CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-444

Correspondence

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOURTON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

29 MAY 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20852

Subject: **NDA 20-272/SLR-016**
Cross reference: NDA 20-588/SLR-010
RISPERDAL® (risperidone) Tablets and Oral Solution
Amendment to Pending Supplement

SUPPLEMENT AMENDMENT

SLR-016(BL)

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets, J&JPRD's "Changes Being Effected" supplemental new drug application dated June 2, 1999, and the Division's approvable letter dated July 19, 2001 (Attachment 1).

We have reviewed the Division's proposed changes to the PRECAUTIONS: Drug Interactions section based on the results of study RIS-SUI-5, entitled "*The effect of fluoxetine on the pharmacokinetics and safety of risperidone in adult psychotic patients.*" This section describes the effects of fluoxetine on the combined plasma concentration of the active compounds, risperidone and 9-hydroxyrisperidone. We recommend rewording the second sentence to advise physicians to re-evaluate Risperdal dosing when fluoxetine is added to Risperdal therapy and to use the lowest effective dose. We agree with all of the other changes proposed by the Division.

Attachment 2 contains the Division's suggested label revisions in the first column and J&JPRD's response in the second column with additions added in ***bold italic*** and deletions in strikethrough. Attachment 3 contains a marked-up copy of the entire labeling. The currently approved labeling containing long-term safety and efficacy of Risperdal has been used for this amendment.

Please contact me at (609) 730-2712 if you have any questions.

Sincerely,

Susan J. Merchant

Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDP RMO)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Janssen Pharmaceutica Products, L.P.	29 MAY 2002
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(609) 730-2712	(609) 730-3091

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 Trenton –Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

On behalf of
Janssen Pharmaceutica Products, L.P.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-272

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
risperidone	RISPERDAL®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
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

CODE NAME *(if any)*
R064766

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
blet	0.25, 0.5, 1, 2, 3, 4 mg	Oral

OPOSED) INDICATION(S) FOR USE: Treatment of schizophrenia

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Amendment to Labeling Supplement to NDA 20-272/SLR-016

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current lication)
A 20-588, IND

This application contains the following items: (*Check all that apply*)

	1. Index
	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify):

CERTIFICATION

ee to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or verse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Susan J. Merchant	**Susan J. Merchant, Manager, Regulatory Affairs**	29 MAY 2002

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560-0200	**(609) 730-2712**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

se DO NOT RETURN this form to this address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Janssen Pharmaceutica Products, L.P.

DATE OF SUBMISSION
29 MAY 2002

TELEPHONE NO. *(Include Area Code)*
(609) 730-2712

FACSIMILE (FAX) Number *(Include Area Code)*
(609) 730-3091

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1125 Trenton –Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

On behalf of
Janssen Pharmaceutica Products, L.P.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

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PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-272

ESTABLISHED NAME *(e.g., Proper name, USP USAN name)*
risperidone

PROPRIETARY NAME *(trade name)* IF ANY
RISPERDAL®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
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

CODE NAME *(if any)*
R064766

DOSAGE FORM:
Tablet

STRENGTHS:
0.25, 0.5, 1, 2, 3, 4 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE: Treatment of schizophrenia

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
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☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Amendment to Labeling Supplement to NDA 20-272/SLR-017

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 20-588, IND

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5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Susan J. Merchant	**Susan J. Merchant, Manager, Regulatory Affairs**	2 9 MAY 2002

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Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOURTON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

29 MAY 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20852

Subject: **NDA 20-272/SLR-017**
Cross reference: NDA 20-588/SLR-011
RISPERDAL® (risperidone) Tablets and Oral Solution
Supplement to Amendment

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets, J&JPRD's letter of December 28, 1998, and the Division's approvable letter dated July 19, 2001 (Attachment 1).

We have reviewed the Division's proposed changes to the PRECAUTIONS sections. The first section, "Drug-Drug Interactions - Drugs Metabolized by CYP 2D6" described a study to assess the CYP 2D6 inhibitory potential by risperidone using dextromethorphan. The proposed wording is acceptable. The Division further requested that we replace [redacted] with 'CYP 2D6' in this section and throughout the labeling. We agree and will update the P450 isoenzyme nomenclature accordingly now. The sections of the labeling where these changes will be made are CLINICAL PHARMACOLOGY: Pharmacokinetics; PRECAUTIONS: Drug-Drug Interactions, Drugs that Inhibit CYP 2D6 and Other CYP Isoenzymes; and PRECAUTIONS: Drug-Drug Interactions, Drugs Metabolized by CYP 2D6.

