

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-444**

**Administrative Documents**

**Table of Contents**  
**NDA 21-444**  
**Risperdal (risperidone)**  
**Orally Disintegrating Tablets**

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Volume 1

- A. Action Package Checklist
- B. Exclusivity Summary
- C. Action Letter
- D. Labeling *: Draft Dear Dr. Comparison of AE vs AP*
  - Final Agreed Upon Labeling
  - Division Labeling
  - Original Sponsor Labeling
  - DMETS review of Proprietary Name
- E. Outgoing Correspondence
- F. Summary Review (Division Director, Team Leaders)
- G. Clinical Review
- H. Pediatric Page
- I. Audits of Bioequivalence Studies (DSI)
- J. Biopharmaceutical Review

Volume 2

- K. CMC Review
- L. Micro Review

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-444	Efficacy Supplement Type SE-	Supplement Number
Drug: Risperdal (risperidone) orally disintegrating tablet		Applicant: Johnson & Johnson
RPM: Steven D. Hardeman, R.Ph.		HFD-120 Phone # 4-5525
Application Type: 505(b)(1)		Reference Listed Drug (NDA #, Drug name): N20-272 Risperdal
❖ Application Classifications:		
• Review priority		Standard
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		
		4/3/03
❖ Special programs (indicate all that apply)		
		None
❖ User Fee Information		
• User Fee		Paid
• User Fee waiver		N/A
• User Fee exception		N/A
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		No
• This application is on the AIP		No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		Verified
❖ Patent		
• Information: Verify that patent information was submitted		Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		N/A
❖ Exclusivity (approvals only)		
• Exclusivity summary		Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		N/A

**General Information**

❖ Actions	
• Proposed action	AP
• Previous actions (specify type and date for each action taken)	AE 9/19/02
• Status of advertising (approvals only)	Requested in AP letter
❖ Public communications	
• Press Office notified of action (approval only)	Yes
• Indicate what types (if any) of information dissemination are anticipated	None
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	In Package
• Most recent applicant-proposed labeling	In Package
• Original applicant-proposed labeling	In Package
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	In Package
• 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)	N/A
• Applicant proposed	In Package
• Reviews	see discipline reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	In Package
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

**Summary Application Review**

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	In Package
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	In Package (7-17-02), Response to AE NAI per M.O.
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Yes
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	Yes (7-26-02 and 3-4-03)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	Yes
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	Yes (9-13-02 and final)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date).	In Package (9-13-02)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	In Package (3-4-02)
❖ Facilities inspection (provide EER report)	Date completed: 9/16/02 (* ) Acceptable ( ) Withhold recommendation
❖ Methods validation	Requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

## Application Information

NDA 21-444	Efficacy Supplement Type SE-	Supplement Number
Drug: Risperdal (risperidone) orally disintegrating tablet		Applicant: Johnson & Johnson
RPM: Steven D. Hardeman, R.Ph.		HFD-120 Phone # 4-5525
Application Type: 505(b)(1)		Reference Listed Drug (NDA #, Drug name): N20-272 Risperdal
❖ Application Classifications:		
• Review priority		Standard
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		
• Special programs (indicate all that apply)		None
❖ User Fee Information		
• User Fee		Paid
• User Fee waiver		N/A
• User Fee exception		N/A
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• Applicant is on the AIP		No
• This application is on the AIP		No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
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		Verified
❖ Patent		
• Information: Verify that patent information was submitted		Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		N/A
❖ Exclusivity (approvals only)		
• Exclusivity summary		N/A for approvable action
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		N/A

### General Information

❖ Actions	
• Proposed action	AE
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	N/A for approvable
❖ Public communications	
• Press Office notified of action (approval only)	N/A
• Indicate what types (if any) of information dissemination are anticipated	None
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	In Package
• Most recent applicant-proposed labeling	In Package
• Original applicant-proposed labeling	In Package
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<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	<b>In Package</b>
<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	<b>In Package (7-17-02)</b>
❖ - Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	<b>N/A for approvable action</b>
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	<b>In Package (7-26-02)</b>
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	<b>Pending</b>
<b>CMC Information</b>	
❖ CMC review(s) <i>(indicate date for each review)</i>	<b>In Package (9-13-02)</b>
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	<b>In Package (9-13-02)</b>
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	<b>In Package (3-4-02)</b>
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	<b>Requested</b>
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

EXCLUSIVITY SUMMARY for NDA 21-444

Trade Name: *Risperdal*

Generic Name: *risperidone orally disintegrating tablets*

Applicant Name: *Johnson & Johnson*

Division of Neuropharmacological Drug Products / HFD-120

Approval Date: 4-2-03

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

- a) Is it an original NDA? YES
- b) Is it an effectiveness supplement? NO  
If yes, what type(SE1, SE2, etc.)? N/A
- 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.") 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.

