CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-346

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA 21-346

Trade Name: **Risperdal Consta**
Generic Name: **risperidone long acting injection**
Applicant Name: **Johnson & Johnson**
HFD-120
Approval Date: **10/29/03**

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.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES

If your answer is " no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity? **YES**

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 ON Page 9.

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 ON Page 9 (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 Tablet**
NDA #20-588	**Risperdal Oral Solution**
NDA #21-444	**Risperdal M-Tab**

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).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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.

YES

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i. e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? **NO**

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation # 1, Study # **RIS-USA-121**

Investigation # 2, Study # **RIS-INT-101**

Investigation # 3, Study # **RIS-INT-57**

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets " new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i. e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation # 1 **NO**

Investigation # 2 **NO**

Investigation # 3 **NO**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # Study #
NDA # Study #
NDA # Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation # 1 **NO**

Investigation # 2 **NO**

Investigation # 3 **NO**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # Study #

NDA # Study #

NDA # Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in # 2(c), less any that are not "new"):

Investigation #1, Study # RIS-USA-121

Investigation #2, Study # RIS-INT-61

Investigation #3, Study # RIS-INT-57

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was " conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation # 1 **IND #52,982** **YES**

Investigation # 2 **IND #52,982** **YES**

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) **NO**

If yes, explain: **N/A**

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
10/30/03 08:40:49 AM

For AF Action

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-346	Efficacy Supplement Type SE-	Supplement Number
Drug: Risperdal Consta (risperidone) Long Acting Injection	Applicant: Janssen Research Foundation	
RPM: Steven D. Hardeman, R.Ph.	HFD-120	Phone # 301-594-5525
Application Type: (*) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	10/29/03 6 mos
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver N/A	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception N/A	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	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	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• 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).	( ) Verified N/A

Exclusivity (approvals only)	
• Exclusivity summary	✓ In Package
• 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!*	( ) Yes, Application #_____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	~~AP~~ Not Approvable 6/28/02
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (✓) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A First
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	✓
• 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)*	✓
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	✓
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
CMC review(s) *(indicate date for each review)*	✓
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (✓) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	✓
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

For N/A Action

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RPM: Steven D. Hardeman, R.Ph.	HFD-120	Phone # 301-594-5525
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• This application is on the AIP	( ) Yes (✓) 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	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
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Exclusivity (approvals only)	
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❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	11/1
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA ( ) AE (✓) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (✓) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	
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• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
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• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
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❖ Clinical review(s) *(indicate date for each review)*	✓
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❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	✓
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
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❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

MEMORANDUM

DATE: October 29, 2003

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

TO: File, NDA 21-346

SUBJECT: Action Memo for NDA 21-346, for the use of Risperdal (risperidone) Consta

NDA 21-346, for the use of Risperdal (risperidone) Consta, an intramuscular depot formulation of the currently available atypical anti-psychotic drug risperidone, was submitted by Janssen Research Foundation on 8/31/01. The application contained the results of a single randomized trial, pharmacokinetic and safety data, and pre-clinical data. While the review team had determined that the clinical data established the effectiveness of the treatment for patients who were acutely psychotic, and there were no clinical adverse events that would preclude approval, several pre-clinical findings were worrisome. In particular, adrenal and renal tumors, and osteodystrophy were seen in the rat carcinogenicity study. These findings raised serious questions about the safety of this product, and, because of these findings, a Not Approvable letter was issued on 6/28/02. In that letter, we noted several points:

1) the sponsor had not submitted a compelling argument that there was a mechanism that explained the appearance of these tumors, and did not present an adequate argument that the tumors were known to be irrelevant for humans,
2) no reproductive toxicology studies had been performed with the depot, and the pre-clinical data suggested that there could be significant differences in the reproductive effects of the depot compared to the oral product,
3) several impurities in the depot formulation were not present in the oral formulation, and had not been qualified.

As a result of these findings, we had concluded that the NDA was Not Approvable. To support approval, the sponsor was given the option of documenting that the depot formulation offered a clinical benefit over the oral formulation or presenting data that the animal findings were not relevant for humans. Further, we asked the sponsor to qualify the new impurities, and perform an embryofetal development study.

In addition to these critical deficiencies, we had a number of CMC questions, and several Clinical Pharmacology questions (including a request for a Phase 4 commitment for the sponsor to submit in vitro dissolution data from on-going stability tests on validation lots of all proposed dosage strengths).

We met with the sponsor on 2/25/03 to discuss these issues. At that meeting, the sponsor proposed to address the primary deficiencies by providing evidence that depot formulations (generically, and not specifically risperidone) prevent more relapses than oral formulations in long-term treatment (presumably due to increased compliance), and to complete the embryofetal study in Phase 4. The Division agreed that the sponsor could attempt to resolve the deficiencies in this manner, although we gave no commitment that this approach would be successful.

The sponsor responded to the Not Approvable letter with a submission dated 4/28/03. The submission consisted of a number of articles from the literature that were intended to address the clinical issues, additional data and arguments intended to further address the relevance of the animal findings (including their previously announced intention to perform the embryofetal study in Phase 4), and responses to the CMC and clinical pharmacology requests. This submission has been reviewed by Dr. Earl Hearst, medical reviewer (review dated 10/24/03), Dr. Lois Freed, pharmacologist (review dated 10/29/03), Dr. Gurpreet Gill-Sangha, chemist (review dated 10/22/03), Dr. Sally Yasuda, Office of Clinical Pharmacology and Biopharmaceutics, (review dated 8/15/03), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (memo dated 10/28/03). The clinical team recommends that the application be approved, while Dr. Freed recommends that the sponsor be required to perform the embryofetal study prior to approval.

In brief, although the sponsor has provided numerous articles from the medical literature that ostensibly address the question of the utility of depot formulations (as compared to oral preparations of drugs to treat schizophrenia), they have submitted only a single non-published, brief attempt to marshal the available evidence on the question of whether or not depot formulations provide an advantage over oral treatments.

Specifically, the sponsor provides a brief document, prepared by Drs. Claudia Mentschel, Stefan Leucht, and John Kane of the Zucker Hillside Hospital in New York, that purports to be a meta-analysis of all available studies in which patients were randomized to depot or oral treatments, and in which relapses were compared. This analysis includes eight (8) studies previously published in the medical literature, and represents a sub-set of the studies included in a meta-analysis of all such studies, performed and published by Adams, et al, in 1999. In this latter publication, the authors concluded that depot formulations did not prevent relapses "more effectively" than oral preparations. However, Mentschel et al have found fault with this analysis for several reasons: 1) Adams included studies that were only 4-8 weeks in duration, too short to adequately assess relapses, 2) Adams included in-patient studies, which by their nature are likely inadequate to assess compliance, and 3) Adams counted patients who discontinued early from these studies for whom the exact reason for discontinuation was unknown as having relapsed. In the Mentschel analysis,

then, only out-patient studies of at least 10 months duration were included, and patients who discontinued for unknown reasons were not counted as having relapsed. The sponsor provided neither the raw data for the studies they included nor the articles that served as the basis for their analysis. Mentschel et al did state that they used the same analytic methodology as Adams (a random effects model with relative risks as effect sizes).

In the sponsor's analysis, a total of 8 studies were included; the most recent was published in 1983; the range of dates for the other 7 studies was from 1974-1980. Study sizes ranged from 36 to 290. All studies were randomized, parallel groups studies in which patients were randomized to either fluphenazine depot or oral medication; in 4 of the studies, the oral preparation was fluphenazine, in 2 studies the oral preparation was pimozide, and in one each the oral drug was penfluridol and trifluoperazine. We have no details about these studies.

According to the sponsor's analysis, the estimate of the relative risk of relapses in 2/8 studies numerically favored the oral drug (in one the oral drug was pimozide, in one it was penfluridol), but in each case the 95% confidence intervals (CI) included 1. In the remaining 6/8 studies, the estimate of the relative risk numerically favored depot, and in 2/6, the 95% confidence intervals excluded 1 (in both cases, the oral drug was fluphenazine; in one case, the upper bound of the CI was 0.99; in the other, the upper bound of the CI was 0.92). In the overall model, the estimate of the relative risk was 0.78, with a 95% CI of (0.66, 0.91). The p-value for the overall effect was 0.002. When, as did Adams, et al, the authors counted patients for whom the reason for discontinuation was unknown as having relapsed, the p-value for the overall effect was 0.14 (the authors state that there was no significant difference in drop-out rates).

As noted above, the sponsor also attempted to address the animal tumor findings, and these data and arguments have been reviewed in detail by Dr. Freed.

Briefly, the sponsor attempted a number of approaches to address these issues:

1) They enlisted Dr. Gordon Hard, an expert whose published work had suggested that renal tumors were associated with severe chronic renal disease (this work had served as the basis for the Division's view, expressed in the Not Approvable letter, that, in this case, the tumors could not be explained by this mechanism, since there was no correlation between chronic renal disease and tumors in the sponsor's study), to examine the renal tissue in the CA study.
2) They performed studies to assess cellular proliferation and apoptosis in renal tissues from the CA study.
3) They performed a re-analysis of renal tissue from control animals in 4 previous CA studies (2 in Wiga rats, 2 in Hannover rats; the latter were the sub-strain used in the CA study).

4) They performed an 8 week mechanistic study in Wiga and Hannover rats.