The second revision to PRECAUTIONS addressed revisions to the "Pregnancy Category" subsection to include information from a cross-fostering study in rat pups. We concur with the Division's suggested recommendation and propose the addition of the phrase 'at the maternally toxic dose of 5 mg/kg' immediately following the words 'were observed' in the middle of the paragraph. The addition of this phrase provides the dose at which toxic effects were observed.

Attachment 2 contains the Division's suggested label revisions in the first column and J&JPRD's response in the second column with the single above phrase added in ***bold italic***. Attachment 3 contains a marked-up copy of the entire labeling. The currently approved labeling containing long-term safety and efficacy of Risperdal has been used for this amendment.

Please contact me at (609) 730-2712 if you have any questions.

Sincerely, ,

Susan J. Merchant

Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDP RMO)

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOURTON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

29 MAY 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20852

Subject: **NDA 20-272/SLR-018**
Cross reference: NDA 20-588/SLR-012
RISPERDAL® (risperidone) Tablets and Oral Solution
Amendment to Pending Supplement

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets, J&JPRD's supplemental new drug application dated December 1, 2000, and the Division's approvable letter dated November 5, 2001 (Attachment 1).

We have reviewed the Division's proposed changes to the PRECAUTIONS: Drug Interactions section based on the results of study RIS-FRA-4, entitled "*Study of the effect of carbamazepine on the pharmacokinetics of risperidone in schizophrenic patients.*" This section describes the effects of carbamazepine on risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, during co-administration. The Division requested changing 'the clearance of risperidone' to describe 'the plasma concentrations of risperidone.' In addition, the Division asked that 'the plasma concentrations of carbamazepine' be listed as 'did not appear to be affected' instead of ——— The Division also requested deletion of the reference to PANSS data. We concur with these changes.

The Division added language to this section describing the need for close monitoring during the first 3-4 weeks of initiation or cessation of carbamazepine therapy to determine if the risperidone dose needs to be adjusted. The sentence immediately preceding it discusses the potential need to titrate the risperidone dose when administered concomitantly with carbamazepine. We propose combining these two sentences to eliminate redundancy. Finally, the Division added language about other CYP3A inducers and that they may cause similar decreases in plasma concentrations of risperidone and 9-hydroxyrisperidone. We recommend deleting specific references to 3A inducers because risperidone is metabolized by 2D6, which is mentioned throughout the labeling. The introduction of 3A establishes another pathway, which is not addressed in the CLINICAL PHARMACOLOGY section. Specific mention of these inducers could be confusing. In addition, we propose changing the last sentence to provide information on the 'combined plasma concentrations of risperidone and 9-hydroxyrisperidone.'

Attachment 2 contains the Division's suggested label revisions in the first column and J&JPRD's response in the second column with additions added in ***bold italic*** and deletions in strikethrough. Attachment 3 contains a marked-up copy of the entire labeling. The currently approved labeling containing long-term safety and efficacy of Risperdal has been used for this amendment.

Please contact me at (609) 730-2712 if you have any questions.

Sincerely,

Susan J. Merchant

Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDP RMO)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

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APPLICATION NUMBER

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NAME OF APPLICANT
Janssen Pharmaceutica Products, L.P.

DATE OF SUBMISSION
29 MAY 2002

TELEPHONE NO. (*Include Area Code*)
(609) 730-2712

FACSIMILE (FAX) Number (*Include Area Code*)
(609) 730-3091

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1125 Trenton –Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

On behalf of
Janssen Pharmaceutica Products, L.P.
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 30 2002
RECEIVED

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-272

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
risperidone

PROPRIETARY NAME (*trade name*) IF ANY
RISPERDAL®

CHEMICAL BIOCHEMICAL/BLOOD PRODUCT NAME (*if any*)
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

