Disorder based on the findings from the protocol RIS-CAN-23. DSI suggests the review division to note the issue on blood glucose and weight gain, given the fact that the protocol did not require measurement of blood glucose or did not define when to report weight gain as AE. The protocol did not specify any follow up on prolactin level in case of amenorrhea or galactorrhea. Although the study sites obtained ECGs at screening and end of the study, the CRFs were not designed to report the ECG parameters other than to check whether the result was normal or abnormal. DSI considers these as the review issues.

Overall, data from these centers that had been inspected appear acceptable for use in support of this NDA.

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Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

_____

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAI-RR= Deviation(s) form regulations, response received and reviewed. Data acceptable
OAI = Significant deviations for regulations. Data unreliable

Note: The review and evaluation of the audit of Dr. Aman was based on the Form FDA-483 inspectional observations. The review and evaluation of the audit of Canadian sites were based on FDA Investigator's Summary of Findings and preliminary EIR package without the exhibits. Should the EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.

cc:
NDA 20-272/SE1-036
HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Khin
HFD-46/George GCPB1 Files

rd:NK:5/24/04

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Table: Data discrepancies noted at Dr. McDougle's inspection

Subject #	Document	Item	Database Report	Correct data based on Source Document
5090	ABC (baseline 6/30/00)	2 4 6 13 15 17 22 24 29 33 34 35 37 38 40 43 44 45 46 47 51	1 1 1 0 2 1 1 2 2 2 1 1 2 2 3 2 2 1 1 2 3	0 0 3 3 3 3 2 3 3 1 2 2 0 3 2 0 3 3 2 3 2
5130	ABC (week 6; 12/21/00)	28 29	3 1	1 3
5084	ABC (1/5/01)	9	1	2
5131	ABC (1/25/01)	48	2	Blank
5131	AE (Head Movement)	Resolution Date	2/9/01	1/18/01
5090	AE (Coughing and Nasal Congestion)	Resolution Date	Blank	1/28/01

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/s/

Ni Aye Khin
5/25/04 10:34:14 AM
MEDICAL OFFICER

Khin U
5/25/04 12:18:40 PM
MEDICAL OFFICER

Addendum to Review of Response to NA Letter (Submission Jan. 16, 2006):

During the process of my review of the sponsor's response to our nonapprovable (NA) letter for sNDA 20-272/S036 (using risperidone for treatment of irritability associated with autism), I found some important safety issues that needed to be clarified. Hence, the questions were sent to the sponsor but the response came back after I finished my review. The following is my review of the sponsor's response to the four questions I sent.

Question #1: Please explain the term "investigations" in the SAE table under the subsection, Postmarketing Surveillance.

There were a total of 140 cases in children and adolescents categorized in this category. The sponsor submits the following list (see Table 1 below) as the response to this question. It is noted that one case can have more than one preferred term in the System Organ Class.

Most of them reflect laboratory test abnormalities, including liver enzymes or function (AST, ALT, and unconjugated bilirubin), serum chemistry (creatinin, glucose, urea, uric acid, CPK, prolactin, amylase, lipase, triglycerides and cholinerasterase), blood cells (white blood cells, neutrophil count, lymphocyte count, hemotocrit), and coagulation function (prothrombin level, coagulation factors, coagulation time, and platelet count). Changes in vital signs, such as blood pressure, heart rate, temperature, as well as weight are also included. The rest of them are about changes in drug levels, such as anti-convulsants and some unspecified drugs.

Table 1: Serious Cases In Patients Aged 5-17 Years With At Least One Preferred Term Coding to the MedDRA System Organ Class 'Investigations'

Preferred Term	Number of Cases
Alanine aminotransferase increased	5
Anticonvulsant drug level decreased	1
Anticonvulsant drug level increased	1
Antiphospholipid antibodies positive	1
Aspartate aminotransferase increased	5
Blood amylase increased	1
Blood bilirubin unconjugated increased	1
Blood cholinesterase decreased	1
Blood creatine phosphokinase increased	12
Blood creatinine increased	3
Blood glucose abnormal	1
Blood glucose increased	1
Blood lactate dehydrogenase increased	1
Blood pressure decreased	1
Blood pressure increased	2
Blood prolactin increased	14
Blood triglycerides increased	1

Preferred Term	Number of Cases
Blood urea increased	1
Blood uric acid increased	1
Blood urine present	1
Body temperature decreased	3
Body temperature fluctuation	1
Body temperature increased	1
Coagulation factor v level decreased	1
Coagulation factor VIII level decreased	1
Coagulation factor X level decreased	1
Coagulation time prolonged	1
CSF test abnormal	1
Drug level decreased	1
Drug level increased	4
Drug screen positive	1
Electrocardiogram abnormal	3
Electrocardiogram qt corrected interval prolonged	3
Electrocardiogram qt prolonged	7
Electroencephalogram abnormal	3
Glucocorticoids increased	1
Haematocrit decreased	1
Haemoglobin decreased	3
Heart rate decreased	1
Heart rate irregular	2
Hepatic enzyme abnormal	1
Hepatic enzyme increased	5
Laboratory test abnormal	1
Lipase increased	1
Liver function test abnormal	7
Lymphocyte count decreased	2
Neutrophil count decreased	2
Platelet count decreased	6
Protein total decreased	1
Prothrombin level decreased	1
Prothrombin time shortened	1
Transaminases increased	1
Weight decreased	6
Weight increased	43
White blood cell count decreased	9
White blood cell count increased	1

The reason that some of these seem to be split terms is unclear to me. For example, increase ALT, hepatic enzyme increase, and liver function test abnormal are listed separately; another example is neutrophil count decrease and white cell count decrease. Overall, there were 43 weight increase events, 23 events related to liver enzymes, 14 events with prolactin increase, 13 events related to ECG changes (10 were QT

prolongation, of which 3 were prolonged QTc), 13 events related to decreased white cell count, and 3 events with EEG abnormality.

Question #2: Please explain the term "Congenital, Familial and Genetic Disorders" in the SAE table also under the subsection, Postmarketing Surveillance.

To answer this question, the sponsor listed the three terms (4 cases) under this category. They are arteriovenous malformation (1), cryptorchism (1), and Tourette's disorder (2).

The case of "arteriovenous (A-V) malformation" was from the report by a mother of a 16-year-old girl who had a "A-V clipping" procedure in her history. In my opinion, it is highly unlikely that it was associated with risperidone use.

Cryptorchism is frequently found in young male. The causal link of this event and risperidone is considered very unlikely.

It is difficult to rule in or rule out the possibility that risperidone is associated with the exacerbation of Tourette's disorder in a 12-year-old boy who was on multiple medications, including Concerta (18mg, once a day), risperidone (unknown dosage), and clonidine (unknown dosage) for ADHD. Of note, the child was hospitalized for sudden onset of abnormal gait ("staggered") which is probably related to drug-drug interaction.

Similarly, it is hard to determine the association of risperidone and the onset of Tourette's disorder in a 13-year-old girl with a history of fetal alcohol syndrome, learning disabilities with impulsive behavior and subsequently diagnosed with mental retardation and Tourette's disorder. She had psychosis, suicidality and violent behavior while taking both risperidone and methylphenidate.

Question#3: A patient in an ongoing open-label study 234 had hepatic lesion but resolved with sequalae. Please provide the sequalae and send the description of the case if available.

Subject A35111 (RIS-234), an 18-year-old male (date of birth (b) (6)), was described by the investigator to have a 'hepatic lesion', hyperuricemia, and mixed hyperlipidemia and reportedly had the SAE resolved but with sequalae. More detailed information is included in the sponsor's response dated June 30, 2006 as follows:

The subject was on 1 mg per day of risperidone (initiated on August 21, 2003) in this uncontrolled, open-label trial. The sponsor also wrote, "During the trial the patient had previously received risperidone up to a dose of approximately 2 mg per day." There was no other concurrent antipsychotic treatment. Other medical history included possible scoliosis. The subject developed elevated ALT, LDH, triglyceride, and uric acid. This is reported as a serious adverse event (SAE) due to hospitalization (for 2 days) occurred on (b) (6) , reportedly because of *continuing abnormal laboratory values*, however, the sponsor only submitted the lab values for the following two days (see Table 2 below).

Table 2: Submitted Laboratory Tests for Subject A35111 (RIS-234)

Labs Tests	(b) (6)	(b) (6)
ALT	96.0	56.0
AST	29.0	28.0
LDH	88	-
HDL	30.8	34.1
Triglyceride	391.0	283.0
Total Cholesterol	197.0	202.0
Uric Acid	7.01	7.9

The sponsor reports that the event 'abated' after discontinuation of risperidone (last dose received on (b) (6)). Additional information received on 30 July 2004 reported that triglycerides and uric acid increase were considered 'non-serious' but continued mild elevation of ALT and triglycerides. Abdominal ultrasound did not reveal any increase in size or focal changes in liver. *The sponsor didn't mention bilirubin value in the summary*. There were no other imaging or biopsy studies. The investigator deemed the changes in liver enzymes, lipids and uric acid to be 'probably' related to risperidone treatment. The sponsor reports that the investigator is reviewing this subject during clinical follow-up on 30 June 2006.

The changes in laboratory values shown in Table 2 are mild; however, since the information still is incomplete (for instance, no values submitted for the duration of hospitalization), it is difficult to have a more thorough assessment of this case. I am also puzzled that this case was listed as a serious adverse event of Study 234 in the SAE table submitted by the sponsor on June 16, 2006 but not in the table submitted this time, June 30, 2006 (see sponsor's response for Question#4). Thus, further clarification from the sponsor for this case is necessary.

Question#4: Do you have a separate list of cases (not the SAEs) discontinued or died from the four ongoing trials they mentioned? If none, please confirm; if yes, please provide numbers and summaries ASAP.

Deaths:

The sponsor's response confirmed that there were no deaths in any of the short terms placebo-controlled studies but one death (complete suicide) in the open-label study (Study 234).

(Review of Serious Adverse Events is included in my review of the sponsor's response to NA letter for this sNDA submitted January 16, 2006.)

Dropouts due to adverse events:

--Dropouts due to non-serious events are presented below:
In Study RIS-301, adverse event was the most frequent reason that led to drop-out in all dose groups.

Table 3: Subject Disposition and Discontinuation Reasons during Study RIS-301

State of Termination Term. Reason	PLACEBO (N=58) n (%)	RIS 0.5-2.5 MG (N=50) n (%)	RIS 3-6 MG (N=61) n (%)	Total (N=169) n (%)
Completed	46 (79)	45 (90)	46 (75)	137 (81)
Discontinued	12 (21)	5 (10)	15 (25)	32 (19)
Adverse event	4 (7)	3 (6)	10 (16)	17 (10)
Insufficient response	2 (3)	0	2 (3)	4 (2)
Subject ineligible to continue the trial	0	1 (2)	0	1 (1)
Subject lost to follow-up	1 (2)	0	2 (3)	3 (2)
Subject withdrew consent	2 (3)	1 (2)	1 (2)	4 (2)
Subject non-compliant	1 (2)	0	0	1 (1)
Other	2 (3)	0	0	2 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Among all the AEs, 12/17 (71%) were due to non-serious adverse events and most of these non-serious AEs seem to be related to higher dose group, risperidone 3-6mg (see table below).