The sponsor notes that Dr. Hard concluded that the renal injury seen in the CA study was insufficient to explain the tumor occurrence (this had been the division's conclusion at the end of the initial review). However, Dr. Hard did conclude that there was no evidence that the tumors were drug related, based on the fact that risperidone is non-genotoxic, and that there was no evidence of increased renal distal tubule hyperplasia or microscopic findings consistent with direct cytotoxicity, although he did recommend additional studies to rule out this latter possibility.

As Dr. Freed notes, none of the other studies submitted support the sponsor's conclusion that the renal tumors seen in rats are either species (there is no mouse study) or sub-strain (Wiga vs Hannover) specific, or that the tumors have no relevance for humans. Indeed, the cellular proliferation study demonstrated that there was an increase in cellular proliferation (a mechanism widely believed to be relevant for tumor formation) in the high dose male rats with tumors, and not in control or high dose male rats without tumors. Based on these findings, the sponsor admits that Dr. Hard's conclusion that there is no evidence that the tumors were drug-related "...becomes questionable.".

Regarding the adrenomedullary tumors, the sponsor suggested that, in fact, these tumors were seen in the oral risperidone CA studies, and that, therefore, there were no real differences (in this regard) between oral and IM depot administration. Dr. Freed notes that this conclusion is not well supported, given that the occurrence of the tumor in the IM study was clearly dose related, and this was not the case in the oral study.

Regarding the impurities issue, the sponsor has lowered the specification for the ——— to '—— (from ——), which is below the level of quantification; this resolves the issue for these impurities.

Regarding the ——— impurity, the sponsor has reduced the specification to —— (also from ——); the limit of quantification for this impurity, however, is —— (the sponsor argues that toxicity studies done using the oral route exposed animals to drug containing '—— of this impurity, and that on a dose basis, assuming 100% bioavailability of the impurity, these studies cover the exposure to this impurity that would result from the depot formulation). They provide no evidence that the bioavailability of this impurity is 100%. Nonetheless, the small difference between the limit of quantification and the proposed specification does not warrant repeating toxicity studies.

However, as Dr. Freed points out, the genotoxic potential of this impurity has not been evaluated. Therefore, she recommends that the sponsor be required to perform an appropriate study in Phase 4.

COMMENTS

The application for Risperdal Consta was initially not approved because pre-clinical data suggested that the IM depot was associated both with tumors and osteodystrophy in rats, findings that were not seen with studies of the oral product. While it was not obvious why these different routes of administration should give rise to such different findings, the markedly increased incidence of osteodystrophy (along with the somewhat less impressive incidence of tumors) strongly suggested that the findings were not artifactual. The division found the sponsor's attempts to identify a mechanism of tumor formation wanting.

At a meeting with the sponsor on 2/25/03, the division agreed that the sponsor could attempt to make the argument that depot formulations offer a benefit over oral preparations, based on improved compliance with treatment, and that this benefit could justify approving the product. The division requested that the sponsor submit evidence to support this conclusion. We agreed that if this argument was made successfully, we would consider not only approving the application, but we would also consider doing so prior to the completion of the embryofetal study.

In response, the sponsor has submitted numerous articles from the literature that they believe support their view that depot formulations are valuable and offer a benefit over oral formulations, and that atypical anti-psychotics are superior to typical anti-psychotic drugs in treating symptoms of schizophrenia. In addition, they have attempted to further address the tumor findings in the rat.

Regarding the clinical issue, much of what the sponsor has submitted addresses the question of the importance of patient compliance with prescribed anti-psychotic medication. We agree that this is, quite obviously, critical to the effective use of these products. However, this obvious conclusion does not address our primary concern.

That primary concern, as expressed in our meeting with the sponsor, is that there should be a demonstrable benefit of this particular proposed treatment over currently available treatments in order to justify the marketing of this product in the face of the existing animal data.

The sole potentially relevant data that the sponsor has submitted to address this point is the analysis by Mentschel et al, which purports to describe a meta-analysis of 8 controlled trials comparing fluphenazine depot to various oral anti-psychotic medications, and that ostensibly demonstrates a statistically significant improvement in relapse rate on depot compared to oral treatment.

There is much that is unknown about this analysis, including the details of the individual studies included (especially the conduct of these studies, whether the doses used produced a fair comparison between oral and depot treatments, the

nature of the discontinuations and whether this produced an important bias, the details of the statistical analyses, etc.). Dr. Laughren has examined the Adams article; while the individual studies included in the sponsor's analysis presumably are a subset of the studies described in this article, we cannot reliably determine if there are other studies included in that (Adams) article that might also have been included in the sponsor's meta-analysis. For example, the sponsor's criteria for including a study in its analysis was that the study enroll outpatients, and be of at least 10 months duration; we are not clear why 10 months was chosen as the minimum duration of a study that should have been included. Did, for example, Adams describe any studies that were of reasonable duration (say, 6 months) that the sponsor excluded from their analysis? Indeed, given the differences in study design across the studies, it is not even clear that such a meta-analysis is appropriate.

Although the review team concludes that this meta-analysis supports the conclusion that depot formulations result, in practice, in fewer relapses compared to oral products, I believe that the analysis is presented in insufficient detail to provide very useful data on this question. (For example, I believe it is not unreasonable to consider patients whose reason for discontinuation is unknown as having relapsed; such analyses are often performed as "worst case" analyses, and although they are not usually primary analyses, it is worth noting that because the meta-analysis is a post hoc analysis, it too is not a primary analysis in a real sense). Even if the analysis could be considered acceptable, it obviously does not address the question of whether or not Risperdal Consta provides a benefit compared to oral risperidone.

For these reasons, then, I consider this effort not to provide particularly compelling evidence that Risperdal Consta confers a benefit beyond that provided by oral risperidone. I do acknowledge, as described by Dr. Laughren, that the sponsor has submitted a few additional articles that purport to demonstrate the superiority of atypical anti-psychotic drugs compared to typical anti-psychotic medications, both in terms of symptom control, side effect profile, and degree of compliance, but these data are not presented in sufficient detail to permit an independent review. In addition, while these studies are intended to address an important issue (the value of having atypical anti-psychotics available [currently only typical antipsychotics are available as depots]) they do not address the primary question posed in this application; namely, does risperidone IM depot provide a benefit compared to risperidone oral?

However, I am convinced, based upon conversations with the review team and other experts, that the availability of a depot formulation of an atypical anti-schizophrenia treatment can provide an important contribution to the armamentarium in this field. While the data submitted do not provide very strong evidence in favor of this conclusion (neither, of course, does it refute this conclusion), nevertheless, there is a prima facie case to be made that the use of a depot formulation will, at least in some patients, increase compliance compared

to the oral formulation (while it is true that there may be patients who would prefer to take the oral medication over the depot, this does not undermine the conclusion that other patients would benefit from the availability of the depot). Further, as noted above, there are currently only two depot formulations of anti-psychotic medications available; fluphenazine and haloperidol. There is general agreement in the expert community that the availability of a depot formulation of an atypical anti-psychotic medication would be very worthwhile. For these reasons, then, it seems reasonable to approve the depot, assuming that it can be used safely.

Obviously, we had concluded earlier, at the time of the Not Approvable action, that, absent evidence that the depot provided a benefit over the oral product, it could not be marketed safely.

While I must acknowledge that, in my view, the sponsor has provided no new compelling evidence **establishing** such a benefit of the depot, as noted above, I am now convinced that the availability of the depot can be considered to provide such a benefit, at least for some patients. Is this (unquantifiable) benefit sufficient to overcome the risk posed by the animal findings?

I believe now that it is. While, as I have just noted, the benefit of the depot cannot, in any real sense, be quantified, neither can the risk to humans of the findings seen in the animals.

The sponsor has submitted no new data that minimizes these signals, either of tumor formation or of the osteodystrophy. In my view, these signals still stand, and their meaning for patients is unknown (in particular, I do not believe that the sponsor has submitted any information that supports the view that these findings are irrelevant for people). Nonetheless, given my current view of the utility of the depot formulation, I now believe that the potential (unknowable) risks posed to humans related to the animal findings are acceptable, given that the animal data are described clearly, and relatively prominently, in product labeling. I believe this latter end can be achieved by including a description of the tumor and osteodystrophy findings prominently in the Precautions section of labeling with a statement that these findings have not been seen in animal studies of oral risperidone. In this way, the prescriber can be made aware that an alternative product, oral risperidone, is not associated with these findings, and can make a more reasonable choice between these products.

I also agree with Dr. Laughren that the embryofetal study may be completed in Phase 4 (I understand that a dose-finding study is on-going).

Finally, there continue to be no clinical adverse events that would preclude approval.

The sponsor has responded to the other requests included in the Not Approvable letter, and has agreed to the completion of additional studies in Phase 4: the embryofetal study; a study to further characterize the osteodystrophy; a study to examine the genotoxicity of the process impurity, ———, and in vitro release data from on-going stability tests on validation lots of all strengths.

For the reasons given above, then, I will issue an Approval letter with appended final labeling to which the sponsor and we have agreed.

Russell Katz, M.D.

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/s/

Russell Katz
10/29/03 02:10:36 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: October 28, 2003

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

SUBJECT: Recommendation for Approval Action for
Risperdal Consta (risperidone long-acting injection) for the treatment of schizophrenia

TO: File NDA 21-346
[**Note:** This overview should be filed with the 4-28-03 response to our 6-28-02 nonapprovable letter.

1.0 BACKGROUND

I refer to my memo of 6-21-02 for a more detailed accounting of the issues leading up to the nonapproval action for this application.