CODE NAME (*if any*)
R064766

DOSAGE FORM:
Tablet

STRENGTHS:
0.25, 0.5, 1, 2, 3, 4 mg

ROUTE OF ADMINISTRATION:
Oral

PROPOSED INDICATION(S) FOR USE: Treatment of schizophrenia

APPLICATION INFORMATION

APPLICATION TYPE

check one ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION

(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Amendment to Labeling Supplement to NDA 20-272/SLR-018

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 20-588, IND

This application contains the following items: (*Check all that apply*)

1.	Index
2.	Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
3.	Summary (21 CFR 314.50 (c))
4.	Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
8.	Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
12.	Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
15.	Establishment description (21 CFR Part 600, if applicable)
16.	Debarment certification (FD&C Act 306 (k)(1))
17.	Field copy certification (21 CFR 314.5 (k) (3))
18.	User Fee Cover Sheet (Form FDA 3397)
19.	OTHER (Specify):

CERTIFICATION

ee to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Susan J Merchant	**Susan J. Merchant, Manager, Regulatory Affairs**	29 MAY 2002

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560-0200	**(609) 730-2712**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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se DO NOT RETURN this form to this address.

FORM FDA 356h (4/97)

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

31 JAN 2003

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Food and Drug Administration
Attention: Document Control Room
1451 Rockville Pike
Rockville, Maryland 20857

SUBJECT: **NDA 21-444**
RISPERDAL® (risperidone) Orally Disintegrating Tablet
Complete Response to September 19, 2002 FDA Action Letter

Dear Dr. Katz:

Reference is made to the September 19, 2002 Approvable Letter received by Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD) for RISPERDAL® (risperidone) Orally Disintegrating Tablets (NDA 21-444). Reference is also made to a meeting with the Division of Neuropharmacological Drug Products (DNDP) on December 3, 2002 to discuss new data regarding the occurrence of cerebrovascular adverse events in clinical trials in patients with dementia and possible labeling to address this finding. Please also refer to the J&JPRD letter dated December 16, 2002 that detailed our proposal to address the Division's request for additional information and analyses to better understand the contribution of diagnostic subgroups and risk factors to the occurrence of cerebrovascular adverse events.

We are now amending the application to provide a complete response to all requests in the Approvable Letter (i.e., proposed label changes, responses to comments on Clinical Pharmacology and Biopharmaceutics, and Chemistry related issues). Also included in the proposed labeling changes for RISPERDAL® Orally Disintegrating Tablets are our responses to the Division's comments on labeling issues for several pending supplements to the NDAs for RISPERDAL® tablet (NDA 20-272/ S-016/ S-017/ S-018) and RISPERDAL® Oral Solution (NDA 20-588/ S-010/ S-011/ S-012). This letter and the enclosed document entitled, "Response to FDA Approvable Letter of September 19, 2002" are organized to follow the sequence of comments in the Approvable Letter.

Please note that, as recommended in the Approvable Letter, we are also providing an alternative proprietary name modifier, with a request that DNDP consult the Office of Drug Safety (ODS) on its acceptability. The alternative name modifier and a back-up name are provided below.

Primary choice of proprietary name

RISPERDAL —— (risperidone) Orally Disintegrating Tablets

Back-up proprietary name

RISPERDAL —— (risperidone) Orally Disintegrating Tablets

Draft labeling is enclosed as both marked and unmarked versions to facilitate your review. We have addressed each of the Division's comments in the labeling section of the September 19, 2002 Approvable Letter as follows:

- NDC numbers have been added to the HOW SUPPLIED section.
- The sentence describing the bioequivalence of RISPERDAL® tablets and RISPERDAL® Orally Disintegrating Tablets has been added to the Pharmacokinetics subsection of CLINICAL PHARMACOLOGY.
- Current information in the Pharmacokinetics subsection of CLINICAL PHARMACOLOGY has been reorganized under the headings of Absorption, Distribution, Metabolism, and Excretion.
- A sentence about gastric lavage has been added under the Management of Overdose section. Please note that for consistency, we used "orally disintegrating" in the sentence rather than —— " as proposed by DNDP in the Approvable Letter.
- The following revisions have been made to PRECAUTIONS: Drug Interactions.
  - J&JPRD agrees with, and has incorporated, the recommended labeling for lithium and carbamazepine.
  - J&JPRD agrees with, and has incorporated, the proposed labeling for fluoxetine and valproate, with minor revisions to correct the plasma concentration of risperidone in the fluoxetine study and to correct the number of subjects included in the pharmacokinetic analysis in the valproate study. Citations to the specific study documents supporting these two changes are provided in the enclosed "Complete Response" document. To facilitate labeling review, the cited pages have been extracted from the clinical study reports and are appended to Attachment 1 of the "Complete Response" document.
  - J&JPRD agrees with, and has incorporated, the proposed revisions to the Pregnancy Category C section.