*The sponsor conducted no clinical efficacy trials, but sought to show that the new formulation is bioequivalent to marketed Risperdal. The sponsor is claiming bioequivalence to marketed Risperdal, based on the pk data from studies RIS-USA-125 and RIS-NED-25.*

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: N/A

- d) Did the applicant request exclusivity? YES

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

Five

- e) Has pediatric exclusivity been granted for this Active Moiety? NO

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration,

and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such). NO

If yes. NDA # \_\_\_\_\_ Drug Name

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

3. Is this drug product or indication a DESI upgrade? NO

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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

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

NDA # 20-272 Risperdal (risperidone) tablets

2. Combination product.

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

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

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

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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. No

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS**

Steven D. Hardeman, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products

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/s/

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Steve Hardeman  
4/2/03 09:45:36 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA 21-444

Action Date: 4/2/03

HFD-120

Trade generic/dosage form: Risperdal (risperidone) orally disintegrating tablet

Applicant: Johnson & Johnson

Therapeutic Class: Antipsychotic

Indication(s) previously approved: indicated for the treatment of schizophrenia

- Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: indicated for the treatment of schizophrenia

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 C: Deferred Studies

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 13 Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 17 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: **Studies ongoing**

Date studies are due (mm/dd/yy): 11/25/07

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/s/

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Steve Hardeman  
4/2/03 09:26:05 AM

**Pediatric Use section or certification statement**

In compliance with 21 CFR 314.55(b), Janssen Research Foundation (JRF) is submitting this statement to NDA 21-444 for RISPERDAL (risperidone) orally disintegrating tablets. RISPERDAL is indicated for the treatment of schizophrenia.

Janssen hereby requests permission to defer a commitment to submit pediatric clinical proposal until completion of discussions with the Division of Neuropharmacological Drug Products (DNDP) regarding appropriate studies to be conducted with RISPERDAL (risperidone) in this population. Please reference meetings or communications with FDA dated March 3, May 5, August 24, September 15, and October 13, 2000 and April 9 and 20, 2001 to obtain Division input and guidance concerning this topic. At the April 20, 2001 meeting the Division acknowledged their commitment to respond to study proposals provided in the May 5, 2000 submission.

This New Drug Application provides bioequivalence and safety data for healthy volunteers and patients with schizophrenia and schizoaffective disorder.



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

06 Nov 2001  
Date

## MEMORANDUM

DATE: September 19, 2002

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

TO: File, NDA 20-272 & NDA 21-444

SUBJECT: Changes to Labeling for Risperdal (risperidone) Regarding Cerebrovascular Events in Patients with Dementia

On 5/18/01, Janssen Research Foundation notified the division of 6 cases of cerebrovascular accidents (CVAs) in a placebo controlled of risperidone in patients with dementia trial (RIS-AUS-5, performed in Australia). All 6 cases were in risperidone-treated patients, and 2 were fatal. As a result of these cases, the sponsor submitted a "Changes Being Effected" labeling supplement, in which they proposed that the expression, "including cerebrovascular accidents" be added to the Postintroduction Reports section of labeling, after the term "cerebrovascular disorder".

These data were reviewed by Dr. Andrew Mosholder, medical officer (review dated 11/17/01), and Dr. Tarek Hammad, safety reviewer (review dated 1/16/02). Based on these reviews and internal discussions, we sent a letter to the sponsor on 1/14/02, in which we asked for additional statistical analyses of the data, as well as more information about the occurrence of adverse events presumed related to risperidone's alpha-adrenergic blocking activity (i.e., orthostatic hypotension, tachycardia, dizziness, and syncope).

Subsequent to the sponsor's submission responding to our requests in the 1/14/02 letter, Dr. Hammad completed another review (4/19/02). As a result of this review, the firm was again asked, on 5/6/02, for narrative summaries for serious and non-serious cerebrovascular adverse events (CVAEs). Dr. Hammad reviewed these summaries in a review dated 7/1/02.

The review team has discussed these reviews and the data in several internal meetings.

The critical data and analyses are presented by Dr. Hammad in his review of 4/19/02, pages 4 and 5, Sponsor's tables 8 and 10. These tables provide the results of analyses of the 3 large placebo controlled trials performed in elderly patients with dementia (AUS-5, INT-24, & USA-63; total N=1306). Importantly, the data were examined for all patients with Alzheimer's Disease and separately for those patients with a vascular component. The essential data from the 3 studies combined are shown below:

## ALZHEIMER'S DISEASE

	RIS	PBO	Rel Risk	P-value
Serious CVAEs	4/525	2/294	1.14	0.88
Serious and Non-Serious CVAEs	15/525	5/294	1.74	0.29

## VASCULAR PATIENTS

	RIS	PBO	Rel Risk	P-value
Serious CVAEs	8/219	1/153	5.63	0.10
Serious and Non-Serious CVAEs	14/219	2/153	4.99	0.03

In addition, Dr. Hammad examined the incidence of ADRs presumably associated with risperidone's alpha-blocking effects, as noted above. These analyses revealed that, although relatively infrequent, the incidence of these events were nominally significantly greater on risperidone than on placebo (see his 7/1/02 review, page 5).

Based on discussions with the review team, I believe it is fair to say that there is general agreement that these data strongly suggest that the use of risperidone in elderly patients with dementia with a vascular component are at increased risk for both serious and non-serious CVAEs. Given this conclusion, we do not believe that the sponsor's addition of the term "cerebrovascular accident" to the Postintroduction Reports section of labeling adequately informs prescribers of this risk. Instead, we believe that the sponsor should amend the WARNINGS section of labeling to include a new sub-section called Cerebrovascular Adverse Events, in which the findings are described.