Table 4: Incidence of Treatment-Emergent Non-Serious Adverse Events With Action Taken of Permanent Stop

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	2 (3)	3 (6)	7 (11)	10 (9)
Psychiatric disorders	1 (2)	1 (2)	5 (8)	6 (5)
Somnolence	0	1 (2)	4 (7)	5 (5)
Aggressive reaction	0	0	1 (2)	1 (1)
Nervousness	0	0	1 (2)	1 (1)
Psychosis manic-depressive	1 (2)	0	1 (2)	1 (1)
Suicide attempt	1 (2)	0	0	0
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	0	0
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.
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In Study 302, the most common reason that led to drop-out was insufficient response and adverse events became the main reason in higher dose group, risperidone 4-6mg (see Table 5).

Table 5: Subject Disposition and Discontinuation Reasons (RIS-302: ITT)

State of Termination Term. Reason	PLACEBO (N=54) n (%)	RIS 1-3 MG (N=55) n (%)	RIS 4-6 MG (N=51) n (%)	Total (N=160) n (%)
Completed	36 (67)	45 (82)	44 (86)	125 (78)
Discontinued	18 (33)	10 (18)	7 (14)	35 (22)
Adverse event	2 (4)	3 (5)	4 (8)	9 (6)
Insufficient response	13 (24)	3 (5)	1 (2)	17 (11)
Subject ineligible to continue the trial	0	1 (2)	0	1 (1)
Subject withdrew consent	2 (4)	3 (5)	1 (2)	6 (4)
Other	1 (2)	0	1 (2)	2 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
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A total of 78% (7/9) of dropouts are from non-serious AEs. Similar to Study 301, there seem to be more incidences of AEs that led to drop-out in higher dose group of risperidone (4-6 mg) in Study 302 (see table below).

Table 6: Incidence of Treatment-Emergent Non-Serious Adverse Events With Action Taken of Permanent Stop (Study 302, ITT)

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)	2 (4)	3 (6)	5 (5)
Psychiatric disorders	2 (4)	1 (2)	3 (6)	4 (4)
Somnolence	0	0	2 (4)	2 (2)
Anorexia	0	0	1 (2)	1 (1)
Anxiety	0	0	1 (2)	1 (1)
Psychosis	2 (4)	1 (2)	0	1 (1)
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.
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In Study 231, the leading cause of dropouts was insufficient response in both high and low dose groups. In higher dose group, AE was the second most cause of dropouts.

Table 7: Subject Disposition and Discontinuation Reasons (Study 231, ITT)

State of Termination Term. Reason	RIS LOW DOSE (N=141) n (%)	RIS HIGH DOSE (N=138) n (%)	Total (N=279) n (%)
Completed	87 (62)	97 (70)	184 (66)
Discontinued	54 (38)	41 (30)	95 (34)
Adverse event	6 (4)	8 (6)	14 (5)
Insufficient response	27 (19)	20 (14)	47 (17)
Subject ineligible to continue the trial	3 (2)	2 (1)	5 (2)
Subject lost to follow-up	3 (2)	0	3 (1)
Subject withdrew consent	10 (7)	6 (4)	16 (6)
Subject non-compliant	0	1 (1)	1 (<1)
Other	5 (4)	4 (3)	9 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Table 8: Incidence of Treatment-Emergent Non-Serious Adverse Events With Action Taken of Permanent Stop (Study 231, ITT)

Trial Phase: Treatment

AE System Organ Class Adverse Event Preferred Term	RIS low dose (N=141) n (%)	RIS high dose (N=138) n (%)	Total (N=279) n (%)
Total no. subjects with perm stop med	3 (2)	6 (4)	9 (3)
Psychiatric disorders	1 (1)	4 (3)	5 (2)
Agitation	1 (1)	2 (1)	3 (1)
Insomnia	0	1 (1)	1 (<1)
Psychosis	0	1 (1)	1 (<1)
Somnolence	0	1 (1)	1 (<1)
Cardiovascular disorders, general	1 (1)	1 (1)	2 (1)
ECG abnormal	0	1 (1)	1 (<1)
Hypertension	1 (1)	0	1 (<1)
Centr & periph nervous system disorders	0	1 (1)	1 (<1)
Eeg abnormal	0	1 (1)	1 (<1)
Respiratory system disorders	0	1 (1)	1 (<1)
Upper resp tract infection	0	1 (1)	1 (<1)
Heart rate and rhythm disorders	1 (1)	0	1 (<1)
Tachycardia	1 (1)	0	1 (<1)
Liver and biliary system disorders	1 (1)	0	1 (<1)
SGOT increased	1 (1)	0	1 (<1)
SGPT increased	1 (1)	0	1 (<1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
ae04c.rtf generated by aenotser.sas.

As in Studies 301 and 302, it also appears that AEs that led to dropouts are more common in higher dose groups (see Table 8 above) in Study 231. Of note, the lower dose group is serving as the placebo group in this study. A total of 64% (9/14) of these dropouts due to AEs are caused by non-serious ones.

The leading causes of dropouts in Study 234 are subject withdrawing consent (10%) and adverse events (10%). Among all cases due to AEs, 41% (12/29) are from non-serious events and the rest are from serious or death (1 from suicidal attempt). Table 9 below depicts the subject disposition and reasons of discontinuation in this study. Most of these events are in the RIS/RIS group.

Table 9: Subject Disposition and Discontinuation Reasons during Study RIS-234 (As of March 31, 2006, ITT)

State of Termination Term. Reason	PLA/RIS (N=41) n (%)	RIS/RIS (N=256) n (%)	Total (N=297) n (%)
Completed	36 (88)	155 (61)	191 (64)
Discontinued	5 (12)	101 (39)	106 (36)
Adverse event	2 (5)	27 (11)	29 (10)
Death	0	1 (<1)	1 (<1)
Insufficient response	1 (2)	16 (6)	17 (6)
Subject ineligible to continue the trial	0	3 (1)	3 (1)
Subject lost to follow-up	0	10 (4)	10 (3)
Subject withdrew consent	2 (5)	28 (11)	30 (10)
Subject non-compliant	0	12 (5)	12 (4)
Other	0	4 (2)	4 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Table 10 (on next page) lists the types of non-serious events that led to discontinuation in Study 234. It appears no unusual events on this list.

From the ongoing trials, it seems that higher dosage is associated with more AEs that led to dropouts.

--SAEs that led to drop-out are psychosis, manic-depressive, suicide attempts, allergy, and brain edema.

In Study 301, one subject had allergy in the 3-6mg group; suicide attempt occurred in both placebo and higher dose (3-6mg) groups (1 of each). All others are “psychosis manic-depressive.”

In Study 302, the two SAEs that led to dropouts are both psychosis, one in 1-3mg group and another in 4-6mg group. None occurred in placebo group.

In Study 231, both dose groups actually equal dropouts from SAEs (3 of each). Except for the patient who developed cerebral edema and suicidality, all others were psychosis.

In Study 234, the only additional reason that causes dropout as SAE is aggressive reaction. All others are similar cases as mentioned in other three studies, such as psychosis, and suicidal attempts.

Table 10: Incidence of Treatment-Emergent Non-Serious Adverse Events With Action Taken of Permanent Stop (RIS-234, ITT)

Trial Phase: Open-label

AE System Organ Class Adverse Event Preferred Term	PLA/RIS (N=41) n (%)	RIS/RIS (N=256) n (%)	Total (N=297) n (%)
Total no. subjects with perm stop med	2 (5)	10 (4)	12 (4)
Centr & periph nervous system disorders	0	3 (1)	3 (1)
Extrapyramidal disorder	0	2 (1)	2 (1)
Dystonia	0	1 (<1)	1 (<1)
Psychiatric disorders	0	3 (1)	3 (1)
Agitation	0	1 (<1)	1 (<1)
Hallucination	0	1 (<1)	1 (<1)
Psychosis	0	1 (<1)	1 (<1)
Liver and biliary system disorders	0	2 (1)	2 (1)
SGPT increased	0	2 (1)	2 (1)
SGOT increased	0	1 (<1)	1 (<1)
Endocrine disorders	0	1 (<1)	1 (<1)
Hyperprolactinaemia	0	1 (<1)	1 (<1)
Metabolic and nutritional disorders	1 (2)	1 (<1)	2 (1)
Hypertriglyceridaemia	0	1 (<1)	1 (<1)
Hyperuricaemia	0	1 (<1)	1 (<1)
LDH increased	0	1 (<1)	1 (<1)
Phosphatase alkaline increased	0	1 (<1)	1 (<1)
Weight increase	1 (2)	0	1 (<1)
Reproductive disorders, female	0	1 (<1)	1 (<1)
Lactation nonpuerperal	0	1 (<1)	1 (<1)
Cardiovascular disorders, general	1 (2)	0	1 (<1)
ECG abnormal	1 (2)	0	1 (<1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
aedc.rtf generated by aenotser.sas.

Clinical Reviewer's Conclusion and Comments: Review of the above added safety information from the sponsor basically does not change my conclusion from the review of this sNDA application. However, the sponsor still needs to provide more detailed information of subject A35111 (RIS-234).

June Cai, MD
Medical Officer, DPP
July 5, 2006

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

/s/

June Cai
7/6/2006 11:17:14 AM
MEDICAL OFFICER

Ni Aye Khin
7/6/2006 01:33:33 PM
MEDICAL OFFICER
See memo to file for more detailed comments

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-272/S-036/041
NDA 20-588/S-024/028/029
NDA 21-444/S-008/015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # / SUPPL # 20-272 / SE1-036; 20-588 / SE1-024 ; 21-444 / SE1-008 HFD # 130

Trade Name RISPERDAL Tablets [NDA 20-272], RISPERDAL Oral Solution [20-588], RISPERDAL M-TAB Orally Disintegrating Tablets [21-444]

Generic Name risperidone

Applicant Name Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Approval Date, If Known See Date of Approval Letter

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Three (3)

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 20-272 Risperdal Tablets

NDA# 20-588 Risperdal Oral Solution

NDA# 21-346 Risperdal CONSTA Intramuscular Injection

NDA# 21-444 Risperdal M-TAB Orally Disintegrating Tablets

2. Combination product. ***Not Applicable***

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Study 1: CAN-23
Study 2: US-150

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 CAN-23 YES ☐ NO ☒

Investigation #2 US-150 YES ☐ NO ☒

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

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

Investigation #1 CAN-23 YES ☐ NO ☒

Investigation #2 US-150 YES ☐ NO ☒

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

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

Investigation #1 CAN-23
Investigation #2 US-150

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

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

Investigation #1 CAN-23	!	
	!	
IND #31,931 YES ☒	! NO ☐	
	! Explain:	
Investigation #2 US-150	!	
	!	
IND #31,931 YES ☒	! NO ☐	
	! Explain:	

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

Investigation #1	!	
	!	
YES ☐	! NO ☐	
Explain:	! Explain:	

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of Person completing form: Doris J. Bates, Ph.D.
Title: Regulatory Health Project Manager, Division of Psychiatry Products

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

Please see DFS Signature Page for Dates of Signature

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Doris Bates
10/5/2006 07:23:52 PM
Indication: treatment of the irritability associated with autistic disorder

Thomas Laughren
10/6/2006 01:28:01 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA Number, Supplement Type, Supplement Number: 20-272/SE1-036, 20-588/SE1-024, 21-444/SE1-008

Stamp Date: December 19, 2003; Resubmission January 16, 2006 **Action Date:** PDUFA Date July 17, 2006

HFD 130 **Trade and generic names/dosage form:** Risperdal (Risperidone) Tablets, Oral Solution, and M-TAB

Applicant: Johnson & Johnson Pharmaceutical R&D, LLC

This indication: irritability associated with autistic disorder

Indication(s) previously approved: schizophrenia (short- and long-term treatment), bipolar disorder (monotherapy and concomitant tx with lithium or valproate)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived. PLEASE SEE PEDIATRIC PAGES FOR THE PRIOR APPROVED INDICATIONS FOR THIS INFORMATION.