In summary, there were several preclinical issues that were the basis for our nonapproval action:
-The tumor profile in the 2-year IM depot carcinogenicity study in the rat was different than observed in the 2-year oral studies in mouse and rat. Mechanistic studies and explanations were inadequate to dismiss the findings, and there was no exposure margin to argue that it was a threshold effect that could be dismissed.
-We found that reliance on the oral risperidone reproductive toxicology studies was problematic, since the chronic tox studies suggested different toxicity profiles for the oral and IM forms.
-There were insufficient data to support 1 impurity found in the IM but not the oral formulation.

In addition, in our 6-28-02 letter, we asked for responses on several other matters in our letter, as follows:
-Several CMC deficiencies
-Several comments regarding biopharmaceutics issues:
    -We asked for a commitment to submit in vitro release data from ongoing stability studies within 4 months of approval, along with revised in vitro release specifications.
    -We proposed slightly revised interim in vitro release specifications.
    -We asked for revised data sets for population pharmacokinetic analyses.

We also made requests for additional data apart from the nonapproval letter:
-In a 2-25-03 meeting, we asked the sponsor to submit a comprehensive package of published papers to support their argument that Risperdal Consta, as the first depot form of an atypical antipsychotic, would provide a clinical benefit that would outweigh our concerns about preclinical data.
-In a 3-18-03 request, we asked for a safety update as part of the complete response.

On 4-28-03, the sponsor submitted a complete response.

2.0 CHEMISTRY

It is my understanding that all remaining CMC issues have been resolved.

3.0 PHARMACOLOGY

3.1 Tumor Profile in the 2-year IM Depot Carcinogenicity Study in the Rat

The pharmacology review of the 4-28-03 response was not complete and available to me at the time of my completion of this memo, however, it is my impression that there remains a signal for 2 different tumor types with the depot form of risperidone not seen for the oral form. In addition, there was revealed a finding of osteodystropy that was not seen in the oral studies. Nevertheless, I am persuaded that the potential clinical benefit of this new formulation for risperidone outweighs the concern raised by these signals, and it is my view that this concern can be adequately addressed by describing these findings in labeling.

3.2 Reproductive Toxicology Studies

As noted, we found that reliance on the oral risperidone reproductive toxicology studies was problematic, since the chronic tox studies suggested different toxicity profiles for the oral and IM forms. There was continued discussion of when a complete report on a repeat IM depot embryofetal developmental toxicity study would need to be submitted. In our 2-25-03 meeting we indicated that ordinarily this would be needed prior to our taking a final approval action, however, at that meeting, we agreed to consider the strength of the case that could be made for clinical benefit in deciding exactly when the final report would be needed. As was the case for the tumor and toxicity findings, I am persuaded that the potential clinical benefit of this new formulation for risperidone outweighs the concern raised by the absence of reproductive toxicology data specific to this depot formulation, at least with regard to the timing for completion of the needed study. While the pharmacology team continues to feel that the results of this study should be available prior to taking a final action, it is my view that this requirement can be satisfied postapproval.

3.3 Qualification of Impurity

It is my understanding that the pharmacology group has reached the conclusion that sufficient data regarding this impurity have been submitted to justify permitting the requirement for an in vitro gentoxicity assay to be conducted postapproval, and I agree.

4.0 BIOPHARMACEUTICS

All the biopharmaceutical concerns delineated in the nonapproval letter have been addressed by the sponsor, and it is the view of OCPB that, once there is agreement on labeling, this application can be approved. I agree.

5.0 CLINICAL DATA

5.1 Rationale for Clinical Benefit

As noted, in a 2-25-03 meeting with the sponsor, we reached agreement that we may well accept an argument that the potential clinical benefit of having a depot form of risperidone available would outweigh the preclinical concerns that were the basis for the nonapproval action. A key issue was the availability of data from controlled trials demonstrating an advantage in lower relapse rates in patients randomized to depot forms of typical antipsychotic drugs compared to those randomized to oral forms. We indicated the possibility of our willingness to rely on such findings in our consideration of making Risperdal Consta available as the first atypical antipsychotic in depot form. We indicated our willingness to consider such a move in part due to the generally accepted better tolerability of atypical drugs like risperidone compared to typical antipsychotic drugs. However, we had asked the sponsor to pull together a comprehensive package of published papers to support their argument, and they have submitted this package as part of their response.

The sponsor provided a response, including 64 references, and, in particular, including the following findings pertinent to this question of potential advantage in making Risperdal Consta available:
-An as yet unpublished manuscript by Mentschel, et al, provides data from a meta-analysis involving RCTs of at least 10 months duration comparing long-acting vs oral typical antipsychotics in outpatients. This effort was prompted by a Cochrane review by Adams, et al, of a larger set of studies, including many that were often only 4-8 weeks in length, and some that were inpatient. The Adams, et al, review, did not find any advantage for the depot typical antipsychotics over oral typical antipsychotics, however, Mentschel, et al, argue that it was not appropriate to include short-term studies, or inpatient studies, since a benefit would not be readily demostrated in either circumstance. Their analysis focusing on 8 longer-term outpatient studies revealed overall relapse rates of 45% for oral medication compared to 30% with depot, yielding an absolute risk reduction of 14% and a relative risk reduction of 32% ($p = 0.002$). These data were submitted to provide support for the view that, in general, depot antipsychotics provide an advantage over oral medications with regard to relapse.

-Several issues need to be addressed for the Mentschel, et al, analysis.

-One question is whether or not the comparisons were fair from the standpoint of dosing. For the studies for which we have information on the dosing of depot and oral medications, it is my view that the oral dose is an adequate match for the depot dose. This is obviously a judgement, since there is no precise guidance for dose equivalencies for these different formulations.

-Another issue is the fact that the Cochrane analysis used a very conservative approach to assessing dropouts for whom no specific cause was listed, i.e., they were all considered relapses. The Mentschel, el al, analysis did not make this assumption, and alternatively, relied on patients meeting protocol specified definitions of relapse to be considered relapses. The analysis favored depot over oral formulations only when the latter approach was taken. I agree with the approach taken by Mentschel, et al, and in fact, this is our usual approach taken when analyzing relapse data. Thus, I am not particularly troubled by lack of significance taking the more idiosyncratic approach proposed by the Cochrane group.

-A third potential concern is the choice of studies for the Mentschel analysis. As noted, they focused on outpatient studies of at least 10 months duration. Unfortunately, it is not clear from either the Mentschel, et al, manuscript or the Adams, et al, paper describing the Cochrane analysis precisely which studies were left out of the Mentschel, et al, analysis. Nevertheless, I agree in principle with the criteria proposed by Mentschel, et al, for their choice of studies.

-A soon to be published manuscript by Leucht, et al, provides data from a meta-analysis involving RCTs comparing oral typical and atypical antipsychotics with regard to relapse, and revealed overall relapse rates of 23% for typical antipsychotics compared to 15% for atypical antipsychotics ($p = 0.0001$). It was not clear from these data that the advantage could be explained on the basis of improved compliance. These data were submitted to provide support for the view that, in general, atypical antipsychotics provide an advantage over typical antipsychotics with regard to relapse.

-In another soon to be published study looking at the occurrence of new cases of TD in patients treated with either a typical antipsychotic, haloperidol, or various atypical antipsychotics, in trials of a year or more in duration revealed annual risks of TD of 0.91% for the atypical drugs compared to 5.3% for haloperidol. These data were submitted to provide support for the view that, in general, atypical antipsychotics provide an advantage over typical antipsychotics with regard to TD.

-There aren't any systematic data comparing compliance rates for oral and depot antipsychotics, at least not from direct comparisons. It is very difficult to define and measure compliance, and this, in part, explains the lack of systematic data on this issue. However, the sponsor has provided data from separate studies, suggesting overall nonadherence rates of 26% for depot antipsychotics compared with 40-50% for oral antipsychotics. It's not clear to me exactly where these numbers are derived from, and my impression is that we simply do not have any good data pertinent to this issue.

Comment: While this is not a completely settled issue, I think the sponsor has made a reasonable case that there would be a sufficient advantage in having a depot form of risperidone available to outweigh our concerns about the preclinical data. Relapse is clearly not a good outcome in schizophrenia, and I think there are sufficient data available to suggest an advantage for depot drugs compared to oral drugs in delaying time to relapse. The key piece of evidence, in my view, is the Mentschel, et al, manuscript. Admittedly, this is not a well-documented review, and it is not an analysis that we have independently replicated. My view that it is sufficient evidence is in part based on my judgment that the advantages of a depot form over an oral form are self-evident (namely, that lack of compliance for

the depot form would be immediately obvious, and, therefore, alert the treatment team that a patient may need special attention), and that little supportive data are needed to buttress this view. While, ideally, one would have data on better compliance as well, this is almost impossible to study, and I am persuaded that relapse is the outcome of real clinical concern in any case. There are also data suggestive of inherent advantages for atypicals over typicals, both with regard to effectiveness in preventing relapse, and regarding safety, in particular a likely lower risk of TD. These data are not directly germane to the question of depot vs oral forms, however, they do support the general view that a depot form of these newer, possible more effective and better tolerated agents, would be desirable. Thus, even though there are no data directly showing an advantage for depot risperidone over oral risperidone with regard to relapse, I think one can get there with reasonable ease by extrapolation.