We are about to issue an Approvable letter to the sponsor for their new NDA 21-444, for an orally disintegrating dosage form. I believe that we should include the new proposed sub-section in the draft labeling accompanying that letter.

Finally, the sponsor has proposed the trade name            for this new orally disintegrating dosage form. I believe that this name inappropriately implies speed of disintegration and/or clinical action. We have consistently rejected similar names that imply "speed" for similar orally disintegrating products. For this reason, we will ask the sponsor to propose another trade name.

RSI

Russell Katz, M.D.

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/s/

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Russell Katz  
9/19/02 11:51:34 AM  
MEDICAL OFFICER

MEMORANDUM

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

DATE: September 17, 2002

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

SUBJECT: Approvable action for NDA 21-444 for orally tablet formulation of risperidone

TO: File for NDA 21-444  
[Note: This memo should be filed with the 11-16-01 original submission of this NDA.]

Risperidone (Risperdal) is approved for the treatment of schizophrenia in both immediate release tablets and an oral solution. This NDA provides data in support of an orally tablet formulation in 0.5, 1, and 2 mg strengths. The rationale is to provide a form that can be used more easily in patients who are resistant to taking medications and in those who have difficulty swallowing tablets. There were no clinical efficacy or safety trials conducted with this new formulation. Rather, the sponsor has sought to show bioequivalence to the currently approved immediate release tablet. The application did include the results of 8 human studies focusing on bioequivalence, bioavailability, and taste. They have also submitted CMC information to support this new formulation. There was no need for pharm/tox information in this NDA.

Biopharmaceutics:

-Results from the two key bioequivalence studies (RIS-USA-125 and RIS-NED-25) were reviewed by Brian Booth, Ph.D. from OCPB, and he concluded that both the 0.5 and 2.0 mg strengths for this new formulation were shown to be bioequivalent (AUC and Cmax, for parent, 9-OH metabolite, and the "active moiety") to the corresponding immediate release Risperdal tablet strengths. The sponsor was granted a bio waiver for the 1 mg strength because of proportional composition and similarity of the dissolution profiles for all 3 strengths of the new formulation.

DSI Inspections:

-Since this NDA is based primarily on bioequivalence, the critical DSI inspections are for the clinical and analytical portions of the two key studies, 25 and 125. For study 25, both portions have been inspected and passed. For study 125, only the clinical portion has been inspected, and passed. The

analytical portion for study 125 will not be completed until late September, 2002, and likely not reported until late October, 2002.

CMC:

-The CMC data have been reviewed by Donald Klein, Ph.D. from chemistry. He has concluded that the application is approvable. The various CMC deficiencies are conveyed in the approvable letter.

Name:

-The sponsor originally proposed the name "Risperidal — " as the brand name for this product. This name was reviewed by DMETS and rejected. The sponsor has subsequently proposed the name "Risperdal — " and this name has been accepted by DMETS. The sponsor has been asked to make several changes to the Blister Label and the Carton Labeling.

Clinical:

-The limited clinical data in this NDA were reviewed by Andrew Mosholder, M.D., from the clinical group. There were a total of n=214 human subjects exposed to this new formulation, including 104 normal volunteers and 110 patients. There were no unexpected safety findings, and no findings that would preclude the approval of this application.

Labeling:

-The sponsor has proposed adding new information regarding this new formulation to the currently approved labeling for the Risperdal tablet and solution. We have also asked them to incorporate recently suggested changes and relevant information for this revised label. We are asking for one additional statement in the Overdose section regarding the fact that pill fragments may not appear in the gastric contents due to the rapid disintegration of these tablets. OCPB and CMC also had minor suggestions for labeling modifications.

Conclusion:

-I recommend that we issue an approvable letter with our proposed labeling for this application.

cc:

Orig NDA

HFD-120/DivFile

HFD-120/TLaughren/RKatz/AMosholder/SHardeman

DOC: NDA21444.01

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/s/

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Thomas Laughren  
9/17/02 03:56:34 PM  
MEDICAL OFFICER

3/27/03

From Biopharm Review of 3/4/03

Hardeman, Steven D

**From:** Hardeman, Steven D  
**Sent:** Thursday, March 27, 2003 8:47 AM  
**To:** Edward Brann [JANUS] (E-mail); Claude McGowan [PRDUS] (E-mail)  
**Cc:** Laughren, Thomas P  
**Subject:** — labeling N21-444

Ned / Claude,

Attached are the final biopharm labeling changes. Please also add the following under 'Management of Overdose' following the sentence about gastric lavage:

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

As we discussed this morning, I would like to roll the CVAE language into this application if at all possible.

Thanks,  
Steve



Final Biopharm  
Labeling Commen...

\*\*\*\*\*

**CAPT Steven D. Hardeman, R.Ph.**  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products / HFD-120  
Food and Drug Administration  
Rockville, Maryland 20857

Phone: 301-594-5525  
Fax: 301-594-2859  
Email: hardemans@cdcr.fda.gov

Fluoxetine

SLR-016

**Hardeman, Steven D**

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**From:** Mosholder, Andrew D  
**Sent:** Tuesday, September 17, 2002 11:26 AM  
**To:** Hardeman, Steven D  
**Subject:** RE: Risperdal

I think it doesn't add much--you could say that in virtually any drug's labeling. My vote would be to take it out.  
-Andy

-----Original Message-----

**From:** Hardeman, Steven D  
**Sent:** Tuesday, September 17, 2002 11:17 AM  
**To:** Mosholder, Andrew D  
**Subject:** FW: Risperdal

Andy,

Does the following sentence stay in?