The Division's letter also requested the addition of a section under WARNINGS to address the occurrence of cerebrovascular adverse events (CAEs) in clinical trials in patients with dementia-related psychosis, and issuance of a "Dear Healthcare Practitioner" letter to convey this information to the healthcare community.

Representatives of J&JPRD and Janssen Pharmaceutical Products, L.P. met with the Division on December 3, 2002 to review the CAE data from clinical trials in patients with dementia. At the meeting, it was agreed that J&JPRD would submit additional information and analyses to better understand the contribution of diagnostic subgroups and risk factors to these events. We also committed to submit revised draft labeling with these analyses. The draft labeling, requested information and analyses, along with a copy of our letter of December 16, 2002 are enclosed.

Based on these discussions and our subsequent analyses, we propose the addition of the following paragraph under PRECAUTIONS:

DRAFT

This proposed text is consistent, although not identical, with the draft labeling discussed at the December 3, 2002 meeting with the Division. The above labeling was drafted to minimize the necessity for additional revisions after the data from the ongoing study, RIS-USA-232, are available. RIS-USA-232 is a study in patients with psychosis of Alzheimer's disease. Study-specific and pooled analyses of CAE data from RIS-USA-232 and other placebo-controlled dementia trials will be completed and submitted as soon as the data become available. We share the Division's interest in the CAE results from RIS-USA-232, and a mutual sensitivity to labeling fatigue. We would therefore recommend that, if the Division agrees with our draft proposal, it not be implemented until J&JPRD and the Division have confirmed that it does not need to be modified based on RIS-USA-232 data. We remain open to the potential that data from RIS-USA-232 may alter the conclusions presented in this report.

As discussed at our meeting of December 3, given the existing PRECAUTION for orthostatic hypotension, we believe a "Dear Healthcare Professional" letter is not warranted, based on available data.

If you have any questions, please contact me at (609) 730-3025.

Sincerely,

Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs

cc: Edward Brann
Director, Regulatory Affairs

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 TRENTON-HARBOURTON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

15 AUG 2002

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20857

DUPLICATE

Subject: **IND [redacted] Risperdal® (risperidone) Orally Disintegrating Tablets**
Request for Evaluation – Alternative Proposed Trademark and General Nomenclature for Risperdal Orally Disintegrating Formulation
Serial no.: 3 4 7

Dear Dr. Katz:

Reference is made to NDA 21-444 for Risperdal® (risperidone) Orally Disintegrating Tablets submitted by Johnson & Johnson Pharmaceutical Research and Development, LLC (JJPRD) on November 16, 2001. Reference is also made to the JJPRD letter submitted to the Division on January 10, 2002 requesting that the Division consult the Office of Post-marketing Drug Risk Assessment (OPDRA) to determine the acceptability of the — trademark.

Please also refer to the FDA response letter issued May 3, 2002 informing JJPRD that the Divisions of Drug Marketing, Advertising and Communications (DDMAC) and Medication Errors and Technical Support (DMETS) determined that the — modifier was not in compliance with 21 CFR 201.10 (c)(3).

The purpose of this letter is to request that the Division consult OPDRA on the acceptability of the alternative proprietary name modifier listed below. We have included a back-up name that we would also like to be evaluated for acceptability.

Primary choice of proprietary name

RISPERDAL —— (risperidone) Orally Disintegrating Tablets

Back-up proprietary name

RISPERDAL —— M (risperidone) Orally Disintegrating Tablets

Please note that we are not providing any new mock-ups with the new name but will make the changes as appropriate to substitute the new name if it is considered acceptable. We will also address the additional recommendations expressed in the Division's May 3, 2002 letter for the blister label, carton labeling and package insert at that time.