Number of indications for this application(s): 1

Indication #1: irritability associated with autistic disorder

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☑ **No: Please check all that apply:** √ **Partial Waiver** ____ **Deferred** ____ **Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived: 0-2, 2-5 and 17 - 18 years

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☑ **Disease/condition is difficult to diagnose accurately and/or to treat medically in children younger than 2**
- ☐ **Too few children with disease to study**

- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ☑ **Other: Information on children 2 - 5 and 17 - 18 can be extrapolated from the data available on children 5 - 16 years old.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies: 5 to 16 years of age

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Doris J. Bates, Ph.D. (see electronic signature page)
Regulatory Project Manager

cc: NDA 20-272 / S-036, 20-588 / S-024, 21-444 / S-008
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Doris Bates
7/7/2006 03:52:55 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA / Efficacy Supplement Type / Supplement Number : NDA 20-272 / SE1-036; SLR-041; NDA 20-588 / SE1-024; SLR-028, SLR-029; NDA 21-444 / SE1-008, SLR-015		
Drug: RISPERDAL (risperidone) Tablets, Oral Solution, and M-TABS, respectively	Applicant: Johnson & Johnson Pharmaceutical R&D, LLC	
RPM: Doris J. Bates, Ph.D.	HFD-130	Phone # 301-796-2260
Application Type: **(√)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	**( )** Standard **(√)** Priority
• Chem class (NDAs only)	--
• Other (e.g., orphan, OTC)	--
❖ User Fee Goal Dates	11 October 2006
❖ Special programs (indicate all that apply)	**(√)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(√)** Paid **UF ID number** (b) 19-Dec-2003
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (√) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(√) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(√) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. ***Not applicable, not a 505(b)(2) application.***	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	√ ***YES but only through 04DEC2006 -- See Exclusivity Summary***
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (√) No
❖ Administrative Reviews (Project Manager, ADRA)	Not applicable
General Information	
❖ Actions	
• Proposed action AP for all SE1s; all SLRs acknowledged/retained & superseded by the SE1s.	(√) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 18 JUN 2004 NA 19 MAY 2005 AE 14 JUL 2006
• Status of advertising (approvals only)	(√) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(√) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter (√) **To be determined by Press Office**
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Final Agreed Upon labeling	√
• Most recent applicant-proposed labeling	√
• Original applicant-proposed labeling	See prior AE package
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of	See prior packages

labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Not applicable, no special container / closure system for the drug products in this indication.
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See approval letter for details
• Documentation of discussions and/or agreements relating to post-marketing commitments	See Correspondence section of this package
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	√
❖ Memoranda and Telecons	√
❖ Minutes of Meetings	
• EOP2 meeting	See previous Packages
• Pre-NDA meeting	See previous Packages
• Pre-Approval Safety Conference	Not Applicable
• July 26, 2006 teleconference	√
• Complete Response Filing Meeting August 23, 2006	√
❖ Advisory Committee Meeting	
• Date of Meeting	Not Applicable
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Not Applicable
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader))	√
Clinical Information	
❖ Clinical review(s)	√
❖ Microbiology (efficacy) review(s)	not applicable
❖ Safety Update review(s)	√
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	not applicable
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	√
❖ Demographic Worksheet *(NME approvals only)*	not applicable
❖ Statistical review(s)	See previous action packages
❖ Biopharmaceutical review(s)	√- Phase 4 Commitment
❖ Controlled Substance Staff review(s) and recommendation for scheduling	not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See previous action packages
• Bioequivalence studies	not applicable
CMC Information	
❖ CMC review(s)	See previous action packages
❖ Environmental Assessment	

• Categorical Exclusion • Review & FONSI • Review & Environmental Impact Statement	See previous action packages
❖ Microbiology (validation of sterilization & product sterility) review(s)	not applicable
❖ Facilities inspection (provide EER report)	not applicable
❖ Methods validation	not applicable
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews	√ - Phase 4 Commitment
❖ Nonclinical inspection review summary	not applicable
❖ Statistical review(s) of carcinogenicity studies	not applicable
❖ CAC/ECAC report	not applicable

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/s/

Doris Bates
10/5/2006 07:29:24 PM

Bates, Doris J

From: Bates, Doris J
Sent: Friday, September 29, 2006 4:46 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal Autism sNDA - Additional FDA Proposal regarding labeling - patients with Parkinson's Disease and Dementia with Lewy Bodies
Importance: High

Dear Dr. Abeysinghe:

Concurrently with our review of your supplemental NDAs for treatment of the irritability associated with autistic disorder, we have now completed our review of your proposal to add language to the "PRECAUTIONS: Use in Patients with Concomitant Illness" section of labeling for Risperdal tablets, oral solution, and M-TABS [NDA supplements 20-272/S-041, 20-588/S-028 and -029, and 21-444 / S-015].

We propose the following language to describe a possibly increased risk of neuroleptic malignant syndrome and 'sensitivity' to antipsychotic medication in patients with Parkinson's Disease and Dementia with Lewy Bodies who are administered risperidone [language proposed by FDA, based in part on your proposal, is shown in green]:

FDA-PROPOSED LABELING TEXT: **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.

Please incorporate this additional language into your response to our labeling proposal of September 28, 2006. We intend to supersede the labeling supplements listed above and incorporate this additional proposed change into the labeling to be acted on under NDA 20-272/S-36, 20-588 S-024, and 21-444 S-008.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
9/29/2006 05:12:02 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Friday, September 29, 2006 3:22 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: NDA 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008: Phase 4 Commitment Finalization Proposal
Importance: High

Dear Dr. Abeysinghe:

We have received and acknowledge your agreement to the Phase 4 Commitment requests as outlined in the attached emails [thread below].

Thank you very much, and best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

From: Abeysinghe, Harindra [PRDUS] [mailto:HAbeysin@PRDUS.JNJ.com]
Sent: Friday, September 29, 2006 3:00 PM
To: Bates, Doris J
Subject: RE: NDA 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008: Phase 4 Commitment Finalization Proposal

Dear Dr. Bates:

With regards to the Risperdal Autism sNDA, we have reviewed the proposals regarding the phase IV commitments for the Juvenile Rat and Dog Toxicology studies as well as the Combined Clinical and Clinical Pharmacology Study, and agree with the particulars as outlined in your email of September 28, 2006.

Please email or call me at (b) (6) if you have any questions.

Best Regards.....Harindra

Harindra R Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical R & D
1125 Trenton-Harbourton Road, P.O.Box 200
Titusville, NJ 08560
Tel: 609-730-6212
Fax: 609-730-3091
Email: habeysin@prdus.jnj.com

-----Original Message-----
From: Bates, Doris J [mailto:doris.bates@fda.hhs.gov]
Sent: Thursday, September 28, 2006 11:28 AM
To: Abeysinghe, Harindra [PRDUS]
Cc: Bates, Doris J
Subject: NDA 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008: Phase 4 Commitment Finalization Proposal
Importance: High

Dear Dr. Abeysinghe:

We have the following responses and proposals with regard to the Phase 4 Commitment Requests presented in our July 14, 2006 approvable letter for the above referenced supplemental new drug applications.

1. Nonclinical Juvenile Rat Toxicology Study

- We note your agreement to perform an additional juvenile rat toxicity study at the requested higher dose of 2.5 mg/kg/day. We request that you modify the hormone assessment section of this study to include measurement of levels of Insulin-like Growth Factor (IGF-1).
- We request submission of the final study protocol on or before 30 June 2007.
- We agree with your proposal for submitting the final study report on or before 31 March 2009.

2. Nonclinical Juvenile Dog Toxicology Study

- We note your agreement to perform a juvenile dog toxicity study, to evaluate the effects of risperidone on the development of the organs of reproduction. We request that you modify the hormone assessment section of this study to include measurement of levels of Insulin-like Growth Factor (IGF-1). We also request that you include assessment of long bone growth in this study.
- We request submission of the final study protocol on or before 30 June 2007.
- We agree with your proposal for submitting the final study report on or before 31 March 2009.

3. Combined Clinical and Clinical Pharmacology Study

- We note your agreement to perform a study in autistic children and adolescents to determine the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. This study will be a 6-week, fixed-dose, parallel-group, placebo-controlled design, to be completed three years after approval of the proposed protocol. We request that the hormone assessment section of this study be modified to incorporate measurement of growth hormone (GH) and Insulin-like Growth Factor (IGF-1) as well as the previously agreed upon measurements.
- We request submission of the final study protocol on or before 30 December 2007.
- We agree with your proposal for submitting the final study report on or before 31 March 2010.

Please respond by reply e-mail to this message. We are required to reach agreement on all the particulars listed above prior to the issuance of an action letter for this review cycle. Reply e-mail will serve as adequate documentation for further negotiation if necessary, and for capturing final agreement in writing.

Thank you and best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
9/29/2006 04:00:23 PM
CSO

This DFS entry captures final agreeement re the Phase 4 commitments for these supplemental applications in writing.

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, September 28, 2006 11:28 AM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: NDA 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008: Phase 4 Commitment Finalization Proposal
Importance: High

Dear Dr. Abeysinghe:

We have the following responses and proposals with regard to the Phase 4 Commitment Requests presented in our July 14, 2006 approvable letter for the above referenced supplemental new drug applications.

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- We request submission of the final study protocol on or before 30 June 2007.
- We agree with your proposal for submitting the final study report on or before 31 March 2009.

2. Nonclinical Juvenile Dog Toxicology Study

- We note your agreement to perform a juvenile dog toxicity study, to evaluate the effects of risperidone on the development of the organs of reproduction. We request that you modify the hormone assessment section of this study to include measurement of levels of Insulin-like Growth Factor (IGF-1). We also request that you include assessment of long bone growth in this study.
- We request submission of the final study protocol on or before 30 June 2007.
- We agree with your proposal for submitting the final study report on or before 31 March 2009.

3. Combined Clinical and Clinical Pharmacology Study

- We note your agreement to perform a study in autistic children and adolescents to determine the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. This study will be a 6-week, fixed-dose, parallel-group, placebo-controlled design, to be completed three years after approval of the proposed protocol. We request that the hormone assessment section of this study be modified to incorporate measurement of growth hormone (GH) and Insulin-like Growth Factor (IGF-1) as well as the previously agreed upon measurements.
- We request submission of the final study protocol on or before 30 December 2007.
- We agree with your proposal for submitting the final study report on or before 31 March 2010.

Please respond by reply e-mail to this message. We are required to reach agreement on all the particulars listed above prior to the issuance of an action letter for this review cycle. Reply e-mail will serve as adequate documentation for further negotiation if necessary, and for capturing final agreement in writing.

Thank you and best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

9/28/2006

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/s/

Doris Bates
9/28/2006 11:40:43 AM
CSO

Bates, Doris J

From: Villalba, Lourdes
Sent: Monday, September 25, 2006 3:35 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Hughes, Alice; Bates, Doris J
Subject: RE: Risperdal Autism sNDA - Complete Response - Request for Clini cal Safety Information - follow-up question

Yes, we confirm that we are interested in the case with protrusion of the lower mandible (CAN-19/A3652).