The lowest effective dose of RISPERDAL should be selected.

-----Original Message-----

**From:** Laughren, Thomas P  
**Sent:** Tuesday, September 17, 2002 11:10 AM  
**To:** Mosholder, Andrew D; Hardeman, Steven D  
**Subject:** RE: Risperdal

I agree with Andy's proposed change.

Tom

-----Original Message-----

**From:** Mosholder, Andrew D  
**Sent:** Tuesday, September 17, 2002 11:08 AM  
**To:** Hardeman, Steven D  
**Cc:** Laughren, Thomas P  
**Subject:** FW: Risperdal

Hi Steve,

Either I assumed Biopharm would review their 5-29-02 response since it pertains to a drug-drug interaction, or I simply lost track of this one--sorry.

Instead of their proposal:

I would suggest this:

I'll forward this to Tom for his comments.

-Andy

-----Original Message-----

**From:** Hardeman, Steven D  
**Sent:** Tuesday, September 17, 2002 10:17 AM  
**To:** Mosholder, Andrew D  
**Subject:** Risperdal

Andy,

I am trying to finish NDA 21-444 and I found three labeling supplements that will impact this NDA's labeling. One is pharm/tox, one is biopharm, and one is yours. We sent an approvable letter on 7/19/01 for a fluoxetine interaction. They responded on 5/29/02 (I retrieved jacket from your office). I have attached their response in a side-by-side format. Take a look

Thanks,  
Steve

<< File: 5-29-02 sponsor proposal.doc >>

\*\*\*\*\*

CAPT Steven D. Hardeman, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products / HFD-120  
Food and Drug Administration  
Rockville, Maryland 20857

Phone: 301-594-5525  
Fax: 301-594-2859  
Email: [hardemans@cder.fda.gov](mailto:hardemans@cder.fda.gov)

Hardeman, Steven D

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**From:** Hardeman, Steven D  
**Sent:** Monday, March 31, 2003 8:04 AM  
**To:** 'McGowan, Claude [PRDUS]'  
**Cc:** Mahmud, Alina  
**Subject:** RE: Name candidates for RISPERDAL Orally Disintegrating Tablets. —

I will send them to DMETS. At this late date, we will issue an action letter without the modifier and will put the following in the letter:

"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."

Steve

Alina-- see following tradename modifiers for NDA 21-444. Thanks, Steve

-----Original Message-----

**From:** McGowan, Claude [PRDUS] [mailto:CMcgowa@PRDUS.JNJ.COM]  
**Sent:** Thursday, March 27, 2003 3:18 PM  
**To:** 'hardemans@cder.fda.gov'  
**Subject:** Name candidates for RISPERDAL Orally Disintegrating Tablets. —

Steve:

Got the information on the CVAE labeling, thanks. Ned will be in touch. Here are two other candidates. Marketing really prefers to have a name for this product rather than go with orally disintegrating tablet. It is kind of hard to figure out what was the fanciful problem with the last 2, particularly [redacted] since its components are already part of products on the market. Note of course that [redacted] is the second choice below. Can we get a read by the end of day tomorrow? Just for clarification, if the name is not resolved before you are ready to issue the action letter, you would still issue the letter, correct? Appreciate your cooperation.

First choice: —

Second choice: —

Claude

Hardeman, Steven D

**From:** Mahmud, Alina  
**Sent:** Tuesday, March 25, 2003 11:13 AM  
**To:** Hardeman, Steven D  
**Cc:** Beam, Sammie  
**Subject:** RE: Risperdal — and Risperdal — NDA21-444

The previously proposed modifiers for this product were found unacceptable from a promotional perspective yet acceptable from a safety perspective. The sponsor has again submitted names considered to be promotional. I would prefer not to continue with the review if the Division concurs with DDMAC. Please discuss this matter with the Division and contact me on the status.

Thanks,  
Alina

LT Alina R. Mahmud  
Team Leader, Division of Medication Errors and Technical Support  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Rm 6-34  
(301) 827-0916

-----Original Message-----

**From:** Hardeman, Steven D  
**Sent:** Tuesday, March 25, 2003 10:31 AM  
**To:** Mahmud, Alina  
**Subject:** RE: Risperdal — and Risperdal — NDA21-444

My advice would be to continue with the review. I will try and get some guidance from Dr. Katz and get back with you.

Thanks,  
Steve

-----Original Message-----

**From:** Mahmud, Alina  
**Sent:** Tuesday, March 25, 2003 9:52 AM  
**To:** Hardeman, Steven D  
**Cc:** Beam, Sammie  
**Subject:** RE: Risperdal\* — and Risperdal — NDA21-444

Hi Steve,

From a promotional perspective, DDMAC does not recommend the use of the proposed modifiers " " or " " since " " is fanciful and " " is misleading. Does the Division want DMETS to continue with the review of the names from a safety perspective in light of DDMAC's objections?