5.2 Safety Update

We informed the sponsor on 3-18-03 that a complete response to the NA letter would need to include a safety update, and the response included safety data covering a period from 3-15-01 to 3-18-03. Safety data were included from completed and ongoing J&J studies, non-IND studies, postmarketing experience (the depot formulation is available in 22 countries worldwide), and worldwide literature.

There were 3 completed and 4 ongoing J&J studies (all open label, however, study 62 involved a 1-year comparison with olanzapine) contributing safety data from n=1664 Risperdal Consta patients (total exposure time for these patients = 2053 person-years). There was an estimated 358 person-years of Risperdal Consta exposure in non-IND studies.
-Completed Studies: There were 2 deaths in patients taking Risperdal Consta, neither reasonably considered drug-related, and 77 other SAEs, mostly psychiatric, and no unusual pattern of other SAEs.

-Ongoing Studies: There were 14 deaths in patients taking Risperdal Consta, with no unusual causes or patterns, and 677 other SAEs, mostly psychiatric, and no unusual pattern of other SAEs.
-Non-IND Studies: There were 12 deaths in patients taking Risperdal Consta, again with no unusual causes or patterns, and 242 other SAEs, mostly psychiatric, and no unusual pattern of other SAEs.
For postmarketing reports, the sponsor estimated person-years of exposure based on sales, and this yielded an estimate of approximately 3000 person-years. There were 12 reports of death in patients taking Risperdal Consta, with a fairly typical distribution of causes, except for 1 case of liver failure. No information was available on this case. There were 47 patients taking Risperdal Consta for whom nonfatal SAEs were reported, the most common being psychiatric, and no unusual pattern for the other SAEs. There was 1 case of SJS.

The sponsor's literature review included 61 published papers. The sponsor provided only a listing of the titles of these papers, along with a warrant that "all adverse events observed in the literature were qualitatively similar to those reported in the Investigator's Brochure." Dr. Hearst reviewed the titles, and indicated that he found nothing to indicate any new safety concerns.

Dr. Hearst reviewed the safety data for certain events of particular interest, i.e., hyperglycemia, diabetes, and stroke. There were several instances of each of these events, however, there were no

comparison groups (with the exception of 1 study), and thus, these reports are difficult to evaluate. The numbers of cases did not seem unusual, given the high background rate for all of these events. Conclusion Regarding Safety: There were no new safety findings that would impact on an approval decision or on labeling.

6.0 WORLD LITERATURE

As noted, a literature review was included in this response, and revealed no important new safety information.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, risperidone LA is now approved for the treatment of schizophrenia in 22 countries worldwide.

8.0 LABELING

We have not yet reached agreement with J&J on final labeling as of the time of completion of this memo.

9.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Janssen has submitted sufficient data to support the conclusion that risperidone LA is effective and acceptably safe in the treatment of schizophrenia. As noted, I feel the animal toxicity and carcinogenicity findings can be adequately addressed by describing them in labeling. Thus, I recommend that we issue the attached approval letter once we have reached agreement with J&J on final labeling.

cc:
Orig NDA 21-346
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/EHearst/SHardeman

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/s/

Thomas Laughren
10/28/03 01:23:02 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: 2/25/03
LOCATION: WOCH - Conf. Room E
APPLICATION: NDA 21-346 Risperdal Consta (risperidone) Long-Acting Injection
TYPE OF MEETING: Complete Response
MEETING CHAIR: Russell Katz, M.D.
MEETING RECORDER: Steve Hardeman, R.Ph.

FDA ATTENDEES

Robert Temple, M.D., Director, ODEI
Russell Katz, M.D., Director, DNDP
Tom Laughren, M.D., Psychopharm Team Leader
Robert Levin, M.D., Medical Reviewer
Teresa Podruchny, M.D., Medical Reviewer
Barry Rosloff, Ph.D., Pharm/Tox Team Leader
Lois Freed, Ph.D., Pharm/Tox Team Leader
Steve Hardeman, R.Ph, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Johnson and Johnson
Garry Neil, M.D., Senior V.P. Research and Development
Jack Grebb, M.D., Senior V.P. CNS/Pain Research and Development
Graham Burton, M.D., Senior V.P. Regulatory Affairs and Quality Assurance
William Powers, Ph.D., V.P. Preclinical Development
Alex Gorsky, President, Janssen Pharmaceutica, U.S.
Fred Grossman, D.O., Psychiatry Franchise Leader
Todd McIntyre, Ph.D., Regulatory Affairs
Claude McGowan, Ph.D., Regulatory Affairs
Tricia Desantis, Regulatory Affairs

Johnson and Johnson Consultant

Alkermes, Inc.
Don Burstyn, Ph.D., V.P. Regulatory Affairs

BACKGROUND

As a follow-up to the Not Approvable letter of 6/28/02 and to the meeting of 7/26/02, the sponsor requested a meeting to discuss their plans for providing a complete response.

DISCUSSION POINTS

- The sponsor outlined the potential clinical benefit of depot risperidone.
  - The Division agreed that there is a potential clinical benefit of having a depot atypical antipsychotic. The complete response should contain a detailed review of the existing data to include depot vs. oral studies data. A compelling argument should be made that depot antipsychotics improve compliance and decrease relapse.
- The sponsor reviewed their proposed response to the toxicology concerns.
  - The Division agreed to consider approving the i.m. depot formulation without a complete resolution of the carcinogenicity findings in rat if the sponsor provides data demonstrating that the i.m. depot formulation provides a clinical benefit. In addition to the nonclinical studies listed by the sponsor as being available at the time of resubmission, the Division requested summary and individual data for incidences of adrenomedullary findings (including adrenal pheochromocytoma) from the oral carcinogenicity study in rat. The Division noted that if the sponsor proposes strain or substrain differences as an explanation for the differences in tumor profile between the oral and i.m. depot studies, it would be important to provide data by which to compare the relevance of each strain or substrain for assessing human risk.
  - It is the Division's position that the full study report for the i.m. depot embryofetal development study should be submitted to the NDA prior to approval. The Division noted that, in contrast to the carcinogenicity issue for which data are available for basing a risk/benefit assessment, no reproduction studies have been conducted using the i.m. depot formulation. The Division also noted that potential reproductive toxicity (e.g., teratogenicity) is more of a concern with an i.m. depot formulation due to the inability to rapidly terminate exposure. The Division will, however, consider the potential for a clinical benefit when making a decision as to the need for the embryofetal development study prior to approval. (The sponsor noted that the Division did not ask for an embryofetal development study at the pre-NDA meeting. The Division responded that the study request was based on data reviewed subsequent to that meeting [i.e., during review of the NDA].)
  - The Division recommended that an oral dose group be included in the i.m. depot embryofetal development study in order to provide a direct comparison between the two routes and to help bridge to the oral embryofetal development study. The sponsor noted that oral and i.m. depot dosing would result in different patterns of exposure. The Division did not consider this a problem, but agreed to further discuss this issue with the sponsor.
  - The sponsor stated that the impurities issue raised by the Division has been resolved and would be adequately addressed in the resubmission.
  - The sponsor requested a copy of the Executive CAC minutes. The sponsor was informed that the ExeCAC had agreed with the Division on the tumor findings in the i.m. depot study and that the minutes would provide no additional information to help the sponsor prepare a complete response.

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/s/

Russell Katz
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Meeting Minutes

Meeting Date:	**5/10/01**
Location:	**WOCII - Rm 4028**
IND:	**52,982**
Drug:	**Risperidone Long Acting Injectable**
Sponsor:	**Janssen**
Type of Meeting:	**CMC Pre-NDA**
Meeting Chair:	**Robert Seevers, Ph.D.**
Meeting Recorder:	**Steven D. Hardeman, R.Ph.**

Participants: see attached.

Meeting Objective: Discussion of Janssen's CMC plans to submit a new drug application for a long acting injectable version of risperidone

Discussion Points (bullets):

Attached sponsor minutes (emailed 5-25-01) appear accurate and will be archived as official minutes of this meeting.

Risperdal® Long Acting Injectable
Minutes of May 10, 2001 FDA/Janssen CMC Pre-NDA Meeting

A CMC pre-NDA meeting was held on May 10, 2001 with the Division of Neuropharmacological Drug Products to discuss Janssen's plans for submission of an NDA in August, 2001. The following attendees were present at the meeting:

Janssen

Jorge Cruz: Post Approval Regulatory Affairs
Peter D'Hoore: Team Leader
Greg Dennis, PhD: Microbiology
Lisa Lumia: CMC Global Regulatory Affairs

Alkermes

Bob Adkins: Manufacturing
Don Burstyn, PhD: Regulatory Affairs
Lionel Murray, PhD: Quality Control
Jim Wright, PhD: Development

FDA

David Hussong, PhD: Microbiologist
Steve Hardemann, R.Ph: Regulatory Project Leader
Robert Seevers, PhD: Chemistry Team Leader
Maria Sunzel, PhD: Biopharmaceutics Reviewer
Ramana Uppoor, PhD: Biopharmaceutics Team Leader

The discussions were based on the list of questions that were submitted in the pre-NDA briefing document (April 25, 2001, Serial No. 032). The questions and major points that were discussed are presented below. FDA responses are highlighted in bold and italics.

Prior to the discussion of the questions a brief overview of the depot project was given by Janssen. Janssen also noted that for purposes of the pre-NDA presentation, the NDA is being referred to as Risperdal® Long Acting Injectable. Janssen acknowledges that the name is pending acceptance by OPDRA.