Thank you

Dr. Villalba

-----Original Message-----
From: Abeysinghe, Harindra [PRDUS] [mailto:HAbeysin@PRDUS.JNJ.com]
Sent: Monday, September 25, 2006 2:55 PM
To: Bates, Doris J
Cc: Hughes, Alice; Villalba, Lourdes
Subject: RE: Risperdal Autism sNDA - Complete Response - Request for Clini cal Safety Information - follow-up question

Dear Drs. Alice Hughes, Maria Villalba, and Doris Bates,

Further to the request for the narrative or CRF for the case from CAN-19/A3661 (protrusion of lower mandible), we have the following questions:

CAN-19/A3661 did not have 'protrusion of lower mandible', this AE was reported for CAN-19/A3652. This event was not an SAE for A3652 nor did the subject have any other SAE and the subject did not drop out for an AE, so a CRF was not submitted. A3661 did not have any SAE and did not drop out for any AE.

Can you confirm that you are requesting the CRF for the case with 'protusion of lower mandible' as an AE, which is A3652?

Thanks.....Harindra

Harindra R Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical R & D
1125 Trenton-Harbourton Road, P.O.Box 200
Titusville, NJ 08560
Tel: 609-730-6212
Fax: 609-730-3091
Email: habeysin@prdus.jnj.com

-----Original Message-----
From: Bates, Doris J [mailto:doris.bates@fda.hhs.gov]
Sent: Monday, September 25, 2006 1:09 PM
To: Abeysinghe, Harindra [PRDUS]
Cc: Hughes, Alice; Villalba, Lourdes; Bates, Doris J

Subject: RE: Risperdal Autism sNDA - Complete Response - Request for Clini cal Safety Information
Importance: High

Dear Dr. Abeysinghe

Our clinical safety team has reviewed your correspondence from last week and has the following additional questions: a reply is requested by COB tomorrow, Tuesday, September 26.
~~~~~~~~
Questions for the sponsor regarding 9/22/06 response:

1. In your 9/22/06 response to the Division's request for clarification, you provided analyses of the incidence of hyperprolactinemia in pediatric subjects who had both baseline and follow-up prolactin levels, with a baseline value below the upper limit of normal [36/82 (44%) in placebo-controlled trials].

Please clarify the following:

A. Which studies were included in these analyses?

B. What was the cut-off value for the upper limit of normal?

2. You provided the incidence of amenorrhea among all patients randomized (boys and girls of any age). Please provide the incidence of amenorrhea among post-pubertal females.

3. Please provide narratives and/or case report forms for the following cases:

A. CAN-19/A3661 (protrusion of lower mandible)

B. INT-41/A03431 (Calve-Legg-Perthes syndrome)

C. INT-41/A03457 (epiphyseolysis)

Please respond to these requests by Tuesday, September 26, 2006. Thank you.

~~~~~~~~~~
As previously, please use the 'reply to all' option to respond to this message so that your reply is not delayed by internal rerouting.

Please contact us if you have any questions regarding these requests.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I

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/s/

Doris Bates
9/25/2006 04:26:26 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Monday, September 25, 2006 1:09 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Hughes, Alice; Villalba, Lourdes; Bates, Doris J
Subject: RE: Risperdal Autism sNDA - Complete Response - Request for Clini cal Safety Information

Importance: High

Dear Dr. Abeysinghe

Our clinical safety team has reviewed your correspondence from last week and has the following additional questions: a reply is requested by COB tomorrow, Tuesday, September 26.
~~~~~~~~
Questions for the sponsor regarding 9/22/06 response:

1. In your 9/22/06 response to the Division's request for clarification, you provided analyses of the incidence of hyperprolactinemia in pediatric subjects who had both baseline and follow-up prolactin levels, with a baseline value below the upper limit of normal [36/82 (44%) in placebo-controlled trials].

Please clarify the following:

A. Which studies were included in these analyses?

B. What was the cut-off value for the upper limit of normal?

2. You provided the incidence of amenorrhea among all patients randomized (boys and girls of any age). Please provide the incidence of amenorrhea among post-pubertal females.

3. Please provide narratives and/or case report forms for the following cases:

A. CAN-19/A3661 (protrusion of lower mandible)

B. INT-41/A03431 (Calve-Legg-Perthes syndrome)

C. INT-41/A03457 (epiphyseolysis)

Please respond to these requests by Tuesday, September 26, 2006. Thank you.

~~~~~~~~~~
As previously, please use the 'reply to all' option to respond to this message so that your reply is not delayed by internal rerouting.

Please contact us if you have any questions regarding these requests.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
9/25/2006 01:32:51 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, September 20, 2006 1:19 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J; Hughes, Alice; Villalba, Lourdes
Subject: Risperdal Autism sNDA - Complete Response - Request for Clinical Safety Information

Importance: High

Dear Dr. Abeysinghe:

Our clinical safety review team has the following requests pertaining to review of your response to the approvable letter.

Please note that we have requested a rapid turnaround on this; I am therefore listing both Dr. Hughes and Dr. Villalba as CC recipients on this message. Please use the 'reply to all' option when responding, so that there will be no delays [due to forwarding] on our end when we receive your response.

1. (b) (4)

2. Since not all trials included prolactin measurement, please provide the number of patients who had prolactin measurement in pediatric protocols and the number and percentage of patients (in whom prolactin was measured) who had hyperprolactinemia in those trials.

3. Review of the November 18, 2004 datasets indicates that there were four patients in trial INT-79 who had elevated IGF-1 levels. Please provide a listing of IGF-1 levels and adverse events for the four patients who had elevated IGF-1 levels (similar to the listings provided for those who had GH excess).

4. As per Table 6 of your August 9 CR, there were 504 subjects enrolled in INT-41. Datasets submitted as part of the CR of November 2004, however, indicate that there were only 481 subjects. Please clarify this discrepancy.

Please contact us if you have any questions regarding these requests. Please provide this response by close of business tomorrow, September 21, 2006. Thank you.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
9/20/2006 01:49:02 PM
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Bates, Doris J

From: Bates, Doris J
Sent: Friday, September 01, 2006 2:42 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal Autism sNDA - Complete Response - Request for CRF

Importance: High

Good afternoon Harindra:

Our clinical reviewer would like you to send us the CRF for subject #RO JNJFOC-20050700284 (ris-usa-231).

If this is available electronically, that would be great - but please follow up with a submission to the supplements as well.

We will not be here on Monday but will be back on Tuesday through the rest of the week.

Thank you as always,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
9/1/2006 02:52:38 PM
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MINUTES: COMPLETE RESPONSE MEETING
NDA 20-272/S-036, 20-588/S-024, 21-444/S-008
Johnson & Johnson PR&D:
RISPERDAL® (risperidone) Tablets, Oral Solution, M-TAB
Autism

Date/Time/Place: August 23, 2006, 1:00 P.M., CDER White Oak CR 4396
Participants: Drs. Laughren, Khin, Cai, Baweja, Jackson, Elayan, Updegraff, Hughes, Bates.

Reviewer Roster:

Discipline	**Reviewer**
Regulatory Project Management:	Bates
Clinical:	Cai
Clinical Safety:	Hughes / Villalba
Controlled Substances:	N/A
DDRE:	N/A
Statistical:	N/A this cycle
Pharmacology:	Elayan
Statistical Pharmacology:	N/A
Chemistry:	N/A this cycle
Environmental Assessment (if needed):	N/A this cycle
Biopharmaceutical:	Jackson
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A this cycle
DDMAC:	N/A this cycle
Other Consults:	none

505(b)(2)? NO

LETTER DATE: 10AUG2006
STAMP DATE: 11AUG2006
14-DAY DECISION DATE: 25AUG2006

DATE OF MIDCYCLE MEETING: ------
DATE OF OFFICE DIRECTOR BRIEFING ------

ACTION LETTER SIGNATORY AUTHORITY: ***Division Director*** or Office Director

DATE REVIEWS ARE DUE:

To Team Leaders:	20SEP2006
To Clinical Team Leader:	27SEP2006
To Division Director:	04OCT2006
To Office Director:	Not Applicable

~~2 Month CR Due Date Is 11-OCT-2006 ~~

Meeting Details:

Clinical & Clinical Safety: Complete, reviewable. Phase 4 commitment response appears acceptable on face. Safety review will focus on hyperprolactinemia, (b) (4) pituitary adenoma labeling issues.

Biopharmaceutics: Complete, reviewable. Phase 4 commitment response is acceptable on face. (b) (4) No further issues anticipated.

Pharmacology: Complete, reviewable. Juvenile animal Phase 4 study commitments submitted for rat and dog. Appears acceptable on face. No labeling input anticipated since presently available juvenile tox does not support labeling changes.

CMC: Not applicable in this cycle.

Statistics: Not applicable in this cycle.

Electronic submissions: All-electronic submission. Labeling submitted as SPL and as WORD files.

Regulatory / Project Management:
1. Note that this submission takes a two month review clock.
2. Note that the labeling for this product is a combined insert affecting three drug products with three NDAs. All are addressed by submissions. There is no PPI and no MedGuide.
3. There is no RiskMAP.

CONCLUSIONS: COMPLETE RESPONSE. Notify Firm by telephone and prepare letter.

ACTION ITEM:

CR acknowledgement letter to be drafted and sent. [Sent 8-23-06 at 1:54 PM.]

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

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/s/

Doris Bates
9/26/2006 04:47:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036
NDA 20-588/S-024
NDA 21-444/S-008

Harindra R. Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development LLC
1125 Trenton-Harbourton Road, PO Box 200
Titusville, NJ 08560-0200

Dear Dr. Abeysinghe:

We acknowledge receipt on August 11, 2006 of your August 10, 2006 resubmissions to your supplemental new drug applications (sNDAs) for Risperdal® (risperidone) Tablets, Oral Solution, and M-TAB.

We consider the resubmissions to be complete, class 1 responses to our July 14, 2006 action letter. Therefore, the user fee goal date is October 11, 2006 for all three sNDAs.

If you have any questions, please contact the undersigned, at (301).796.1040.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
8/23/2006 01:54:18 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-860, Dr. Baweja, Dr. Jackson			FROM: HFD-120, Dr. Bates for Dr. Cai	
DATE 15AUG06	IND NO.	NDA NO. 20-272 S-036, 20-588 S-024, 21-444 S-008	TYPE OF DOCUMENT Complete Response to AE letter	DATE OF DOCUMENT 10AUG2006
NAME OF DRUG Risperidone	PRIORITY CONSIDERATION Supplement Complete Response [2 or 6 month clock]		CLASSIFICATION OF DRUG autism	DESIRED COMPLETION DATE: CR meeting 23AUG06 2 month deadline 11OCT06 6 month deadline 11FEB07

NAME OF FIRM: Johnson & Johnson PR&D, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ *OTHER (SPECIFY BELOW): Phase 4 commitments.*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Complete Response in electronic format submitted 10-aug-06. Posted to server 15-AUG-06. Hard copy desk copy accompanies this consult. Submission is in COMIS and in EDR. Please link review to N20272 SE1 036 AZ 10-AUG-2006 in DFS. Please also link to AZ 10-AUG-2006 for N20588 SE1024 and N21444 SE1 008. Clinical Reviewer is J. Cai, PM is D. Bates. *Please make sure Dr. Bates is designated PM, or review will go to Dr. Kiedrow.*

OCPB Review requested regarding Phase 4 commitment proposals from applicant.

