CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-444

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-444

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Claude McGowan, Ph.D.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) dated November 16, 2001, received November 19, 2001, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) 0.5 mg, 1 mg and 2 mg orally disintegrating tablets.

We acknowledge receipt of your submission(s) of October 11, 2002, November 22, 2002, January 31, 2003, and March 13, 2003.

The submission of January 31, 2003 constituted a complete response to our action letter of September 19, 2002.

This new drug application provides for an orally disintegrating tablet formulation of Risperdal (risperidone).

We have completed our review of this application, as amended. It is approved effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

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

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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved NDA 21-444."** Approval of this submission by FDA is not required before the labeling is used.

If you choose to use a proprietary name modifier for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. Please submit any proprietary name and/or modifier to the Agency for our review prior to its implementation.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will

work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) and to the Agency's formal Written Request of November 25, 2002, for details.

We have granted an expiration date of 24 months for all strengths (0.5 mg, 1.0 mg, 2.0 mg) of Risperdal® Orally Disintegrating Tablets in —Alu blister packaging.

Please 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 directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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

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

Sincerely,

/S/

{See appended electronic signature page}

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

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-444

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20272/S-016
NDA 20588/S-010

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

Dear Mr. Brann:

Please refer to your supplemental new drug applications of June 2, 1999, received June 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets and Oral Solution.

These "Changes Being Effected" supplemental new drug applications propose changes to the PRECAUTIONS: Drug-Drug Interactions section of labeling.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows (changes marked in bold text):

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/
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ussell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272/SLR-017
NDA 20-588/SLR-011

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

Dear Mr. Brann:

Please refer to your supplemental new drug applications of December 28, 1998, received January 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets and Oral Solution.

These supplements propose changes to the Precautions and Pregnancy Category sections of the label.

We have completed the review of these applications and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. "PRECAUTIONS: Drug-Drug Interactions, Drugs Metabolized by CYP 2D6:

Please replace ——— with 'CYP 2D6' thoughout the labeling and also update the other cytochrome P450 isoenzyme nomenclature accordingly.

2. Please implement the following changes (strikethrough, caps) to the Pregnancy Category of labeling:

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m2 basis. **In a cross-fostering study in Wistar rats, ~~risperidone exhibited direct~~ 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 the pups were cross-fostered or not. 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 higher than the human dose on a mg/m2 basis.**

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL therapy is unknown.

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

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272/SLR-018
NDA 20-588/SLR-012

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

Dear Mr. Brann:

Please refer to your supplemental new drug applications dated December 1, 2000, received December 4, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Tablets and Oral Solution.

These supplements provide revised draft labeling. Under PRECAUTIONS: Drug Interactions, the current statement regarding carbamazepine is updated.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows (changes marked in bold, deletions as strike-through text):

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according

to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

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

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

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

Sincerely,

/S/

{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
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-444

Johnson & Johnson Pharmaceutical Research & Development, LLC
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. McGowan:

Please refer to your new drug application (NDA) dated November 16, 2001, received November 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) 0.5 mg, 1 mg and 2 mg orally disintegrating tablets.

We acknowledge receipt of your submissions dated:

- February 22, 2002
- April 22, 2002
- August 23, 2002
- September 10, 2002

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Proprietary Name Modifier

We have determined that the — modifier is not in compliance with 21 CFR 201.10(c)(3) which prohibits the employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness. — does not clearly describe that this dosage form is a quickly disintegrating tablet. Rather, — may imply efficacy claims of superiority. For example, this name suggests "acceleration" or that it works more quickly than other agents or Risperdal tablets.

We request that you amend your application with the removal of the proprietary name modifier, or with an alternative proprietary name modifier.

Labeling

1. Please insert complete NDC numbers for each proposed tablet strength in the **HOW SUPPLIED** section of labeling.

2. Please replace your proposed bioequivalence description with the following:

   CLINICAL PHARMACOLOGY, Pharmacokinetics

3. Please reorganize the clinical pharmacology information in the labeling under the headings of Absorption, Distribution, Metabolism, and Excretion (ADME). Please also replace with 'CYP 2D6' throughout the labeling and update the other cytochrome P450 isoenzyme nomenclature accordingly.

4. Under the **Management of Overdosage** section of labeling, we request that you add the following sentence about gastric lavage:

   "Because of the rapid disintegration of risperidone orally dissolving tablets, pill fragments may not appear in gastric contents obtained with lavage."