Drug Substance: Based upon the revised strategy discussed in the Drug Substance section of this pre-NDA package, does FDA agree that risperidone extended release microspheres for injection may be manufactured with risperidone drug substance produced at Cork, Ireland with the new synthetic process?

FDA did not object to the manufacture of risperidone extended release microspheres with the optimized risperidone drug substance. FDA acknowledged that this statement is based upon the assumption that the risperidone drug substance comparability (current synthesis vs optimized synthesis) will be demonstrated and submitted in conjunction with the current commercial product.

Janssen acknowledged that the risperidone DMF (DMF ———) will be updated with the appropriate comparability data and a Prior Approval Supplement will be submitted to the Risperdal® tablets NDA 20-272 in May,2001.

FDA further commented that this strategy should present no problems assuming that all data are acceptable. Depending upon the nature of the questions and issues that could arise with the NDA Supplement, there could be implications for the Risperdal Long Acting Injectable NDA. FDA noted that if this situation does occur, Janssen would be made aware of the situation as expeditiously as possible.

Drug Product – Specifications

Does FDA agree with the proposed regulatory tests and specifications for risperidone extended release microspheres for injection and diluent?

FDA noted that there was nothing objectionable with regard to the proposed specifications for the microspheres and diluent. However, the Agency can not really agree to the proposed specifications until all data and justifications are reviewed during the NDA process.

The following specific items were discussed by FDA with regard to the microspheres:

- *For ——— , if the specification is not the same or tighter than the specification for the current commercial product, a justification will need to be provided in the NDA. The Agency pointed out that a wider specification is not an issue as long as appropriate justification (ie: data) for the specification is included in the submission.*

- ——— *specifications should reflect the manufacturing capability of the process, not simply the ICH limits. The limits proposed in ICH are considered safety limits, but limits for this product should take into consideration the capability of the process, as well.*

- *For Sterility testing, Dr. Hussong noted that a ——— is acceptable. Additionally, he requested that Janssen demonstrate that* ———

- *Dr. Hussong further requested that the calculation/computation used to determine the ——— needs to be included in the NDA.*

The following specific item was discussed by FDA with regard to the diluent:

- *FDA noted that the diluent testing references the EP methodology. FDA stated that Janssen should be performing the corresponding USP testing for these methods, including* ——— *or stating why the method*

is not performed. Comparability for the two methods can be demonstrated or in cases where the methods are harmonized, simply state USP.

Does FDA agree with Janssen's proposal for a combination (37° C water bath and accelerated 45° C water bath) *in vitro* release test for risperidone extended release microspheres for injection, based upon the correlation and supporting information provided in the Drug Product Specifications/Methods section of this pre-NDA package?

The Agency agreed in principle that the combination method for in vitro release testing was acceptable. The Biopharmaceutics Division has requested that a teleconference be set up to further discuss the specifics of the method, specifications, etc. A briefing package will be prepared by Janssen for this teleconference which will include the proposed methodology and specifications, rational/justification for the combination method and a discussion of the discriminating ability of the 45 °C water bath method.

The Biopharmaceutics Division requested that all dissolution data, methods, etc. included in the CMC section of the NDA also be included in Item 6 of the NDA. Janssen agreed with this request.

Container Closure: Does FDA agree that Janssen may implement the safety needle design recognizing that [redacted] for the risperidone extended microspheres for injection vials and diluent syringes will need to be adjusted, in addition to the current [redacted] As discussed in the Container Closure section of this pre-NDA package, the [redacted] will be determined once the commercial safety needle is available.

FDA recognized Janssen's intention to comply with the current requirements for safety needles. Dr. Seevers agreed with the outlined approach to justify the [redacted]. He further noted that all data and rational used for the justification should be included in the NDA.

Drug Product – Stability: Does FDA agree that the stability data package planned for submission in the NDA is acceptable? Specifically, we would like FDA's concurrence on the proposed protocols for the commitment and marketed stability batches for both the risperidone extended release microspheres for injection and the diluent.

Dr. Seevers requested clarification on whether or not the planned storage for the product in the kit is under refrigeration. Janssen confirmed that the instructions for the kit will be to store under refrigerated conditions.

Dr. Seevers further questioned whether or not the NDA will be filed with all stability data necessary for assessment of expiration dating at the time of submission. He further explained that submission of a large volume of data during the end phase of the review process may constitute a major amendment

and as such re-start the review time clock. Janssen confirmed that the NDA will be filed with 12 months of stability data for both the microspheres and diluent.

Dr. Seevers questioned the availability of in-use reconstituted stability data since these data are necessary to include in the labeling for hospital use of the product. Janssen confirmed that these studies have been conducted and these data will be part of the NDA.

Dr. Seevers noted that the protocols for the commitment batches (microspheres and diluent) seemed appropriate. Janssen clarified that it is our intention to use the diluent and microspheres validation batches as the commitment batches. FDA acknowledged and agreed with this approach.

Dr. Seevers deferred the acceptance/agreement of the marketed stability protocols until the NDA review process. He suggested that if it is our intention to study [redacted] time intervals) as noted in the protocols contained in the briefing package, then these time points should be studied with the commitment batches (ie: validation batches). Janssen clarified that it is our intention to study the microspheres and diluent separately on marketed stability. It is not our intention to test the same lot of diluent included in the kit with the microspheres. Again the Agency acknowledged and accepted this approach.

Planned Post Approval Activities – Monovial Adapter:

With regard to the proposal outlined for the post approval change associated with the monovial adapter, does FDA agree with the following:

Modifications may be made to the current Alkermes facility, as proposed and explained in this package, even though the new [redacted] will not be included at the time of the original NDA.

Dr. Seevers noted that he could not comment on the planned facility modifications and that Janssen should contact the District Field Office to coordinate the facility changes and their impact on the planned PAI inspection for the NDA.

The [redacted] may be submitted as a Changes Being Effected – 30 Day Supplement, based on the information proposed in this package, including the information outlined to demonstrate product comparability and [redacted] stability data for [redacted] of risperidone extended release microspheres for injection in the new container-closure system.

FDA did not agree that the change for the [redacted] could be submitted as a CBE. This change in the container closure system is a Prior Approval

Supplement, as noted in the current guidance.

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/s/

Robert H. Seevers
7/25/01 10:26:59 AM

Minutes of the Pre-NDA Meeting for RISPERDAL (risperidone) Depot Microspheres April 20, 2001

SUMMARY OF DISCUSSIONS AT MEETING

A pre-NDA meeting was held on April 20, 2001 with the Division of Neuropharmacological Drug Products to discuss JRF's plans for submitting an NDA for risperidone long-acting injectable in August, 2001. Attendees at the meeting were as follows:

JRF	FDA
Marielle Eerdekens, MD: Clin. Development	Russell Katz, MD: Division Director
Erik Mannaert, PhD: Pharmacokinetics	Thomas Laughren, MD: Team Leader
Claude McGowan, PhD: Reg. Affairs Liaison	Andrew Mosholder, MD: Clinical Reviewer
Patrick Sterkens, IR: Nonclinical	Maria Sunzel, PhD: Biopharm Reviewer
Keith Karcher, MS: Biostatistics	Barry Rosloff, PhD: Pharm/Tox Team Leader
Todd McIntyre, PhD: Global Reg. Affairs	Lois Freed, PhD: Pharm/Tox Reviewer
Grant Ko, MD: Clinical Development	Kun Jin, PhD: Statistical Team Leader
	Kallappa Koti, PhD: Statistician
	Steve Hardeman, RPh: Reg. Project Manager

The discussions were based on the list of questions that were submitted in the briefing document. Therefore, the questions and the major points that were discussed are listed below (FDA responses are italicised and bolded).

CLINICAL/BIOSTATISTICS/AND CLINICAL PHARMACOKINETICS

1. At our End-of-Phase (EOP) 2 meeting on April 13, 1999, the Division stated that a single study with assay sensitivity would be required to support the submission of a fileable NDA for the risperidone long-acting injectable formulation. The Division also stated that if the results from the placebo-controlled trial, RIS-USA-121, are positive, no other clinical data would be required for a fileable NDA.

   The NDA for the risperidone long-acting injectable formulation will include the following Phase 3 trials:

   Placebo-controlled trial

   RIS-USA-121 To demonstrate the efficacy and safety of risperidone long-acting injectable formulation.

   Supportive trials

   RIS-INT-61 Comparative, 'noninferiority' trial with oral risperidone

   RIS-INT-57 Open-label, long-term safety trial

- Does the Division agree that the efficacy and safety data from these trials (see Section 4.5.3) are adequate for the filing and review of the NDA?

  Dr. Katz responded that yes, there appears to be adequate information for the filing and review of the NDA.

- Given the efficacy and safety results of RIS-USA-121 (see Section 4.5.3), do the data from RIS-USA-121 appear to demonstrate sufficient evidence of the efficacy and safety of risperidone long-acting injectable for the Division to approve the NDA?

  Although this was considered a review issue, RIS-USA-121 seems sufficient for approval. Efficacy data from RIS-INT-61 can be included in the NDA, but the FDA has no interest in this trial and it will not be used in the label. Dr. Laughren reiterated what had been said at the EOP-2 meeting: oral supplementation would need to be included in the dosing section of the label because the effectiveness of the entire treatment regimen was tested. The proposed paragraph in the labeling section of the briefing document probably does not reflect sufficient information about oral supplementation.