SIGNATURE OF REQUESTER see DFS signature page	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
8/15/2006 12:28:01 PM
Submissions are being recoded to AZ in DFS. Please link review to 10-AUG-2006 [AZ] submissions for 20-272/S036, 20-588/024, 21-444/S-008.

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, July 27, 2006 4:56 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal Autism sNDA - FDA teleconference - follow-up information

Hello Harindra - to save time I will 'embed' my replies within your message, point by point; see responses below, in purple for contrast. I have cleared this information with Drs. Cai, Khin, and Laughren as appropriate.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

-----Original Message-----
From: Abeysinghe, Harindra [PRDUS] [mailto:HAbeysin@PRDUS.JNJ.com]
Sent: Thursday, July 27, 2006 3:59 PM
To: Bates, Doris J
Subject: Risperdal Autism sNDA - FDA teleconference - follow-up information

Dear Doris,

Further to the FDA teleconference yesterday, there is some follow-up information that I would like to request from you.

1. Can you please provide the case numbers that the Agency requested additional information on:
A. Follow-up information on 1 cerebral edema case in clinical study RIS-USA-231
this case number is RO-JNJFOC-20050700284.

B. Follow-up information on 2 cases of fatal NMS with cerebral edema, and 4 cardiac deaths cases from post marketing reports
the two NMS case numbers are US-JNJFOC-20040908713 and JP-JNJFOC-20041106870
the cardiac case numbers are AU-JNJFOC-20040305038, ES-JNJFOC-20040706670, NL-JNJFOC-20040907839, and JAOCAN-2000001168.

2. Can you please clarify the request to provide information regarding growth hormone from module 2.7.4/Safety Update that was part of the 18 Nov 2004 Complete Response. Is the FDA requesting an explanation of the Adverse Event of growth hormone excess in the table. Can you also provide the page number and table that was referred to at the meeting?
The referenced table is Table 2.7.4.24, on page 255 of the resubmission. Our question was (1) why the hormone levels were measured in the study subjects, i.e. why this hormone was measured in this particular study, and (2) how many subjects actually had this measurement done, i.e. was it standard for all subjects, a limited sample gleaned from subjects selected at random, or were there 'triggering' criteria for performing the measurement in certain subjects only [if so, please explain]. We would also like to know if the reported results were adjusted to compensate for age and for pubertal development.

3. With the Complete Response, are we required to submit draft labeling in XML format or can we submit draft labeling in MS word?
Please submit draft labeling in WORD. We will ask you to submit in XML after we have completed negotiations, immediately post approval. I do recommend that you have your IT persons contact the EDR to make sure they

understand that **we will still consider the response complete if it arrives without the XML file, as long as it is complete in all other respects and includes the WORD version of draft labeling**. [This has been precleared with Dr. Laughren.]

4. At the teleconference, we discussed information and proposed labeling text from the 21 July 06 Briefing Document and the 25 July 06 Addendum document that was submitted by email in preparation for the meeting. These were not formally submitted to the NDA 20-272. Should I submit theses two documents formally with the meeting minutes?

That would be ideal, since the review team could then reference them directly 'in situ'. Thank you!

In closing, thank you so much for all your efforts in arranging this very productive teleconference meeting.

Thank you too, with special thanks to your overseas colleagues who were calling from their homes or stayed late at work. We understand and appreciate their efforts and yours.

Kind Regards.....Harindra

Harindra R Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical R & D
1125 Trenton-Harbourton Road, P.O.Box 200
Titusville, NJ 08560
Tel: 609-730-6212
Fax: 609-730-3091
Email: habeysin@prdus.jnj.com

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/s/

Doris Bates
7/27/2006 05:17:06 PM
CSO
Sent to applicant on 7-27-06 at 4:56 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA / Efficacy Supplement Type / Supplement Number : NDA 20-272 / SE1-036; (b) (4) -043, -044 NDA 20-588 / SE1-024; (b) (4) -032, -034 NDA 21-444 / SE1-008; (b) (4) -017, -018		
Drug: RISPERDAL (risperidone) Tablets, Oral Solution, and M-TABS, respectively	Applicant: Johnson & Johnson Pharmaceutical R&D, LLC	
RPM: Doris J. Bates, Ph.D.	HFD-130	Phone # 301-796-2260
Application Type: (√) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	( ) Standard (√) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	17 July 2006
❖ Special programs (indicate all that apply)	(√) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(√) Paid **UF ID number** (b) (4) 19-Dec-2003
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)

	_____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (√) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(√) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(√) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. ***Not applicable, not a 505(b)(2) application.***	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). ***Not applicable, not a 505(b)(2) application***	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).* ***Not applicable, not a 505(b)(2) application***	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No ( ) Yes ( ) No

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	( ) Yes ( ) No
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	√ YES
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (√) No

❖ Administrative Reviews (Project Manager, ADRA)	Not applicable
General Information	
❖ Actions	
• Proposed action AE for all SE1s; all SLRs acknowledged/retained & superseded by the SE1s.	( ) AP ( ) TA (√) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 18 JUN 2004 NA 19 MAY 2005
• Status of advertising (approvals only)	will be requested in AP letter when AP letter is issued
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (√) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter ( ) To be determined by Press Office
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	√
• Most recent applicant-proposed labeling	√
• Original applicant-proposed labeling	-
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	See prior packages
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Not applicable, no special container / closure system for the drug products in this indication.
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	not applicable
• Documentation of discussions and/or agreements relating to post-marketing commitments	not applicable
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	√
❖ Memoranda and Telecons	√
❖ Minutes of Meetings	
• EOP2 meeting	Early Consultation Meeting
• Pre-NDA meeting	√
• Pre-Approval Safety Conference	Not Applicable
• Other	End of Review Conference
❖ Advisory Committee Meeting	
• Date of Meeting	Not Applicable
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Not Applicable

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader))	√
Clinical Information	
❖ Clinical review(s)	√
❖ Microbiology (efficacy) review(s)	not applicable
❖ Safety Update review(s)	see clinical review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	not applicable
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	√
❖ Demographic Worksheet *(NME approvals only)*	not applicable
❖ Statistical review(s)	See previous action packages
❖ Biopharmaceutical review(s)	√- Sheiner analysis
❖ Controlled Substance Staff review(s) and recommendation for scheduling	not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	√
• Bioequivalence studies	not applicable
CMC Information	
❖ CMC review(s)	See previous action packages
❖ Environmental Assessment	
• Categorical Exclusion	See previous action packages
• Review & FONSI	
• Review & Environmental Impact Statement	
❖ Microbiology (validation of sterilization & product sterility) review(s)	not applicable
❖ Facilities inspection (provide EER report)	not applicable
❖ Methods validation	not applicable
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews	√ - See also previous action pkg
❖ Nonclinical inspection review summary	not applicable
❖ Statistical review(s) of carcinogenicity studies	not applicable
❖ CAC/ECAC report	not applicable

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/s/

Doris Bates
7/19/2006 12:06:40 PM
Action taken on July 14, 2006. See signed approvable letter issued on that date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Epidemiology & Surveillance	FROM: Dr. J. Cai, DPP, HFD-130 THROUGH: Dr. N. A. Khin, Dr. T. P. Laughren, HFD-130

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Jul. 14, 2006		20272/S-036	AZ	January 16, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE:
risperidone	Standard	Antipsychotics	August 20, 2006

NAME OF FIRM: Johnson & Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: *A subject experienced brain edema in an ongoing active control trial of risperidone. This event was reported in a recent Safety Update. Additionally, the sponsor reported brain edema or increased intracranial pressure in two pediatric patients who died from NMS in the post-marketing setting. To my knowledge, this phenomenon has not been reported previously and brain edema is not in the current labeling for risperidone.*

In light of these three events, we are requesting a search of AERS for cases of brain edema in patients aged 5-18 years old. Please call June Cai (796-1049) or Ni Khin (796-2260) with any questions about this consult. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
June Cai (medical officer) Ni Khin (team leader)	X MAIL ☐ HAND

Alice Hughes (acting safety team leader)	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Thomas Laughren
7/17/2006 10:01:25 AM

Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, June 27, 2006 5:05 PM
To: 'Malchow, Rodney D [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal - autism- clarification on clinical reviewer questions

Hi Rodney,

Our clinical reviewer and team leader are in agreement that your proposed response as outlined should meet our needs.

Many thanks and I do apologize for the delay - we had to clarify one point internally before I could respond to you.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

-----Original Message-----
From: Malchow, Rodney D [PRDUS] [mailto:RMalchow@PRDUS.JNJ.COM]
Sent: Tuesday, June 27, 2006 12:12 PM
To: Bates, Doris J
Subject: Risperdal - autism- clarification on clinical reviewer questions

Dear Dr. Bates,

Per your email of June 26, 2006, our post-marketing safety surveillance group, Benefit Risk Management, (BRM) is compiling the information requested in question's 1 and 2:

1) Please explain the term, "investigations" in the SAE of PM surveillance table;

2) Please also explain what are the disorders/conditions included in "congenital & familial genetic disorders" also in the SAE of PM surveillance table -- Please provide summaries and descriptions if available.

In response to these questions, we intend to provide:

* A frequency tabulation of preferred terms for all (140) serious spontaneous events within the "Investigations" MedDRA SOC for children or adolescents (ages 5-17 years) on risperidone through 30 April 2005.
*
* A frequency tabulation of preferred terms for all (4) serious spontaneous events within the "Congenital, familial, and genetic disorders" MedDRA SOC for children or adolescents (ages 5-17 years) on risperidone through 30 April 2005.
*
* CIOMS forms for the 4 serious cases within the Congenital, familial, and genetic disorders SOC.

Please let me know if this will meet the reviewer's needs.

Kind regards,
Rodney Malchow, JD
Manager, Regulatory Affairs
J&JPRD
Phone: +1.908.704.5668
Fax: +1.908.722.5113
email: rmalchow@prdus.jnj.com

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/s/

Doris Bates
6/30/2006 01:52:15 PM
CSO
Sent to firm on June 27, 2006 at 5:05 P.M.

Bates, Doris J

From: Bates, Doris J
Sent: Monday, June 26, 2006 10:52 AM
To: 'Abeysinghe, Harindra [PRDUS]'; 'Malchow, Rodney D [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal - autism - questions from clinical reviewer
Importance: High

Dear Drs. Abeysinghe and Malchow:

I have received the following questions from our clinical reviewer with regard to your pending efficacy supplement:

1) Please explain the term, "investigations" in the SAE of PM surveillance table;

2) Please also explain what are the disorders/conditions included in "congenital & familial genetic disorders" also in the SAE of PM surveillance table -- Please provide summaries and descriptions if available.

3) Additionally, a patient in an ongoing open-label study 234 had hepatic lesion but resolved with sequelae. Please describe the sequelae? --Please send the description of the case if available.

4) Do you have a separate list of cases (not the SAEs) discontinued or died from the four ongoing trials mentioned? If none, please confirm; if yes, please provide numbers and summaries ASAP.

Please reply by secure email or FAX, with a copy of the reply submitted to the official record.

Please feel free to contact me if you have any questions about this message,

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
6/30/2006 01:47:02 PM
CSO
Sent to firm on June 26, 2006 at 10:52 a.m.