5. We have amended the labeling proposed in your response to the approvable letters of May 29, 2002 (Risperdal Tablet NDA 20-272 /S-016/S-017/S-018 and Risperdal Oral Solution NDA 20-588 /S-010/S-011/S-012).

   a. Under the **PRECAUTIONS: Drug Interactions** section of labeling we request that you edit/insert the following sections:

      1) When concomitant fluoxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL. The effects of discontinuation of concomitant fluoxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

      2) Please delete the statement "Risperidone does not affect the pharmacokinetic parameters of Lithium and Valproate" and add the following separate statements:

         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 exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=2). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

3) Please insert the following statement about Carbamazepine:

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.

b. Under the **Pregnancy: Pregnancy Category C** section of labeling, we request that you edit the text to read as follows:

The teratogenic potential of RISPERDAL 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/m2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses **of 0.16-5 mg/kg or** 0.1 to 3 times the **MRHD** on a mg/m2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose **of 2.5 mg/kg or** 1.5 times **the MRHD** on a mg/m2 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 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/m2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship

to RISPERDAL therapy is unknown.

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

6. Please refer to your supplements of August 24, 2001, for Risperdal (risperidone) tablets and oral solution (NDA 20-272 / S-022 and NDA 20-588 / S-014). These "Changes Being Effected" supplemental new drug applications propose strengthening the ADVERSE REACTIONS: Postintroduction Reports section of labeling with the addition of the phrase "including cerebrovascular accidents" following "cerebrovascular disorder."

   Due to the statistically significant and clinically meaningful increase in the risk of cerebrovascular adverse events in patients with vascular or mixed (vascular/Alzheimer) dementia, we have determined that stronger labeling is required.

   Please amend the WARNINGS section of labeling with the insertion of the following:

Additionally, we request that you submit a draft "Dear Healthcare Practitioner" letter to convey this new information to the healthcare community.

To be consistent with the labeling, patients with vascular or mixed dementia in ongoing trials should be followed more closely through more frequent monitoring of orthostatic changes.

Clinical Pharmacology and Biopharmaceutics

Please adopt the following dissolution method and specification:

- USP apparatus 2,
- 50 rpm,
- 500 mL of 0.1 N HCl
- Q = — % in 10 minutes

Chemistry

1. As stated in the August 26, 2002 Information Request Letter, [redacted] DMF [redacted] has been sent a letter dated August 20, 2002 stating that DMF [redacted] is inadequate for Amberlite [redacted] resin. Please be advised that DMF [redacted] must be found adequate for approval of NDA 21-444.

2. Please provide the analytical results for the Identified Degradant [redacted] at all storage conditions for the Primary Stability Batches: [redacted] Blister Package and [redacted] Blister package.

3. Refer to the Method Validation section, Attachment 2 in Volume 1.2. Please provide the chemical structure and name for the following two synthetic impurities: [redacted]

4. For each of the following compounds provide a Certificate of Analysis of the reference standard and/or working standard that is utilized in the Test Methods STM-780, STM-899, STM-781.

   a. Two Synthetic Impurities: [redacted]
   b. Known Degradants: [redacted]
   c. Drug substance.

5. Refer to the Moisture Test Method, STM-810. The procedure description is incomplete. Please detail the steps that are taken to ensure that the amount of moisture present is accurate.

6. Due to the complexity of the manufacturing process, please provide an outline of the maximum temperatures achieved at each manufacturing step (Volume 1.2, pages 28 – 63). Along with the temperature, provide the accompanying maximum vacuum pressure if appropriate.

7. The seven critical (primary stability and clinical) drug product batches were manufactured in 1998. Please provide the Certificate of Analysis for all batches manufactured after 1998.

8. As recommended in ICH Q3B (Guidance for Industry: Q3B Impurities in New Drug Products), degradation products should be reported when found to be greater than or equal to 0.1%. Therefore, we recommend a specification limit of NMT 0.1% for Individual Unspecified Degradation Compounds. Please provide updated drug product release specifications incorporating the change.

9. Based on the data submitted, we suggest you consider lowering the following specification limits:

Degradation Compounds, Individual Specified:
— NMT — %;
— NMT — %.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the attached labeling (text for the package insert) and should be updated with any changes effected under the tablet and oral solution NDAs (NDAs 20-272 and 20-588).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999).

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

Our investigators have completed all but one foreign analytical site inspection. The last inspection is scheduled for completion during the first week of October 2002. A satisfactory inspection will be required before this application may be approved.

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. In the absence of any such action FDA may proceed to withdraw the application. 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 drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

{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

attachment

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