  As a follow-up question, JRF asked for confirmation that, based on what was provided in the briefing package, FDA had not identified any refusal-to-file (RTF) issues. Dr. Katz stated that, with one exception, no other RTF issues had been identified (for more details, see pp 8-9 for the discussion regarding Question 2 of the nonclinical section).

2. Based on recommendations from the FDA (correspondence dated January 21, 2000), JRF submitted an amendment to RIS-USA-121 (Serial No. 016, February 29, 2000), which limited the patient population to those patients with schizophrenia. As shown in the following table, 39 patients with schizoaffective disorder had entered the trial before this amendment was made. Similarly, 615 patients in RIS-INT-57 had a diagnosis of schizophrenia, although 110 patients had schizoaffective disorder. To comply with recommendations from the FDA, the primary efficacy and safety analyses will be based on data from patients with schizophrenia. Additional analyses of patients with schizoaffective disorder and all patients were conducted. (JRF acknowledges the ongoing discussions with the FDA regarding the indication for RISPERDAL.)

Trial	Number of Patients		
	Schizophrenia	Schizoaffective	Total
RIS-USA-121	400	39	439
RIS-INT-57	615	110	725

- Is this approach acceptable to the Division?

Yes, the approach appears acceptable, providing the primary analysis of patients with schizophrenia is positive.

3. As discussed during the EOP-2 meeting, an open-label, 12-month safety trial (RIS-INT-57) was conducted to support the long-term safety of the risperidone long-acting injectable formulation. As shown in the following table, a total of 725 treated patients participated in the trial, including 615 patients with schizophrenia and 110 patients with schizoaffective disorder. A total of 579 patients (489 patients with schizophrenia) have been treated for approximately 6 months (≥155 days), and 361 patients (301 patients with schizophrenia) have been treated for approximately 1 year (≥337 days).

Study	Number of Patients		
	Schizophrenia	Schizoaffective	Total
RIS-INT-57	615	110	725
Treated for 6 mos	489	90	579
Treated for 1 yr	301	60	361

- Does the Division concur that there are a sufficient number of patients in this trial to support a statement in the label about the safety of the long-term use of risperidone long-acting injectable?

Yes, the number of patients was considered sufficient for this decision, although FDA was noncommittal regarding a statement about long-term use in the label and indicated that it would ultimately be a review issue. JRF should only describe findings.

On a related point, JRF noted that there seemed to be a difference in language regarding long-term use of antipsychotics in several labels, citing as examples those for olanzapine and ziprasidone. FDA responded that they had labeled what the companies had studied, did not intend to create confusion, and would investigate possible inconsistencies.

The design of a long-term maintenance/relapse prevention trial was also discussed. Dr. Laughren stated that the design of such a trial would preferably include a stable

baseline period of 12 weeks and for responders, a subsequent randomized treatment period (placebo versus active) of a minimum of 6 months duration.

4. The FDA requested that JRF demonstrate, from a pharmacokinetic perspective, bioequivalence between risperidone oral and long-acting injectable formulations. Bioequivalence has been established in a Phase 2, pharmacokinetic trial (RIS-INT-32), and through limited pharmacokinetic blood sampling in a Phase 3, non-inferiority trial (RIS-INT-61).

   The FDA also requested that JRF compare the Phase 3 (to-be-marketed) formulation with formulations used in Phase 1 and Phase 2 trials. Data from a single-dose, pharmacokinetic study, RIS-INT-54, demonstrated that Phase 2 and Phase 3 formulations were equivalent with respect to extent of absorption (AUC), but not for C_{max}.

   The long-acting injectable formulation used in Phase 3 clinical trials (N=~1500 patients treated with risperidone long-acting injectable) is the same as the to-be-marketed formulation. Therefore, no formal bioequivalence trial was performed with the to-be-marketed formulation.

- Does the Division concur that JRF has fulfilled the requests for the biopharmaceutical approach?

  The Division agreed.

APPEARS THIS WAY
ON ORIGINAL

5. At the EOP-2 meeting, JRF described a phenomenon of high fluctuations in plasma levels observed in a few patients (9 of 145 patients) treated with risperidone long-acting injectable formulations during Phase 1 and Phase 2 trials, although these peak plasma concentrations did not exceed values observed with an oral dose of 8 mg risperidone. In line with the Division's agreement at the EOP-2 meeting on the proposed sampling scheme (1st, 4th, and 7th day after the injection) for the Phase 3 clinical trials with the optimized injectable formulation, JRF plans to use these data to describe the variability in plasma exposure in the pharmacokinetic section of the label.

- Is this approach still considered acceptable to the Division?

JRF's approach seems reasonable, but the Division will need to see the results. Dr. Katz acknowledged that the briefing document indicated that peak plasma concentrations for all patients observed to date were below those observed with the 8 mg oral formulation, information presumably intended to assure the FDA that there was no safety issue. However, Dr. Katz stated that the Division was more concerned about whether this was a potential product performance issue: with early release, plasma levels may fall below therapeutic levels before the end of the treatment cycle. With the aid of back-up slides, JRF illustrated that early release was considered to be a Phase 1 formulation issue. JRF further stated that two datasets will be available to allay these concerns:

- ***Data from two pharmacokinetic studies (RIS-INT-54 and RIS-INT-72) in which the to-be-marketed formulation was used and frequent plasma samples were collected.***
- ***Pharmacokinetic data from plasma samples collected on Days 1, 4, and 7 after injection from more than 1000 patients who participated in the Phase 3 trials.***

FDA agreed that these data would help JRF address this issue in the NDA and would facilitate their review.

6. In the placebo-controlled trial, RIS-USA-121, and in pharmacokinetic trials, JRF has provided pharmacokinetic evidence of dose proportionality of 25, 50, and 75 mg of the risperidone long-acting injectable formulation (see Section 4.4.4.1). Single-dose, pharmacokinetic data have also been obtained with the intermediate doses of 37.5 and 62.5 mg in trial, RIS-INT-72.

- Based on the pharmacokinetic evidence of dose proportionality, does the Division agree that data from RIS-INT-72 will be sufficient to support the recommended use of the intermediate dose of 37.5 mg in the product label (see Section 4.1.1)?

If the Division agrees with JRF that the 25 mg – 75 mg data demonstrate dose proportionality, then the 37.5 mg dose should be acceptable. Of course, text in the label depends on the outcome of the review.

7. The pooled analysis for the ISS will include all completed Phase 1, 2, and 3 trials, except for RIS-INT-72 (see Section 4.4.1, Table 6). This single-dose, pharmacokinetic trial was designed to assess the intermediate doses of 37.5 mg and 62.5 mg of risperidone long-acting injectable. The trial will not be completed in time for incorporation into the pooled database and, for this reason, safety data from RIS-INT-72 will be presented separately in the ISS.

- Is this approach acceptable to the Division?

Yes

- The ISS pooled datasets, excluding RIS-INT-72, will be provided electronically. Is this approach acceptable to the Division?

Yes

8. Pharmacokinetic, efficacy, and safety data from 49 elderly patients (≥65 years old) have been collected during the long-term safety trial, RIS-INT-57. During the EOP-2 meeting, the Division agreed that JRF did not need to conduct a separate efficacy trial in elderly patients, as long as some data (preferably pharmacokinetic and safety data) were provided for these patients.

- Does the Division agree that JRF has provided information from a sufficient number of elderly patients to support a recommended dose of 25 mg IM every 2 weeks in elderly patients [i.e. identical to the recommended dose for nonelderly patients (Section 4.1.1)]?

Dr. Laughren asked whether JRF had collected pharmacokinetic data in elderly patients. He noted that in the label for oral risperidone, a lower starting dose for the

elderly (0.5 mg b.i.d) is recommended. However, for the new formulation, JRF is proposing the same starting dose in elderly and nonelderly patients. Dr. Laughren said that dosing recommendations for the elderly will be determined during the review and will depend on the similarity of the pharmacokinetic profiles for the elderly and nonelderly. If the pharmacokinetic profile of the elderly is markedly different from that of the nonelderly with the new formulation, JRF may need to provide a lower starting dose for elderly patients – to which Dr. Katz added, "if you have a lower dose". If pharmacokinetic profiles of the elderly and nonelderly are substantially different, FDA may request that JRF conduct a pharmacokinetic trial. This will be determined during the review.

Dr. Katz confirmed that no separate efficacy trial in the elderly would be required.

9. On May 5, 2000, JRF submitted a proposal to the Division for conducting 2 trials with RISPERDAL Oral Solution in children and adolescent patients with schizophrenia (see Section 4.5.10). The proposal included protocol outlines for a pharmacokinetic trial (RIS-USA-160) and a placebo-controlled trial in children and adolescent patients with schizophrenia (RIS-USA-231). We will address requirements for the risperidone long-acting injectable formulation in children and adolescents when discussions concerning the proposed studies have concluded.

The Division noted that they have been remiss in responding to JRF, that they still owe JRF a response, and hope to provide one soon. It was further noted that the Division has yet to respond to other sponsors with antipsychotics.

10. Based on the statistical analysis plan for the Phase 3 studies (RIS-USA-121, RIS-INT-61, and RIS-INT-57), the ISE, and ISS (see Sections 4.5.5 to 4.5.7), does the Division agree that the clinical data will be analysed and presented in a manner suitable for the Agency to file and review the NDA?

FDA asked if JRF's imputation scheme for missing items in the PANSS subscales was specified in the protocol. JRF responded that although the imputation scheme was not in the protocol, it was included in the statistical analysis plan (SAP), which was finalised and approved prior to breaking the blind.