Bates, Doris J

From: Bates, Doris J
Sent: Friday, June 23, 2006 4:07 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: 'Malchow, Rodney D [PRDUS]'; Bates, Doris J
Subject: RE: Risperdal - NDA 20-272 / S036 and related submissions: Request for base labeling text

Dear Dr. Abeysinghe and Mr. Malchow:

We are currently reviewing labeling in connection with the above referenced submission and are attempting to consolidate labeling language from multiple prior submissions into one text document.

Would it be feasible for you to provide us with the following review aid documentation:

(1) A marked-up WORD file, using the most recent approved version of the package insert as basis, which includes the following additional changes:
- the proposed language for the autism indication
- the CBE language for the amitriptyline, cimetidine, ranitidine, digoxin and paroxetine interactions, as per your May 18, 2006 submission to this Division, also including the revised PK language noted therein
- the CBE language for the furosemide labeling, again as per the May 18, 2006 submission
- the CBE language related to (b) (4) pituitary adenomas and reversible extrapyramidal symptoms in neonates, as proposed in your October 25, 2005 submission to this Division.

(2) A clean WORD file, with 'track changes' turned off, formatted as 'final', which is identical to the marked-up file described above, in terms of content.

If you would be able to provide these files, we would greatly appreciate receiving them at your earliest convenience; they may be provided by secure e-mail to this address, and need not be separately submitted to the archive.

Please feel free to contact me if you have any questions about this request.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
6/30/2006 01:58:43 PM
CSO
Sent to company on June 23, 2006 at 4:07 PM

Bates, Doris J

From: Bates, Doris J
Sent: Friday, June 23, 2006 4:07 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: 'Malchow, Rodney D [PRDUS]'; Bates, Doris J
Subject: RE: Risperdal - NDA 20-272 / S036 and related submissions: Request for base labeling text

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(2) A clean WORD file, with 'track changes' turned off, formatted as 'final', which is identical to the marked-up file described above, in terms of content.

If you would be able to provide these files, we would greatly appreciate receiving them at your earliest convenience; they may be provided by secure e-mail to this address, and need not be separately submitted to the archive.

Please feel free to contact me if you have any questions about this request.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
6/23/2006 04:17:15 PM
CSO

Barry N. Rosloff, Ph.D.
6/20/06

NDA 20-272 (S-036)
SUPERVISORY MEMO

I am in agreement with the recommendations made in Dr. Elayan's review of 6/12/06, i.e. this NDA is approvable, with the following Phase IV commitments: (1) Performance of a rat juvenile study using a higher dose than was used in the study submitted, and (2) Performance of a juvenile study in dogs.

Regarding the rat study, as discussed by Dr. Elayan, a dose higher than the HD of 0.63 mg/kg could have and should have been used. In a rangefinding study, a dose of 2.5 mg/kg produced similar toxicity to the next lowest dose of 0.63 mg/kg, the only clear difference being cold body surface and cold/dark extremities transiently (during the first few days of dosing only) at the 2.5 mg/kg dose; in addition 1 pup at the higher dose was dehydrated and had labored breathing on a single day. Bodyweight gains were decreased at both doses, with the effects at 2.5 mg/kg equal to or slightly *less* than those at 0.63 mg/kg. Plasma AUC values (for parent drug + 9-OH risperidone) at the 0.63 mg/kg dose are estimated to be roughly similar to those in humans receiving the currently proposed maximum dose; based on data from the rangefinding study achievable levels at 2.5 mg/kg are about 3X greater than those at 0.63 mg/kg.

I concur with Dr. Elayan that rat data at a higher dose could be obtained as a phase IV commitment. Some toxicity (clinical signs, decreased bodyweight gain) was seen at the high dose of 0.63 mg/kg (although these effects tended to decrease during the study; there were no effects on bodyweight at the end of the treatment period), and this dose (as well as lower doses) caused (expected) increases in plasma prolactin. Thus, the HD was likely not many fold less than an MTD.

Regarding a juvenile dog study, as noted by Dr. Elayan it had previously been agreed to perform such a study; in fact there were discussions with the sponsor about the specifics of a protocol. However, in the minutes of the meeting with the sponsor of 12/7/05 it is stated that "The need for [a juvenile dog study] …will be determined based on review of…the [juvenile] rat study"; the rationale for this departure from the previous agreement is not clear; no pharm/tox personnel were present at this meeting. At any rate, effects on reproductive organs were seen in both the juvenile rat study and in previous adult dog toxicity studies, and thus a juvenile dog study should be performed.

In conclusion,

(1) A juvenile rat study of risperidone should be performed using doses greater than 0.63 mg/kg; based on rangefinding data it appears that a dose of 2.5 mg/kg would be tolerated. It is noted that the sponsor is being asked to conduct a juvenile rat study for the active

metabolite 9-0H risperidone (IND (b) (4) it would be acceptable to add an arm using risperidone to that study.

(2) A juvenile dog study should be performed to evaluate the effects of risperidone on the development of the organs of reproduction; such a study should include a recovery period.

Both of the above may be performed as phase IV commitments.

(b) (4)

Barry Rosloff, Ph. D.

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/s/

Barry Rosloff
6/23/2006 12:28:30 PM
PHARMACOLOGIST

Bates, Doris J

From: Bates, Doris J
Sent: Friday, June 09, 2006 1:46 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal Autism sNDA [20-272 /S036 and referenced]: Question from Clinical Reviewer

Hello Dr. Abeysinghe:

I have one additional request from our clinical reviewer.

May we have the same information presented in the same way as the information you have just provided, but for the ongoing studies in children and adolescents with schizophrenia and bipolar that were submitted in the recent Safety Update to the complete response? In this safety update, there are 85 SAE events reported in 65 cases, from Study 301, 302, 231, and 234 (we know 234 is the open label extension of 231).

Tables for these 85 events / 65 cases would suffice for this request. Forwarding copies via secure email, with followup submission to the file, would be very helpful.

Again, please feel free to contact me if there are any questions regarding this additional inquiry.

Thank you again,

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

-----Original Message-----
From: Abeysinghe, Harindra [PRDUS] [mailto:HAbeysin@PRDUS.JNJ.com]
Sent: Thursday, June 08, 2006 1:40 PM
To: Bates, Doris J
Subject: RE: Risperdal Autism sNDA [20-272 /S036 and referenced]: Question from Clinical Reviewer

Dear Dr. Bates,

The submission did not contain a table with such a listing. Dosing information for SAEs was listed in the subject narratives. However, we can generate such a listing as described in the email below and provide it to you tomorrow (9 June 06). Please let me know if this would be acceptable.

Best Regards.....Harindra

Harindra R Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical R & D
1125 Trenton-Harbourton Road, P.O.Box 200
Titusville, NJ 08560
Tel: 609-730-6212

Fax: 609-730-3091
Email: habeysin@prdus.jnj.com

-----Original Message-----
From: Bates, Doris J [mailto:doris.bates@fda.hhs.gov]
Sent: Wednesday, June 07, 2006 5:12 PM
To: Abeysinghe, Harindra [PRDUS]
Cc: Bates, Doris J
Subject: RE: Risperdal Autism sNDA [20-272 /S036 and referenced]: Question from Clinical Reviewer

Dear Dr. Abeysinghe:

I have the following question on behalf of our clinical reviewer for the risperidone autism sNDA:
*****
We are having difficulty locating a table of SAEs which includes information related to the dosage the patient was taking at time of event [i.e., unblinded information on dose of study drug, or placebo].

Could you direct us to such a table in the submission, or provide the dosage information [i.e. SAEs sorted by indication and stratified by dose] if it was not previously incorporated into an available table?
*****
Please feel free to contact me if there are any questions regarding this inquiry,

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
6/9/2006 02:01:33 PM
CSO
sent to firm on June 9 2006 at 1:46 PM

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, June 07, 2006 5:12 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal Autism sNDA [20-272 /S036 and referenced]: Question from Clinical Reviewer

Dear Dr. Abeysinghe:

I have the following question on behalf of our clinical reviewer for the risperidone autism sNDA:
*****
We are having difficulty locating a table of SAEs which includes information related to the dosage the patient was taking at time of event [i.e., unblinded information on dose of study drug, or placebo].

Could you direct us to such a table in the submission, or provide the dosage information [i.e. SAEs sorted by indication and stratified by dose] if it was not previously incorporated into an available table?
*****
Please feel free to contact me if there are any questions regarding this inquiry,

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
6/7/2006 05:23:40 PM
CSO
Sent to applicant on June 7 2006 at 5:12 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-120 / Drs. Katz, Feeney, Dimitrova			FROM: HFD-120 / Drs. Laughren, Andreason, Hearst	
DATE 22 MAY 2006	IND NO. ---	NDA NO. 20-272 SLR 041 20-588 SLR 028 20-588 SLR 029 21-346 SLR 009 21-444 SLR 015	TYPE OF DOCUMENT CBE Labeling supplement with proposed class labeling	DATE OF DOCUMENT 23 FEB 2005
NAME OF DRUG risperidone	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG antipsychotic, antimanic	DESIRED COMPLETION DATE: July 30, 2006

NAME OF FIRM: Johnson and Johnson Pharmaceutical Research and Development (formerly Janssen)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION [PROPOSED]
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW -- PHASE $ COMMITMENT ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Per discussion 5-22-06 and attached background information [hard copy only], please provide a brief clinical description of the term 'sensitivity' as it is used by neurologists with respect to patients with Parkinson's Disease or Dementia with Lewy Bodies and their response to antipsychotic medication.

If labeling changes are recommended, either as class labeling or to the applicant's own CBE revisions, please indicate how the applicant's proposed language [see attachments] might best be revised to reflect the understanding of practicing neurologists.

Please link the consult response to the supplements referenced above.

SIGNATURE OF REQUESTER Doris J. Bates, Ph.D.	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
5/22/2006 02:06:00 PM
with concurrence of clinical reviewer and clinical team leader

Thomas Laughren
5/22/2006 02:13:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-860, Dr. Baweja, ?			FROM: HFD-120, Dr. Bates for Dr. Cai	
DATE 2-2-06	IND NO.	NDA NO. 20-272 S-036, 20-588 S-024, 21-444 S-008	TYPE OF DOCUMENT Complete Response to NA letter	DATE OF DOCUMENT January 16, 2006
NAME OF DRUG Risperidone	PRIORITY CONSIDERATION Supplement Complete Response [6 month clock]		CLASSIFICATION OF DRUG autism	DESIRED COMPLETION DATE: Review due by June 12 2006 PDUFA goal date July 17, 2006

NAME OF FIRM: Johnson & Johnson PR&D, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ *OTHER (SPECIFY BELOW):* *Sheiner anal sis, mean dose week anal.*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
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III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Complete Response in electronic format submitted 1-16-06. Hard copy desk copy accompanies this consult. Submission is in COMIS and in EDR. Please link review to N20272 SE1 036 AZ 16-Jan-2006 in DFS. Please also link to AZ 16-Jan-2006 for N20588 SE1024 and N21444 SE1 008. Clinical Reviewer is J. Cai, PM is D. Bates.

OCPB Review requested following Admin Rounds 2-2-06, with respect to attempted dose-response analyses [post hoc] including Sheiner analysis of dose response.