If you have any questions regarding this submission, please contact me at (609) 730-3025.

Sincerely,

Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs

G:\regulato\wpdocs\cns\risperdal [redacted] opdraletter.doc

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSER
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

2. DATE OF SUBMISSION
15 AUG 2002

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

4. TELEPHONE NUMBER *(Include Area Code)*
609-730-3025

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
RISPERDAL® (risperidone) Tablets

6. IND NUMBER *(If previously assigned)*
[redacted]

7. INDICATION(S) *(Covered by this submission)*
Schizophrenia

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)*, REFERRED TO IN THIS APPLICATION.
NDA 21-444

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
3 4 7

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S).	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☒ OTHER Request for Evaluation - Alternative Proposed Trademark and General Nomenclature *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/OBIND/OGD RECEIPT STAMP	OOR RECEIPT STAMP	DIVISION ASSIGNMENT:
	RECEIVED AUG 16 2002 HFD-120/CDER	IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Fred Grossman, D.O., Director – Global Clinical Research and Development

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Fred Grossman, D.O., Director – Global Clinical Research and Development
Werner Coussement, DVM, Ph.D., Vice President, Non-Clinical Safety Evaluation

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Claude McGowan, Ph.D. **Associate Director, Regulatory Affairs**	Claude McGowan	
18. ADDRESS *(Number, Street, City, State and Zip Code)* **1125 Trenton-Harbourton Road** **Titusville, NJ 08560-0200**	19. TELEPHONE NUMBER *(Include Area Code)* **609-730-3025**	20. DATE **15 AUG 2002**

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-444

INFORMATION REQUEST LETTER

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) dated January 31, 2003, and received February 4, 2003 that was submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) Orally Disintegrating Tablets, 0.5 mg, 1.0 mg, and 2.0mg Tablets.

We are reviewing the chemistry, manufacturing, and controls section of your submission. Provide two copies of each of these analytical methods and the respective validation data.

1. Assay and Impurities
2. Identification for Risperidone
3. Identification for Risperidone
4. Content Uniformity
5. Dissolution:

Also, provide a copy of the most current specifications.

Donald N. Klein, Ph.D., will be submitting these analytical methods to a FDA laboratory for method validation.

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301)594-5537.

Sincerely,

/S/

Thomas Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Thomas Oliver
3/13/03 01:51:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-444

INFORMATION REQUEST LETTER

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) dated January 31, 2003, and received February 4, 2003 that was submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) Orally Disintegrating Tablets, 0.5 mg, 1.0 mg, and 2.0mg Tablets.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Refer to Attachment 2 in the attach.pdf that is a section of your EDR – NDA 21-444 dated January 31, 2003. Specifically, refer to the **Information for Patients** section, page 12 of the revised package insert. Also, refer to 21 CFR 201.21(c). Revise the **Phenylketonurics** section of the revised package insert such that the phenylalanine amount present in each tablet strength is stated.

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

Sincerely,

/S/

Thomas Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Thomas Oliver
3/11/03 07:31:12 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-444

INFORMATION REQUEST LETTER

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your November 16, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal —— (risperidone) Orally Disintegrating Tablets, 0.5mg, 1.0mg, and 2.0mg.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA.

[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.

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

Sincerely,

/S/

Thomas F. Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Thomas Oliver
8/26/02 01:26:46 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-444

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Risperdal —— (risperidone) 0.5 mg, 1.0 mg, and 2.0 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: November 16, 2001

Date of Receipt: November 19, 2001

Our Reference Number: NDA 21-444

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 18, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 19, 2002 and the secondary user fee goal date will be November 19, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

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}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Steve Hardeman
11/26/01 03:00:48 PM
Signed for John Purvis

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-444

DISCIPLINE REVIEW LETTER

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your November 16, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) Orally Disintegrating Tablets.

The Divisions of Drug Marketing, Advertising, and Communications (DDMAC) and Medication Errors and Technical Support (DMETS) have completed their reviews of your proposed proprietary name "Risperdal ——

DDMAC has 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 that the drug —— your problem, or that it works —— 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.