FDA also asked if the pooling strategy for small sites that JRF used for exploring treatment-by-investigator interactions was specified in the protocol. JRF responded that this also was specified in the SAP. While acceptable, FDA suggested that the two documents should be consistent.

There was some discussion about the planned ANCOVA analysis of change from baseline in total PANSS score. Due to disagreement between the biostatistics reviewer and the statistical team leader about the importance of treating the baseline PANSS score as a random effect, it was decided that a separate teleconference would be held to discuss the issue further. [Postmeeting note: Claude McGowan contacted Steve Hardeman on Friday, 27 April 2001, about the need for a teleconference to discuss this issue. Steve responded to Claude on Monday, 30 April 2001, and related that Dr. Jin, the statistical team leader, indicated this would not be an issue and that no further discussion would be required. Steve further added that the SAP for the Phase 3 studies is adequate for the filing and review of the NDA.]

11. Individual trial datasets will be provided for the three Phase 3 trials, RIS-USA-121, RIS-INT-61, and RIS-INT-57.

- Is this approach acceptable to the Division?

Yes

12. Patient exposure (duration of treatment) to risperidone long-acting injectable will be calculated as the number of days from the date of the first injection to the date of the last injection. This definition includes the 3 weeks of oral supplementation following the first injection.

- Is this approach acceptable to the Division?

Yes

13. Treatment-emergent adverse events will be defined as those adverse events with an onset between the first injection with risperidone long-acting injectable and up to 49 days after the last injection. This definition includes the 3 weeks of oral supplementation following the first injection and, for the majority of patients, the main release phase of risperidone (see Section 4.4.4.1) following the last injection.

- Is this definition of treatment-emergent adverse events acceptable to the Division?

Yes

14. ECGs were centrally read by ——— Cardiac Alert in RIS-USA-121, RIS-INT-61, and RIS-INT-57. Three correction factors will be applied to the analysis of QT data, using Bazett's formula, Fridericia's formula, and the linear formula according to Sagie et al. (see Section 4.5.5.1.3.5). Based upon discussions with a number of academic cardiologists, JRF

believes that Fridericia's formula is a more reliable correction factor for risperidone, which causes an increase in heart rate. For this reason, the focus of the clinical research reports and integrated summary documents will be on analysis results using Fridericia's formula. However, reference will be made to results based on all 3 correction factors.

- Is this approach acceptable to the Division?

While the FDA agreed that Bazett's formula overcorrects for increased heart rate, they also believe that Fridericia's formula undercorrects and, therefore, may also be misleading. The Division offered to share with JRF an internal guidance document, which describes two correction factors that the Division prefers to either the Bazett's or Fridericia's correction factors. Steve Hardeman will provide a copy to Claude McGowan. [Postmeeting note: The guidance on QT analysis has been received by JRF.] JRF noted that the clinical research reports are almost finalized and requested that the proposed analysis be included only in the ISS. FDA agreed that the results of the QT analysis proposed by the Division need only be included in the ISS.

15. The NDA will include data up to April 30, 2001 (inclusive); the incidence of deaths and serious adverse events reported in the 4 ongoing trials (RIS-INT-63, RIS-USA-196, RIS-JPN-16, RIS-INT-62) would be summarized in the ISS up to this data cut-off date. The 4-month safety update will include all safety data from the 2 ongoing, open-label extension trials, RIS-INT-63 and RIS-USA-196 (see Section 4.5.4), up to and including the data cutoff date of May 15, 2001. For the two remaining ongoing trials, RIS-JPN-16 (single-dose, pharmacokinetic trial) and RIS-INT-62 (comparative, non-inferiority trial with olanzapine tablet), interim safety data will not be available at the time of the 4-month safety update. However, the incidence of deaths and serious adverse events in these trials will be updated as of August 31, 2001.

- Is this approach acceptable to the Division?

Yes

NONCLINICAL

1. At the Carcinogenicity Assessment Committee (CAC) meeting of April 13, 1999, the design and dose selection of the rat carcinogenicity study were discussed. Based on this meeting, the FDA made recommendations to JRF. The written reply to these recommendations is included in Attachment 2 of this briefing document.

- Does the FDA concur with the responses to these recommendations?

Yes

- Has JRF adequately addressed all issues related to the local site carcinogenic potential of risperidone long-acting injectable?

Yes, although it will depend on review of the data.

2. JRF has conducted several toxicology studies with the risperidone long-acting injectable formulation (Section 4.3.4.1, Table 5), including tolerance studies in several species, primary irritation studies in the rabbit, and repeated-dose toxicity studies in the rat and dog. Although no reproductive or mutagenicity studies were conducted with the risperidone long-acting injectable formulation, these studies are available for oral risperidone (RISPERDAL Tablet NDA, 20-272). In addition, acute and chronic toxicology studies of the microspheres vehicle have been conducted by Alkermes (DMF).

- Does the FDA concur that reproductive and mutagenicity studies conducted with orally administered risperidone are sufficient for the filing and review of the NDA for the risperidone long-acting injectable formulation?

When JRF inquired about potential RTF issues (see Question 1 in the clinical/ biostatistics/and clinical pharmacokinetic section), FDA noted that there was one potential issue. There was some concern about the lack of reproductive data with the copolymer, which could become a RTF issue if not adequately addressed. JRF asked whether FDA's concern was specific or was based on a general lack of information about the copolymer. FDA confirmed that the concern was based on a general lack of knowledge about the copolymer, although there are several products on the market that use the microsphere technology. JRF explained that the copolymer is broken down into two endogenous compounds, lactic acid and glycolic acid (hydroxyacetic acid). After some discussion, FDA agreed that if JRF addressed the metabolic disposition of the copolymer, a RTF would be avoided. JRF responded that this data would be included in the NDA. FDA noted that addressing the issue proactively would probably avoid a RTF, but added that if the data were not compelling, Segment 2 and Segment 3 reproductive studies could be requested.

Dr. Sunzel asked if JRF had evaluated the effect of temperature increase (fever) on the microspheres. JRF responded that in vitro release data as a function of temperature are available.

With respect to the Division's request for in vitro genotoxicity data, FDA asked whether JRF intended to cite another company's data. If so, Dr. Katz noted the NDA might have to be filed as a 505 b (2) application, which is used when the sponsor relies

on data in the label of another product. After the business relationship between JRF and Alkermes was explained, it was considered not to be relevant to the toxicity data provided by Alkermes in their DMF. However, if JRF were to cite data from a mutagenicity study conducted by a third party, it might still be relevant. JRF indicated that it would probably be easier to conduct the study.

GENERAL

1. In Section 3.1.2 of this briefing document, we have provided a summary of issues raised by the Division during the EOP-2 meeting (Table 2). Resolution of these issues, as well as others raised since the submission of the IND, are summarized in Table 1 (see Section 3.1.1).

- Does the Division agree that these issues have been adequately addressed (Table 1)?

Yes

- Does the Division agree that no additional issues have been identified?

Yes

2. The proposed label changes have been outlined in Section 4.1.

- Does the Division concur that the proposed changes to the label would be acceptable, providing that the Division's review of the data substantiate and agree with JRF's conclusions?

The proposed changes to the label are probably acceptable, but this is a review issue. FDA asked whether JRF was planning to use a separate label for the new formulation. JRF replied that it was still considering options vis-à-vis ease of use by prescribers once launched. FDA noted that they preferred one label for the oral and new formulations for ease of tracking.

3. The nomenclature, risperidone depot microspheres, has been used in clinical and nonclinical research reports that will be submitted in the NDA. However, JRF is contemplating using nomenclature such as 'risperidone long-acting injectable' for the RISPERDAL label.

- Is the proposed nomenclature for the label consistent with that used for this type of formulation?

The Division will consult with OPDRA on this issue, but encouraged JRF to submit a proposal under the IND, which would be forwarded to OPDRA. JRF noted that the

term, 'long-acting', was being explored as an alternative to 'depot' because of the negative connotations of the latter term for some patients. For this reason, JRF is considering use of the term 'long-acting' both in the trademark and, more generally, as a descriptive term in publications and promotional material. FDA indicated that they could not guarantee its acceptability, but OPDRA would make the determination of whether the terminology was confusing or was a potential safety issue.

Before leaving, JRF reminded FDA that while clinical data for all doses would be submitted, JRF does not intend to market doses above 50 mg.

Dr. Katz indicated that they were flexible, but that the decision would depend on their review of the data.

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/s/

Thomas Laughren
5/17/01 08:59:31 AM

MEMORANDUM

DATE: June 28, 2002

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

TO: File, NDA 21-346

SUBJECT: Action Memo for NDA 21-346, for the use of Risperdal Consta in patients with schizophrenia

NDA 21-346, for the use of Risperdal Consta, an intramuscular injection of risperidone to be administered every 2 weeks in patients with schizophrenia, was submitted by Janssen Research Foundation on 8/31/01. Risperidone is already marketed for the same indication in several oral formulations. The application includes reports of numerous studies, including a single adequate and well-controlled trial (Study 121) that purports to demonstrate the effectiveness of the treatment in patients with schizophrenia.