Alina

LT Alina R. Mahmud  
Team Leader, Division of Medication Errors and Technical Support  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Rm 6-34

(301) 827-0916

-----Original Message-----

**From:** Hardeman, Steven D  
**Sent:** Monday, March 24, 2003 11:58 AM  
**To:** Beam, Sammie  
**Cc:** Mahmud, Alina  
**Subject:**

Sammie,

Could you let me know if Johnson and Johnson's proposal to use Risperdal — is acceptable. Dr. Katz did not accept the — modifier since it seems to convey acceleration or speed.

Copy of consult attached.

<< File: 3rd Tradename Consult.pdf >>

\*\*\*\*\*

CAPT Steven D. Hardeman, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products / HFD-120  
Food and Drug Administration  
Rockville, Maryland 20857

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

REQUEST FOR CONSULTATION

(Division/Office):

Office of Drug Safety  
Division of Medication Errors and Technical Support  
(Rm. 15B-03, PKLN Bldg.)

FROM:

Division of Neuropharmacological Drug Products / HFD-120  
Steven D. Hardeman, R.Ph., Regulatory Project Manager  
WOCII Rm 4035  
[Hardemans@cderr.fda.gov](mailto:Hardemans@cderr.fda.gov)  
301-594-5525

DATE <b>2/20/03</b>	IND NO.	NDA NO. <b>21-444</b>	TYPE OF DOCUMENT <b>Response to Approvable</b>	DATE OF DOCUMENT <b>1/31/03</b>
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NAME OF DRUG <b>Risperdal (risperidone)</b>	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG <b>schizophrenia</b>	DESIRED COMPLETION DATE <b>PDUFA Date is 4/3/03</b>
--	------------------------	--	--

NAME OF FIRM: **Johnson & Johnson Pharmaceutical Research & Development**

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

**Request Trade-Name Assessment:**

J&J's 4th and 5th proposed trade names attached. They prefer Risperdal (risperidone) orally Disintegrating Tablets.

The NDA is located at \\Cdsub1\21444

APPEARS THIS WAY  
ON ORIGINAL

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(DMETS; HFD-420)**

**DATE RECEIVED:** August 15, 2002

**DUE DATE:** September 6, 2002

**ODS CONSULT #:** 02-0009-1

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

**THROUGH:** Steven D. Hardeman  
Project Manager  
HFD-120

**PRODUCT NAME:**  
Risperdal  
(Risperidone Orally Disintegrating Tablets)  
0.5 mg, 1 mg, and 2 mg

**NDA SPONSOR:** Janssen

**NDA #:** 21-444

**SAFETY EVALUATOR:** Alina R. Mahmud, RPh.

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name "Risperdal" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:** DMETS has no objections to use of the proprietary name Risperdal.

The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

IS/

IS/

\_\_\_\_\_  
Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Phone: (301) 827-3242  
Fax: (301) 443-5161

\_\_\_\_\_  
Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support  
Office of Drug Safety (ODS)  
HFD-420; Parklawn Building Room 15B-32  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 28, 2002  
NDA NUMBER: 21-444  
NAME OF DRUG: Risperdal —  
(Risperidone Orally Disintegrating Tablets)  
0.5 mg, 1 mg, and 2 mg  
NDA SPONSOR: Janssen

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the proprietary name, *Risperdal* —

*Risperdal* — the second proposed proprietary name for this product. The sponsor initially proposed "*Risperdal* —" which was reviewed by DMETS on March 4, 2002. From a safety perspective, DMETS had no objections to the use of the name whereas DDMAC found the name objectionable from an advertising and promotional perspective. The container labels, carton and package insert labeling were reviewed at that time.

PRODUCT INFORMATION

*Risperdal* — contains the active ingredient, risperidone. *Risperdal* — will be an addition to the product line of *Risperdal* tablets and oral solution currently marketed by Janssen. *Risperdal* — will be available as risperidone orally disintegrating tablets. According to the sponsor, *Risperdal* — tablets are bioequivalent to *Risperdal* tablets. However, *Risperdal* — tablet disintegrates in the mouth within seconds and can be swallowed subsequently with or without water. *Risperdal* — is indicated for the treatment of schizophrenia. A dose of 1 mg twice daily is recommended initially, with increases in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dose of 3 mg twice daily by the third day. Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day. *Risperdal* — will be available as 0.5 mg, 1 mg, and 2 mg tablets.

## II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Risperdal" has been utilized in the U.S. marketplace since December 1993. The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names that sound-alike or look-alike to Risperdal — to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis<sup>4</sup> Pharma-In-Use database was searched for drug names with potential for confusion. In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name "Risperdal."

The Division of Drug Marketing, Advertising, and Communications (DDMAC) was also contacted to access the acceptability of the name from a promotional perspective.

### A. EXPERT PANEL AND DDMAC COMMENTS

1. Several product names were identified by the Expert Panel that were thought to have potential for confusion with the proposed modifier. — These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other
Risperdal —	Risperidone Orally disintegrating Tablets 0.5 mg, 1 mg, 2 mg	3 mg twice daily	
Asacol	Mesalamine Delayed-Release Tablets 400 mg	800 mg three times daily for 6 weeks	Look-alike
Exelon	Rivastigmine Tartrate Capsules 1.5 mg, 3 mg, 4.5 mg, 6 mg Solution: 2 mg/mL	6 mg to 12 mg/day given twice daily	Sound-alike,
Accolate	Zafirlukast Tablets 10 mg and 20 mg	20 mg twice daily	Look-alike

\*Frequently used, not all-inclusive.