In the review of the draft blister label, draft carton and insert labeling, DMETS identified the following issues (note - all references in the following section to the modifier —— are informational):

1) BLISTER LABEL
   a) The sponsor's name "JANSSEN" appears as large as the proprietary name. The proprietary name should have more prominence than the sponsor's name. Therefore, we recommend that the sponsor's name "JANSSEN" be decreased in size and prominence. In addition, we recommend that the proprietary name, established name, and strength appear above the sponsor's name.
   b) The established name should read as "risperidone orally disintegrating tablet" rather than "(risperidone) orally disintegrating tablets".

c) See comment 2.g.

2) CARTON LABELING (0.5 mg, 1 mg and 2 mg)
   a) We recommend deleting or relocating the logo that is incorporated in the proprietary name since it detracts attention from the proprietary name.
   b) We recommend relocating the modifier —— to appear next to the proprietary name (e.g., Risperdal ——
   c) We recommend revising the format of the established name as follows: Risperidone Orally Disintegrating Tablets.
   d) We recommend placing the statement, "Rx Only," on the front panel of the label.
   e) Delete the terminal zero when specifying the product strength. Specifically, "1.0 mg and 2.0 mg" should be designated as "1 mg and 2 mg." The use of terminal zero can increase the risk of dosing errors by 10 fold.
   f) We recommend including the strength in conjunction with the proprietary name on the back panel. Omitting the strength on labels and labeling could cause errors as multiple strengths of the same drug lie side by side on pharmacy shelves.
   g) In order to prevent medication errors due to the visual similarity of the labels and labeling among the three strengths, we recommend differentiating the product strengths with the use of contrasting colors, boxing, or some other means.
   h) We recommend revising the statement "Dosage: For information for use, see accompanying product literature" to read "Usual Dosage: For information for use, see accompanying product literature".

3) PACKAGE INSERT
   Dosage and Administration
   In this section, the "Direction for Use of Risperdal —— is long, redundant, and difficult to follow. For example, the statements, "Do not push the tablet through the foil" and "patients should not attempt to split or chew the tablet" are mentioned repetitively in this section. Please simplify and clarify this section.

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

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
5/3/02 02:33:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND [redacted]

Janssen Research Foundation
Attention: Cynthia D'Ambrosio
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Ms. D'Ambrosio:

Please refer to your Investigational New Drug Application (IND) for Risperdal (risperidone).

Refer also to your amendment (N-189) of July 13, 1998, requesting guidance in reference to the bioequivalence study requirements for development of a Quickly Disintegrating Oral Tablet form of risperidone.

The Office of Clinical Pharmacology and Biopharmaceutics has completed the review of your submission and finds that your biopharmaceutical development program is acceptable. We agree that this formulation is exempt from the requirements to file an IND for the purposes of performing standard bioequivalence studies, however, we have several comments:

1. We suggest that you use higher strengths (1 and 4 mg to represent suspensions of different risperidone concentrations) to conduct bioequivalence studies. In case the 4 mg strength can't be used in healthy volunteers due to safety concerns, then the 2 mg strength could be used to conduct the bioequivalence study. You should establish bioequivalence based on risperidone and its active metabolite 9-hydroxy risperidone.

2. As per CFR 320.21 , you can request a biowaiver for lower strengths or higher strengths (i.e., 0.5,3, and 4 mg tablets), based on compositional proportionality, solubility, permeability, and similar dissolution profiles.

3. Please provide dissolution profiles as per SUPAC supporting the request of a biowaiver (at least in three media viz: 0.1 N HCl, water, and physiological buffer (pH 6.8).

4. You should compare dissolution profiles of all strengths using an appropriate method, e.g., F2 values (refer to SUPAC guidance).

5. If the quickly disintegrating tablets are not bioequivalent to the commercial tablets, you should evaluate the clinical efficacy and safety of the new dosage form in the target population.

Should you have any further questions, please contact Steven D. Hardeman, R.Ph., Regulatory

Management Officer, at (301) 594-5533.

Sincerely yours,

/S/

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

cc:
Orig IND
Div File
HFD-120/Laughren/Mosholder
/Hardeman
HFD-860/Sahajwalla/Tammara

Final: October 19, 1998

C: DOCS\IND [redacted] N-189.L1

ADVICE