SIGNATURE OF REQUESTER see DFS signature page	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
2/2/2006 03:25:28 PM
See comments on bottom of consult form regarding requested links: three supplemental NDAs affected.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036
NDA 20-588/S-024
NDA 21-444/S-008

Harindra R. Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development LLC
1125 Trenton-Harbourton Road, PO Box 200
Titusville, NJ 08560-0200

Dear Dr. Abeysinghe:

We acknowledge receipt on January 17, 2006 of your January 16, 2006 resubmissions to your supplemental new drug applications (sNDAs) for Risperdal® (risperidone) Tablets, Oral Solution, and M-TAB.

We consider the resubmissions to be complete, class 2 responses to our May 19, 2005 action letter. Therefore, the user fee goal date is July 17, 2006 for all three sNDAs.

If you have any questions, please contact the undersigned, at (301).796.1040.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates

1/31/2006 01:36:38 PM

MINUTES: COMPLETE RESPONSE MEETING
NDA 20-272/S-036, 20-588/S-024, 21-444/S-008
Johnson & Johnson PR&D:
RISPERDAL® (risperidone) Tablets, Oral Solution, M-TAB
Autism

Date/Time/Place: January 30, 2006, 3:00 P.M., CDER White Oak CR 4396
Participants: Drs. Laughren, Andreason, Yang, Rosloff, Bates.
Contributing: Drs. Cai, Elayan

Reviewer Roster:

Discipline	**Reviewer**
Regulatory Project Management:	Bates
Clinical:	Cai
Clinical Safety:	N/A
Controlled Substances:	N/A
DDRE:	N/A
Statistical:	Yang
Pharmacology:	Elayan
Statistical Pharmacology:	N/A
Chemistry:	Bouie [RPM]
Environmental Assessment (if needed):	N/A this cycle
Biopharmaceutical:	Jackson
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A this cycle
DDMAC:	N/A this cycle
Other Consults:	none

505(b)(2)? NO

LETTER DATE: 16JAN2006
STAMP DATE: 17JAN2006
14-DAY DECISION DATE: 31JAN2006

DATE OF MIDCYCLE MEETING: 26APR2006
DATE OF OFFICE DIRECTOR BRIEFING ------

ACTION LETTER SIGNATORY AUTHORITY: ***Division Director*** or Office Director

DATE REVIEWS ARE DUE:

To Team Leaders:	12JUN2006
To Clinical Team Leader:	26JUN2006
To Division Director:	03JUL2006
To Office Director:	Not Applicable

~~6 Month CR to NA Letter Due Date Is 17-JUL-2006 ~~

Meeting Details:

Clinical & Clinical Safety: Complete, reviewable. Note that actual label claim is (b) (4) 'irritability associated with autism'.

Statistics: No issues. Scheiner analysis requires Biopharmaceutics assessment; no statistics review per se is needed otherwise.

Biopharmaceutics: Consult sent February 2, 2006. Firm reports that Scheiner analysis infeasible post hoc, because of study design.

Pharmacology: Juvenile animal tox study submitted, full study reports. Firm provided CD-ROM desk copy. Response appears complete for tox.

CMC: Not applicable in this cycle.

Electronic submissions: All-electronic submission, with full desk copies including CD-ROM of juvenile animal tox study. Labeling submitted as SPL and as WORD files.

Regulatory / Project Management:
1. Note that this is a CR to an NA letter and therefore takes a six month review clock. The Division will attempt to act on the submission prior to that deadline; the six month time frames are listed as defaults.
2. Note that the labeling for this product is a combined insert affecting three drug products with three NDAs. All are addressed by submissions. There is no PPI and no MedGuide.
3. There is no RiskMAP.

CONCLUSIONS: COMPLETE RESPONSE. Notify Firm by telephone and prepare letter.

ACTION ITEMS:

1. OCPB consult to be sent ASAP. [Sent 2-2-06]
2. Mid-cycle meeting to be scheduled. [To be held 4-26-06]
3. CR acknowledgement letter to be drafted and sent. [Sent 1-31-06]
4. Briefing for Dr. Temple. [To be scheduled.]
5. Labeling discussion meetings. [To be scheduled.]

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

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/s/

Doris Bates

3/23/2006 04:29:28 PM

Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, December 20, 2005 3:18 PM
To: 'Abeysinghe, Harindra [PRDUS]'
Cc: Bates, Doris J
Subject: RE: Risperdal Autism

Hello Dr. Abeysinghe:

I have discussed your question with Dr. Laughren. We do understand that it seems redundant to submit information to both an IND and an NDA in close succession, but I'm afraid we have to ask you to do that. An NDA must contain all reviewable components directly in order to be complete 'on face' and a Complete Response must do likewise.

We don't generally review an NDA by referring to the IND for essential documentation. If this were the case, we would have extensive IND cross-referencing in all sections of all NDAs, and actual NDAs would be much smaller in size, more or less routinely. So we do need to ask that the clinical safety information and the rat study be in the resubmission, even though it will be in the IND.

There is an additional aspect as well, which is that information under an IND is not commonly accessed during FOI inquiries or other such processes, but information in an NDA may be potentially accessible to such inquiries. To cross-refer to an IND in support of an NDA is potentially to bring the entire IND into the NDA. We understand the importance of protecting proprietary information and I therefore did want to note this point.

As a result, we do need your clinical safety information in PSUR format as part of the NDA resubmission, and we will need the rat study is part of the NDA resubmission also.

We hope this information is helpful to you,

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

-----Original Message-----
From: Abeysinghe, Harindra [PRDUS] [mailto:HAbeysin@PRDUS.JNJ.com]

Sent: Tuesday, December 20, 2005 11:26 AM
To: Bates, Doris J
Subject: Risperdal Autism

Dear Doris,

Further to the Dec 7th FDA meeting and preparations for submitting the Complete Response for the Risperdal Autism sNDA, we will be filing the Clinical Study report (CSR) for the INT-84 (RIS-INT-84, an open-label extension of the previously submitted study RIS-INT-79) to the Risperdal IND-31,931. We will also include some of the relevant safety information from this study in the Complete Response and cross reference to the CSR as appropriate.

In addition, can we also submit the CSR for the Juvenile Rat Tox study to the Risperdal IND-31,931 and include a synopsis with the Complete Response?

If this is acceptable, we can submit the CSRs for INT-84 & the Juv Rat Tox study to the IND next week. The idea being that we can provide this information to the Division sooner to perhaps to help facilitate the review.

Best Regards and happy holidays to you.

Harindra

Harindra R Abeysinghe Ph.D.
Associate Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical R & D
1125 Trenton-Harbourton Road, P.O.Box 200
Titusville, NJ 08560
Tel: 609-730-6212
Fax: 609-730-3091
Email: habeysin@prdus.jnj.com

PLEASE NOTE NEW ADDRESS & PHONE

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/s/

Doris Bates
12/20/2005 03:27:48 PM
CSO
Concurrence obtained on content before sending.

Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, December 20, 2005 3:10 PM
To: 'Abeysinghe, Harindra [PRDUS]'; Bates, Doris J
Subject: RE: Risperdal Autism: FDA Minutes for December 7 Meeting Attached

Dec 7 05 Mtg Mins DFS.pdf (31 .

Dear Dr. Abeysinghe:

I am attaching the signed FDA minutes from our December 7 meeting to this email. [I will be replying to your email from earlier this morning in a separate message.]

Note that Dr. Laughren has signed these minutes for both himself and Dr. Andreason.

Please let me know if you have any difficulty opening or printing the attachment. If you have any questions or concerns regarding our minutes, please contact me for follow up.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
12/20/2005 03:25:01 PM
CSO

Risperdal (Autism)
Meeting with Firm
NDA 20-272/S-036, 20-588/S-024, 21-444/S-008

DATE: December 7, 2005 **Time:** 10:00 A.M. **LOCATION:** WO 22 Rm. 1313

PARTICIPANTS*: (FDA)* R. Temple, T. Laughren, P. Andreason, J. Cai, P. Yang, J. Zhang, D. Bates *(J&J)* H. Abeysinghe, K. Basmadjian, I. Caers, P. DeSantis, B. Goldmann, K. Karcher, S. Kushner, V. Kusumakar, J. Palumbo, G. Pandina, S. Reines, K. Stranick.

Administrative History: Autism is a relatively uncommon, serious neurodevelopmental disorder manifested by a spectrum of signs and symptoms, including irritability, which can significantly add to the distress and burden of the illness and interfere with patients' functioning and receptivity to treatment.

In a pre-NDA meeting on April 1, 2003, FDA and J&J agreed that two pivotal studies [150 and 23] would suffice for filing a supplement. The supplement was submitted December 19, 2003 for treatment of irritability associated with autism. Priority review status was assigned.

An approvable action was taken on June 18, 2004. FDA's letter acknowledged that J&J demonstrated efficacy for this indication, but was concerned that most patients received doses near the maximum allowable dose and that many experienced significant adverse events (AEs). The Division could not tell whether the high doses were actually necessary, and was concerned about longer-term risks such as tardive dyskinesia, prolactin elevation, weight gain, and tachycardia. FDA suggested a fixed-dose study could be necessary to adequately explore dose-response, but offered to begin labeling discussions based on available data, to optimize dosing. Juvenile animal toxicity studies [2 species] were requested as a Phase 4 commitment.

J&J submitted a Complete Response on November 18, 2004. On May 19, 2005 FDA issued a Not Approvable letter concluding (1) that the incidence of AEs remained unacceptably high even at the lowest doses studied and (2) that the proposed dosing recommendations did not permit the identification of a dose that was both effective and adequately safe. This letter reiterated concerns about long-term risks and noted new concerns regarding coding of events such as akathisia and dyskinesia. A dose-response study, and two juvenile animal toxicity studies, were requested as part of any Complete Response.

J&J then requested and was granted a meeting with the Division and Dr. Temple to discuss key issues related to the incidence of adverse events, coding of adverse events, long-term safety, efficacy, and the proposed dosing regimen.

Background: At FDA's internal meeting on December 5, the following decisions were made. Yes/no decisions were conveyed to J&J by the PM following the internal meeting. Details and follow up were discussed with J&J in the December 7 face to face meeting.

Adverse Events. *J&J* took the position that the AEs reported in the autism program were largely mild to moderate in severity, qualitatively similar to AEs reported in adults, transient, and led to discontinuation in only about 1.3% of cases. In addition, they suggest that: (1) the use of a questionnaire to elicit AEs in study 150 may have resulted in a higher incidence of AEs compared to other risperidone trials, (2) the fidgetiness, movements, and posturing inherent in autism may have been mistaken for EPS, and (3) many patients in this program were treatment naïve, unlike in many

other risperidone programs, and this could have resulted in a higher reported incidence of AEs. Nevertheless, J&J is willing to develop an education program regarding AEs with this drug.

FDA found J&J's position and proposal reasonable and acceptable.

Coding of Adverse Events. In response to FDA's concern that certain events that may have represented "akathisia" were misclassified, J&J recalculated the EPS rate, including agitation, nervousness, and anxiety, resulting in a reduction of the drug-placebo difference with respect to EPS. In response to FDA's concern that certain events that may have represented tardive dyskinesia (TD) were misclassified as "dyskinesia," J&J obtained additional information on the 5 patients with events classified as dyskinesia, and felt that these events were not TD.

FDA agreed that J&J made a reasonable argument that events possibly representing akathisia and tardive dyskinesia had not been misclassified.

Long-Term Safety. *J&J* obtained followup information on 5 events of particular interest, in response to FDA's concern about long-term safety. For dystonia and dyskinesia, J&J was confident that this followup confirmed that the events did not represent tardive dystonia or tardive dyskinesia. For prolactinemia, the company found that the increase was temporary and tended to normalize by 1 year. Regarding growth and maturation, the company has accumulated data suggesting no delay in growth or maturation.