2. DDMAC did not have concerns about the name with regard to promotional claims.

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).

<sup>2</sup> Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.

<sup>4</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

## B. AERS DATABASE SEARCH

We searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Risperdal. The Meddra Preferred Term (PT), "Medication Error" and the drug names, "Risperdal%," and "risperidone%," were used to perform the search.

*A total of 95 reports from the AERS search were retrieved and reviewed. Of the 95 reports reviewed, 6 accounts involved name confusion with Risperdal (see attachment I).*

## C. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has received six (6) medication error reports involving name confusion with Risperdal. Two reports involved medication errors between Risperdal and Requip (ropinirole). Four other medication error reports involved confusion between Risperdal and Relafen, Remeron, Rocaltrol, and carbergoline. Although Risperdal products have been available since December 1993, only six (6) medication error reports between Risperdal and various drug products were randomly received by the Agency. These reports did not show any specific pattern with respect to name or packaging similarity with the drug product dispensed in error. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Risperdal, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Risperdal.

Risperdal — contains the same active ingredient, risperidone, as the currently marketed Risperdal Tablets and Oral Solution. However, Risperdal — will be available as an orally disintegrating tablet. We recognize the need to differentiate the currently marketed Risperdal tablets from this new product. Consequently, DMETS does not object to the use of a modifier for this proposed product, since this is common practice for similar "orally disintegrating tablet" dosage forms marketed in the U.S. (e.g., Claritin Reditabs™, Zyprexa Zydis™, Zofran ODT™, Maxalt MLT™, Zomig ZMT™, and Remeron-SolTab™).

In reviewing the modifier, — the drug products Asacol and Accolate were identified as having look-alike potential while Exelon was found to have sound-alike potential.

Asacol contains 400 mg of mesalamine and is indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. Asacol and Risperdal — differ in strength and dosing regimen. Asacol is available as a 400 mg tablet and is dosed three times daily whereas Risperdal — will be available as 0.5 mg, 1 mg, and 2 mg tablets and is sublingually dosed twice a day. Additionally, — will most likely be prescribed with the proprietary name Risperdal. Given that Asacol and — lack convincing look-alike potential and differ in strength and dosing regimen, the likelihood of confusion should be low.

Accolate is indicated for prophylaxis and chronic treatment of asthma in adults and children greater than 5 years of age. Accolate and Risperdal — share numerically similar strengths (20 mg vs. 2 mg, respectively) and an identical dosing regimen (twice daily). However, Accolate and — lack convincing look-alike potential and — will most likely be prescribed in conjunction with the proprietary name Risperdal.

Exelon contains rivastigmine and is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. Exelon and Risperdal — share an overlapping strength (2 mg/mL vs. 2 mg, respectively) and dosing regimen (twice daily); however, Exelon 2mg/mL is available as an oral solution while Risperdal . — 2 mg is available as a tablet. Although Exelon and the modifier — share the above mentioned similarities, the names lack convincing sound-alike potential. In addition, the modifier — ' will most likely be used in conjunction with the proprietary name Risperdal.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Refer to ODS consult 02-0009.

### IV. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name Risperdal —

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

**/S/**

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Alina R. Mahmud, RPh.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

## Attachment I

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3274299-1	5/21/99	Relafen 500 mg	Risperdal 1 mg	Actual Error. A pharmacy technician filled Risperdal 1 mg instead of Relafen 500 mg for a long-term-care (LTC) patient. According to the reporter, the error occurred, because the two products are located next to each other and are similar in appearance. A LTC nurse discovered the error before administration.
2	3450738-8	6/23/99, 7/30/99	Remeron 30 mg	Risperdal 3 mg	Actual Error. A retail chain pharmacist misread the prescription for Remeron 30 mg, and filled it with Risperdal 0.3 mg instead. A physician discovered the error on 8/4/99 after reviewing the patient's prescription vial. The patient ingested the incorrect medication and this "did not contribute to patient's mental health."
3	3508601-X	5/24/00	Rocaltrol 0.25 mcg	Risperdal 0.25 mg	Actual Error. A hospital pharmacist misinterpreted the written prescription for Rocaltrol 0.25 mcg and filled it with Risperdal 0.25 mg. A nurse discovered the error prior to administration.
4	3513894-9	12/29/99	Dostinex 2 mg (Carbergoline)	Risperdal 2 mg	Actual Error. A 68 year-old male patient with Parkinson's disease received Risperdal 2 mg instead of carbergoline 2 mg. He took Risperdal 2 mg daily from 12/27/99 to 01/01/00. He reported "feeling out of it", loss of appetite, bouts of sobbing, sweating, panic attacks, and restlessness.
5	3626379-6	11/06/00	Requip	Risperdal	Actual Error. A patient was admitted to the hospital for "altered mental status." The patient's supply of "Requip" was determined to be "Risperdal." The incorrect prescription was filled at a community pharmacy 8 days ago. The patient recovered without complication 12 to 14 hours after the admission.
6	3237479-7	11/29/01	Requip 0.5 mg (ropinirole)	Risperdal 0.5 mg	Actual Error. A 79 year-old patient received Risperdal 0.5 mg instead of ropinirole (Requip) 0.5 mg. Apparently, a doctor misspelled "ropinirole." The patient became lethargic and confused temporarily after ingesting Risperdal.

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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.  
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/s/

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Alina Mahmud  
9/9/02 12:16:06 PM  
PHARMACIST

Jerry Phillips  
9/10/02 08:12:46 AM  
DIRECTOR

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(ODS; HFD-400)**

**DATE RECEIVED:** January 18, 2002

**DUE DATE:** March 30, 2002

**ODS CONSULT #:** 02-0009

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

**THROUGH:** Steven D. Hardeman  
Project Manager  
HFD-120

**PRODUCT NAME:**  
Risperdal —  
(Risperidone Orally Disintegrating Tablets)  
0.5 mg, 1 mg, and 2 mg

**NDA SPONSOR:** Janssen

**NDA #:** 21-444

**SAFETY EVALUATOR:** Hye-Joo Kim, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name "Risperdal —" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:** From a safety perspective, DMETS has no objections to use of the proprietary name Risperdal —. However, DDMAC has found the name objectionable from an advertising and promotional perspective. *DMETS decision* is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

/S/

/S/

Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Phone: (301) 827-3242  
Fax: (301) 443-5161

Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support  
Office of Drug Safety (ODS)  
HFD-400; Parklawn Building Room 15B-32  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 4, 2002  
NDA NUMBER: 21-444  
NAME OF DRUG: Risperdal —  
(Risperidone Orally Disintegrating Tablets)  
0.5 mg, 1 mg, and 2 mg  
NDA SPONSOR: Janssen

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the proprietary name, *Risperdal* —. The container labels, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The sponsor, Janssen, currently markets several Risperdal products in the following strengths and dosage forms:

Risperdal (Risperidone Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg)  
Risperdal (Risperidone Oral Solution: 1 mg/mL)

PRODUCT INFORMATION

Risperdal — contains the active ingredient, risperidone. Risperdal — will be an addition to the product line of Risperdal tablets and oral solution currently marketed by Janssen. Risperdal — will be available as risperidone orally disintegrating tablets. According to the sponsor, Risperdal — tablets are bioequivalent to Risperdal tablets. However, Risperdal — tablet disintegrates in the mouth within seconds and can be swallowed subsequently with or without water. Risperdal — is indicated for the treatment of schizophrenia. A dose of 1 mg twice daily is recommended initially, with increases in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dose of 3 mg twice daily by the third day. Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day. Risperdal — will be available as 0.5 mg, 1 mg, and 2 mg tablets.

## II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Risperdal" has been utilized in the U.S. marketplace since December 1993. An Expert Panel discussion was conducted to address concerns with the use of the modifier

In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name "Risperdal."

### A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name *Risperdal*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS's Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel expressed concerns that the modifier, "orally disintegrating tablet," which represents the dosage form, makes the proprietary name too long and cumbersome. However, the panel does not object to the use of a modifier for this proposed product, since this is common practice for similar "orally disintegrating tablet" dosage forms marketed in the U.S. (e.g., Claritin Reditabs™, Maxalt-MLT, and Zyprexa Zydis). Lastly, the panel commented that could be confused with "QuickCare" and "QuickVue."<sup>1</sup> QuickCare contains a disinfecting solution that cleans soft contact lenses and QuickVue is a pregnancy test kit.
2. DDMAC objects to the proposed proprietary name, Risperdal, for the following reasons: 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 than other agents or Risperdal tablets."

### B. AERS DATABASE SEARCH

We searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Risperdal. The Meddra Preferred Term (PT), "Medication Error" and the drug names, "Risperdal%," and "risperidone%," were used to perform the search.

**A total of 95 reports from the AERS search were retrieved and reviewed. Of the 95 reports reviewed, 6 accounts involved name confusion with Risperdal (see attachment I).**

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<sup>1</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

### C. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has received six (6) medication error reports involving name confusion with Risperdal. Two reports involved medication errors between Risperdal and Requip (ropinirole). Four other medication error reports involved confusion between Risperdal and Relafen, Remeron, Rocaltrol, and carbergoline. Although Risperdal products have been available since December 1993, only six (6) medication error reports between Risperdal and various drug products were randomly received by the Agency. These reports did not show any specific pattern with respect to name or packaging similarity with the drug product dispensed in error. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Risperdal, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Risperdal.

Risperdal — contains the same active ingredient, risperidone, as the currently marketed Risperdal Tablets and Oral Solution. However, Risperdal — will be available as an orally disintegrating tablet. We recognize the need to differentiate the currently marketed Risperdal tablets from this new product. Consequently, DMETS does not object to the use of a modifier for this proposed product, since this is common practice for similar “orally disintegrating tablet” dosage forms marketed in the U.S. (e.g., Claritin Reditabs™, Zyprexa Zydis™, Zofran ODT™, Maxalt MLT™, Zomig ZMT™, and Remeron-SolTab™).