FDA agreed that this was plausible based on the information provided.

Efficacy and Proposed Dosing Regimen. *J&J* argued that a "start low, go slow" recommendation is the optimal approach, and is in fact more conservative than the current standard of care with risperidone use in pediatric practice. Nevertheless, J&J expressed willingness to conduct a fixed-dose trial during phase 4, if deemed necessary.

FDA agreed that J&J made a reasonable argument that the proposed dosing recommendations, based on the 2 autism studies, might improve prescribing practices for this population. Nevertheless, FDA felt that more work needs to be done to better understand the dose response relationship for risperidone in autism. FDA decided to request that J&J further evaluate existing data from these trials to explore dose response:

(1) examine mean dose by week correlated to irritability rating;
(2) attempt a reanalysis of available data using approaches developed by Sheiner, et al.

If such approaches prove useful, they might reasonably substitute for an additional dose response trial.

Conclusions and next actions: At the December 7 meeting, the following agreements were reached.

1. J&J will submit a Complete Response to the Division. This will take a six month review clock, but the Division does not anticipate requiring the entire six months to complete the action.
2. The Complete Response will include:
   - Presentation of mean dose by week for study 150 [linked to irritability ratings]
   - Sheiner analysis for both trials, as feasible; J&J should discuss efforts made, if the analysis is infeasible or otherwise fails.
   - Revised proposed labeling.
   - Safety-related information as follows: (1) new fasting glucose data [from Study 84, which is an open label extension of Study 79 in pediatric patients with disruptive behavioral disorders,

age range 5 – 17 y.o.]; (2) a full safety update to include new information available [Pediatric Pharmacovigilance report, cutoff is April 2005] and all SAEs from ongoing pediatric studies; (3) clarification of the response to FDA's question about EKG data [viz., how many patients' data was obtained from the original traces, from copies of original traces, or was not available]; (4) a reanalysis of dyskinetic events, corresponding to information presented in the meeting background package; (5) additional analysis of hormone levels [prolactin, leptin; from Study 150].

- A regulatory update, to include (1) regulatory status worldwide, (2) worldwide literature search, with translations as appropriate (3) foreign labeling with translations as appropriate.
- The rat juvenile toxicity study will soon be available and will be included in the Complete Response. N.B.: the dog study has not been initiated. The need for this study as a Phase 4 commitment will be determined based on review of the resubmission, including the rat study.

3. Minutes will be exchanged. Because the conclusions presented in the NA letter have been revised, the meeting minutes may be referenced as the basis for the Complete Response.

Post Meeting Notes:

Please see appended electronic signature page. Dr. Laughren's signature indicates acceptance of these minutes for provision to the firm and for the Agency files.

Doris J. Bates, Ph.D.
Regulatory Project Manager

P. Andreason, M.D.
Deputy Director, Division of Psychiatry Products

Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products

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/s/

Doris Bates
12/20/2005 02:53:08 PM

Thomas Laughren
12/20/2005 02:56:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036
NDA 20-588/S-024
NDA 21-444/S-008

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Jackie Brown, R.Ph.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Brown:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) Tablets, Oral Solution and M-TAB.

We consider this a complete, class 2 response to our June 18, 2004 action letter. Therefore, the user fee goal date is May 19, 2005.

If you have any question, call Melina Griffis, R.Ph., Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
12/24/04 10:43:55 AM

Griffis, Melina

From: Griffis, Melina
Sent: Wednesday, May 26, 2004 8:43 AM
To: 'Zoschg, Megan [PRDUS]'
Subject: RISPERDAL - Autism NDA 20-272/S-036

Hi Megan,

Below are our recommendations for the juvenile animal toxicity studies in rat and dog (submission dates April 2, 2004 and May 17, 2004):

1. The rat juvenile study protocol appears to be adequate except that assessment of neurobehavioral development (i.e., motor and sensory function, learning and memory) needs to be conducted during treatment and after an appropriate washout period following the cessation of treatment (in order to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals need to be used at the two assessment times. Therefore, neurobehavioral testing could be conducted in subset I during treatment and in subset II following cessation of treatment (after an appropriate washout period). As you have planned, reproductive effects should be evaluated after cessation of treatment following completion of the neurobehavioral assessment (i.e., in subset II).

2. The protocol for the dog juvenile study needs to be revised as follows:

   (a) the study should be conducted in both males and females, not only in males as proposed.

   (b) a detailed neurological examination needs to be conducted at the end of the treatment period (prior to the last dose) and at the end of the recovery period.

   (c) evaluation of cardiovascular parameters should be conducted.

   (d) hormonal and sperm assessment should be conducted at the end of the treatment and recovery periods.

   (e) the histopathological evaluation needs to include examination of a full battery of tissues, in addition to a thorough evaluation of male reproductive organs.

****

Melina Griffis, R.Ph, LCDR-USPHS
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, FDA
(301) 594-5526
(301) 594-2858 (fax)
melina.griffis@fda.hhs.gov (email)

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/s/

Melina Griffis
5/26/04 08:42:18 AM
CSO

Griffis, Melina

From: Griffis, Melina
Sent: Tuesday, May 04, 2004 10:48 AM
To: 'Zoschg, Megan [PRDUS]'
Subject: RE: RISPERDAL - Autism NDA 20-272/S-036 - Question re: CRFs/ summ ary

Hi Megan,

Below is a comment from my pharm/tox team regarding your April 2, 2004 submission.

In your submission dated April 2, 2004 you propose to conduct a juvenile toxicity study in only one animal species (i.e., rat), based on the extent of previous clinical (pediatric and adult) and nonclinical experience. However, we continue to believe that juvenile studies in rodent and nonrodent are needed to support the use of risperidone for autism, based on the age of the intended patient population (≥5 years) and the adverse effects on male reproductive organs (testis, prostate) observed in the oral toxicity studies of risperidone in dogs (NDA 20-272).

Also there were some formatting problems with the PK files that you sent me over the last few days. Before I email you the specific problems I think we should wait for the formal electronic submission. Can you tell me when that was sent?

Melina

****

Melina Griffis, R.Ph, LCDR-USPHS
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, FDA
(301) 594-5526
(301) 594-2858 (fax)
melina.griffis@fda.hhs.gov (email)

> -----Original Message-----
> **From:** Zoschg, Megan [PRDUS] [mailto:MZoschg@PRDUS.JNJ.com]
> **Sent:** Friday, April 16, 2004 8:37 AM
> **To:** Griffism (E-mail)
> **Subject:** RE: RISPERDAL - Autism NDA 20-272/S-036 - Question re: CRFs/ summ ary
>
> Hi Melina:
>
> Just to let you know, we sent the case summaries (b) (4) to the Division yesterday, so you should receive them today. We summarize in them the data available to us, which unfortunately does not include IND Safety Reports because this study was not conducted under the U.S. IND (RUPP/ NIMH were primary trial sponsors). As of yesterday, we still had not received approval from the site to obtain the CRFs ourselves, but

the site did indicate that they could send the CRFs directly to FDA. We have provided the instructions to the site consistent with your advice for the CRF from Indiana. You should receive these in the next few days.

Also, I wanted to follow-up with you in regard to our response to the Filing Communication issue #6 (re: animal studies). Within our response, we requested the opportunity for a teleconference to discuss any questions the Division might have regarding our proposal; I am wondering if you have yet gotten any feedback from the toxicology reviewer on this response and request?

Best regards,
Megan

-----Original Message-----
From: Griffis, Melina [mailto:GriffisM@cder.fda.gov]
Sent: Wednesday, April 07, 2004 12:18 PM
To: 'Zoschg, Megan [PRDUS]'
Subject: RE: RISPERDAL - Autism NDA 20-272/S-036 - Question re: CRFs/ summ ary

Hi Megan,

Below is a reply from my clinical team leader regarding your inquiry (see below). Also another option that my team has suggested is to get at the relevant data from the IND Safety Reports. Presumably, the study was conducted under the U.S. IND and reports of deaths and SAE's during the trial should have been submitted to the IND soon after occurrence and also summarized in the IND Annual Reports. Maybe you can explore this avenue and resubmit the data to the NDA.

> Please realize that I am answering your question about what should be contained in a case summary for a death or serious adverse adverse event without knowing exactly what is present in the submission. If what I describe is already in the submission, please be so kind as to direct us to its whereabouts since I am told that we have not been able to find it. In general, one should approach these summaries from the context that these are patients who have had treatment related serious adverse events and deaths and that we want to know what a physician or group of physicians would want to know when reviewing and discussing a patient's treatment related death or serious outcome at Mortality and Morbidity rounds.
>
> -Chief complaint/identifying profile at study entry
> -History/Physical/labs at baseline
> -History of onset of serious event/physical findings and labs associated with event
> -Initial differential diagnosis and workup of the event
> -Results of the workup and intervention or post mortem if a death (history/physical/labs)
> -Differential diagnostic and prognostic conclusions based on results of intervention (this includes whether or not one concludes that the event was likely to be drug related and why)
> -Further interventions or work-up, why they were done, their results and further conclusions based on history/physical/labs.
> -Additionally, since this is an NDA review, an unambiguous description as to why these required documents can not be produced and why we should wave the requirement to have them produced.

This is what we want our reviewers to produce in their reviews when they discuss a serious adverse event or death that they feel is likely to be drug related. If the history is not clear and these details are not present in a submission, then our reviewers must assume that the event is drug related since they have insufficient information on which to make a judgment otherwise.

These summaries need not be long, but they should be appropriately thorough and thoughtful.

Again, if you feel that this information is already present in the submission in an easily accessible way please direct us to it.

Hope this helps.

****

Melina Griffis, R.Ph, LCDR-USPHS
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, FDA
(301) 594-5526
(301) 594-2858 (fax)
melina.griffis@fda.hhs.gov (email)

-----Original Message-----
From: Zoschg, Megan [PRDUS] [mailto:MZoschg@PRDUS.JNJ.com]
Sent: Tuesday, April 06, 2004 4:51 PM
To: Melina Griffis (E-mail)
Subject: RISPERDAL - Autism NDA 20-272/S-036 - Question re: CRFs/ summary

Hi Melina:

I received your voice message, am sorry I missed your call. I spoke with my team regarding the Division's suggestion that we submit a summary of the relevant information on the patient cases for which we have yet been unable to obtain the outstanding reportable CRFs.

The team confirms that we do not have any additional information for these patients, beyond that currently contained in the NDA database, summarized via the narratives in the study report and the patient profiles. Thus, we would like to clarify what a summary should contain. We could pull the narrative from the study report, link it to the patient profile, and include a cover sheet referencing the problems obtaining the CRF, but because this wouldn't truly provide anything additional beyond that already contained within the NDA, we wanted to ensure that this would satisfy what the Division is proposing.

Also, the team confirms that we will decide by the end of this week, based upon feedback from the UCLA site, whether we will request that the site send the CRFs directly to FDA or whether to receive the CRFs soon enough to allow for processing and sending to you in a timely fashion. I will keep you informed.

I look forward to your feedback.

Best regards,
Megan

Megan Zoschg, Pharm.D.
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 Trenton-Harbourton Road, Titusville, NJ, USA 08560
P: 609-730-4659 F: 609-730-3091 E: mzoschg@prdus.jnj.com

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/s/

Melina Griffis
5/4/04 10:57:40 AM
CSO