In reviewing the modifier, — the expert panel identified QuickCare and QuickVue as possible sound-alike and/or look-alike product names. These names should not pose a problem, since QuickCare and QuickVue are not drug products. QuickCare is a disinfecting solution for soft contact lenses and QuickVue is an over-the-counter pregnancy test kit. However, DDMAC objects to the modifier, — for the following reasons: “ — 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 — quickly than other agents or Risperdal tablets.”

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the draft blister label, draft carton and insert labeling of Risperdal — DMETS has attempted to focus on safety issues relating to possible medication errors. Following our review we have identified several areas of possible improvement, which might minimize potential user error.

#### A. BLISTER LABEL

1. 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.
2. The established name should read as “risperidone orally disintegrating tablet” rather than “(risperidone) orally disintegrating tablets”.
3. See comment B7.

## B. CARTON LABELING (0.5 mg, 1 mg and 2 mg)

1. We recommend deleting or relocating the logo that is incorporated in the proprietary name since it detracts attention from the proprietary name.
2. We recommend relocating the modifier \_\_\_\_\_ to appear next to the proprietary name (e.g., Risperdal \_\_\_\_\_).
3. We recommend revising the format of the established name as follows:

Risperidone Orally Disintegrating Tablets.

4. We recommend placing the statement, "Rx Only," on the front panel of the label.
5. 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.
6. 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 lay side by side on pharmacy shelves.
7. 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.
8. 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".

## C. 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.

**IV. RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name Risperdal — from a safety perspective. However, DDMAC has found the name objectionable from an advertising and promotional perspective.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DMETS recommends the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

ISI

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Hye-Joo Kim, Pharm.D.  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety (ODS)

Concur:

ISI

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Alina R. Mahmud, RPh.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Attachment I

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3274299-1	5/21/99	Relafen 500 mg	Risperdal 1 mg	Actual Error. A pharmacy technician filled Risperdal 1 mg instead of Relafen 500 mg for a long-term-care (LTC) patient. According to the reporter, the error occurred, because the two products are located next to each other and are similar in appearance. A LTC nurse discovered the error before administration.
2	3450738-8	6/23/99, 7/30/99	Remeron 30 mg	Risperdal 3 mg	Actual Error. A retail chain pharmacist misread the prescription for Remeron 30 mg, and filled it with Risperdal 0.3 mg instead. A physician discovered the error on 8/4/99 after reviewing the patient's prescription vial. The patient ingested the incorrect medication and this "did not contribute to patient's mental health."
3	3508691-X	5/24/00	Rocaltrol 0.25 mcg	Risperdal 0.25 mg	Actual Error. A hospital pharmacist misinterpreted the written prescription for Rocaltrol 0.25 mcg and filled it with Risperdal 0.25 mg. A nurse discovered the error prior to administration.
4	3513594-9	12/29/99	Dostinex 2 mg (Carbergoline)	Risperdal 2 mg	Actual Error. A 68 year-old male patient with Parkinson's disease received Risperdal 2 mg instead of carbergoline 2 mg. He took Risperdal 2 mg daily from 12/27/99 to 01/01/00. He reported "feeling out of it", loss of appetite, bouts of sobbing, sweating, panic attacks, and restlessness.
5	3626379-6	11/06/00	Requip	Risperdal	Actual Error. A patient was admitted to the hospital for "altered mental status." The patient's supply of "Requip" was determined to be "Risperdal." The incorrect prescription was filled at a community pharmacy 8 days ago. The patient recovered without complication 12 to 14 hours after the admission.
6	3237479-7	11/29/01	Requip 0.5 mg (ropinirole)	Risperdal 0.5 mg	Actual Error. A 79 year-old patient received Risperdal 0.5 mg instead of ropinirole (Requip) 0.5 mg. Apparently, a doctor misspelled "ropinirole." The patient became lethargic and confused temporarily after ingesting Risperdal.

cc: NDA 21-444  
HFD-120: Division Files/Steven Hardeman, Project Manager  
HFD-120: Russell Katz, Division Director, DNDP  
HFD-400: Sammie Beam, Project Manager, DMETS  
HFD-400: Hye-Joo Kim, Safety Evaluator, DMETS  
HFD-040: Andrew Haffer, DDMAC

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/s/  
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Hye-Joo Kim  
3/29/02 03:11:32 PM  
PHARMACIST

Alina Mahmud  
3/29/02 03:21:09 PM  
PHARMACIST

Carol Holquist  
3/29/02 03:31:41 PM  
PHARMACIST

Hardeman, Steven D

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**From:** Mosholder, Andrew D  
**Sent:** Monday, September 16, 2002 11:29 AM  
**To:** Hardeman, Steven D  
**Cc:** Laughren, Thomas P  
**Subject:** Labeling for Risperdal — (NDA 21-444)

Hello Steve,

Please add the following to the draft labeling for this NDA, under "Management of Overdose," following the sentence about gastric lavage.

**DRAFT**

*Don't  
want  
this*

Here is the bracketed comment to explain the change:

[We have added this comment because of the nature of this new risperidone formulation.]

We have added similar statements for other orally disintegrating formulations, but I failed to suggest this in my clinical review of this NDA.

Thanks,  
Andy

Redacted 22

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information