The application has been reviewed by Dr. Gurpreet Gill-Sangha, chemist (review dated 6/24/02), Dr. Vinayak Pawar, microbiologist (review dated 4/29/02), Dr. Maria Sunzel, Office of Clinical Pharmacology and Biopharmaceutics (review dated 6/21/02), Dr. Lois Freed, pharmacologist (review dated 6/25/02), Dr. Sharon Yan, statistician (review dated 5/2/02), Dr. Earl Hearst, medical reviewer (review dated 5/13/02), and Dr. Tom Laughren, team leader, psychiatric drugs (memo dated 6/21/02). The review team has concluded that the treatment is effective, and that the clinical safety data support approval, and I agree.

However, Dr. Freed has identified several findings that are of concern. Specifically, she has noted the occurrence of adrenal and kidney tumors in males, as well as osteodystrophy in both sexes, in a rat carcinogenicity study of the injectable product, findings that were not seen with the oral product. In addition, she has identified [redacted] impurities in the final product that would require qualification, for which the sponsor has not provided appropriate data.

In particular, the frequency of the tumors (benign and malignant combined), in male rats is:

	Saline Control	Vehicle Control	Low Dose	High Dose
Pheochromocytoma	3/50	3/50	3/50	12/50
Renal Tubular tumors	0/50	0/50	0/50	5/50

The frequency of osteodystrophy (sternum) is as follows:

	Saline Control	Vehicle Control	Low Dose	High Dose
Males	0/50	1/50	1/50	33/50
Females	7/50	4/50	8/50	21/50

(This study also revealed increases in other tumor types, including mammary gland, pituitary, and pancreas; these are tumors often seen with anti-psychotic drugs, as well as with oral risperidone, and are considered to be related to elevated prolactin and of no relevance for humans.) The sponsor has addressed the unique tumor data, suggesting that these tumors are also the result of elevated prolactin (prolactin is increased with injectable risperidone).

In particular, the sponsor proposes that the elevated prolactin resulted in an exacerbation of chronic renal disease, which, through a complex sequence of metabolic events (including derangements of calcium homeostasis), resulted in osteodystrophy and kidney tumors. Dr. Freed has performed an extensive review of this proposed mechanism through a detailed literature review, and concludes that this explanation is not persuasive.

I agree. Briefly, as Dr. Freed points out, although the literature describes associations between chronic renal disease and kidney tumors and osteodystrophy in the rat, and there are multiple histologic findings in the kidney in this study, these findings are not consistent with the typical description of chronic renal disease. Further, the literature suggests that tumors/osteodystrophy are only seen in the context of severe renal disease, which is not seen in this study (indeed, the sponsor has concluded that chronic renal disease was not increased in the male rats, in which tumors occurred, while it was increased in females, in which tumors did not occur). Dr. Freed also contemplates the possibility that increased prolactin might directly cause osteodystrophy, but support for this mechanism in the literature is not compelling.

Regarding the occurrence of pheochromocytoma, the sponsor again proposes increased prolactin as the cause, with or without a contribution of chronic renal disease. Again, while the literature discusses a possible association between elevated prolactin and these tumors, it is not definitive on this point. In addition, and critically, the sponsor has performed a study to examine the potential mechanism(s) responsible for the differences seen between the oral and injectable product, and has determined that, in fact, the AUC for prolactin after oral administration is greater than that seen after intramuscular administration. If elevated prolactin were a critical step in the genesis of these pathologies, we would expect to see them in studies of the oral product; we, of course, do not (the sponsor's claim that the difference in the pattern of the prolactin increase with the oral as compared to the injectable is responsible for the different findings is entirely conjecture and also not at all persuasive).

It is also important to note that these findings occur at a dose that results in AUCs of risperidone (and its active metabolite) that are ***lower*** than those seen with the recommended maximum human dose. Therefore, there is no threshold for the tumor findings (the sponsor has documented that the drug is not genotoxic).

I believe that these findings, as well as the absence of other studies now necessary as a result of these findings (see below), support a Not Approvable action.

Although there is a statistically significant increase in the occurrence of adrenal and renal tumors in male rats at the high dose, one could argue that these findings are not numerically large, and could be considered a chance finding. That is, it might be argued that this finding is not unique to intramuscular risperidone, and that had another study been performed with the oral drug, such a finding might have emerged.

I believe, however, that this finding is a "real" finding, and, at least in the context of this single study, not likely to be a chance finding. I believe that the pharmacology team (Drs. Freed and Rosloff) agrees with this. Whether or not such a finding would have emerged had additional studies been performed with the oral drug is, of course, unknown (even if it had, our actions as a result of it would likely have been different-see below).

The appearance of these new tumors (and the magnitude of their occurrence) as a result of a simple change in route of administration may raise questions about the validity or meaning of these results; after all, such a finding is unexpected (we had asked the sponsor to perform this study because we were concerned about local, not systemic, tumor production). However, the occurrence and strikingly high incidence of osteodystrophy in this study (in both sexes), cannot be subject to the claim that this is a chance finding. This finding, coupled with the absence of this finding with oral risperidone, makes it clear, beyond doubt, that a change in route can give rise to important, new toxicities. Of course, the mechanism of this finding is unknown (it is worth noting that this product represents not just a simple change in route of administration, but also, of course, a change in the formulation, which, in addition to the presence of new components [with potential toxicities], could have effects on the distribution of the drug itself, with unknown consequences), but this does not negate the finding, of course.

Therefore, the tumor findings must, in my view, be given credence. That is, we have seen that a change in route can give rise to a clear, unambiguous, new finding (osteodystrophy). We have also seen that the tumor findings are statistically significant in this study, establishing that, while not representing an overwhelming numerical increase, they are likely not a chance finding. Further, as discussed earlier, the sponsor's attempts to dismiss the findings on the basis

of a proposed mechanism are not, in my view, persuasive (indeed, even if one accepted their proposed mechanism(s), this would not establish the findings as irrelevant for humans, as Dr. Freed has pointed out). Taken together, these factors lead me to conclude that IM risperidone, in this formulation, should be considered carcinogenic in animals, at this time.

Despite this conclusion, one could argue that the application should be approved, with appropriate language in labeling. I do not agree.

I can see little justification for making this product available while the question of its potential carcinogenicity is open. This product is not a therapeutic advance of the sort that might justify its marketing with this finding. While the product was designed, ostensibly, to increase compliance in schizophrenic patients (an important goal), the sponsor has not demonstrated that this would result. One could imagine that patients might, in fact, be less compliant with this product than with the oral product (for example, they might not return to the clinic to receive the injection, they might not tolerate an injection in the long term, etc.). In any event, this product represents, at best, a potential advantage that has not been demonstrated. Of course, the sponsor might be able to either justify the marketing of this product in the face of these findings (perhaps by performing a study that documents increased compliance), or document that these findings are not relevant to humans. However, at this time, they have done neither.

It is possible that these findings might be considered relevant for oral risperidone as well. However, even if these findings had been seen with oral risperidone when that application was under review, we might have still approved it with appropriate language in labeling; such an action might have been justified because a new treatment for schizophrenia is considered an important advance. As I have noted above, however, these considerations do not obtain at this point for the injectable. Beyond this, of course, the signal exists only for the injectable, and, as explained above, there is sufficient reason to believe, at this time, that this finding is real, and that such a difference in findings between the two products is believable. For this reason, I believe that no action is indicated at the moment with regard to the oral product. If subsequent events support the conclusion that these findings are relevant for the oral product, we will need to take appropriate action.

In addition, as Dr. Freed points out, the tumor and osteodystrophy findings necessitate additional embryofetal studies. Although we had told the sponsor at early meetings that no such studies would be required with this product, this was with the understanding that no important findings would emerge in the other animal studies; unfortunately, other findings were seen that make the new studies necessary prior to approval. The lack of such studies, by itself, would support a Not Approval action.

As Dr. Freed has also noted, the sponsor has not provided evidence that ~of the —— impurities that require qualification have been qualified.

Finally, Drs. Sunzel and Gill-Sangha have additional comments to be sent to the sponsor. These are not reasons for a Not Approvable action. Importantly, as Dr. Gill-Sangha notes, the ultimate approval of the application is dependent upon a satisfactory inspection of the API facility in Italy.

For the reasons stated above, then, I have concluded that the application is Not Approvable, and I will issue the attached letter.

Russell Katz, M.D.

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/s/

Russell Katz
6/28/02 10:12:14 AM
MEDICAL OFFICER

6/25/02

NDA 21-346 – MEMO TO FILE

I concur with the recommendations made in Dr. Freed's review of 6/25/02. Differences in the chronic toxicity and to a lesser extent carcinogenicity findings suggest a meaningful difference in the preclinical safety profiles of the p.o. and i.m. formulations of risperidone. An embryofetal development study of the i.m. formulation would help determine if this difference extends to the area of reproduction. It is recommended that such a study use a group dosed orally for comparison.

Barry Rosloff
Supervisory Pharmacologist

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/s/

Barry Rosloff
6/25/02 05:33:58 PM
PHARMACOLOGIST

M E M O R A N D U M

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

DATE: June 21, 2002

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

SUBJECT: Recommendation for Approvable Action for
Risperdal Consta (risperidone long-acting injection) for the treatment of schizophrenia

TO: File NDA 21-346
[**Note:** This overview should be filed with the 8-31-01 original submission.]

1.0 BACKGROUND

Risperidone is a 5HT2/D2 receptor antagonist that is currently marketed in an immediate release tablet and a solution (Risperdal) for the treatment of schizophrenia. This formulation consists of extended release microspheres that are to be suspended in a diluent provided with the microsphere powder just prior to deep, IM gluteal injection every two weeks. The sponsor wishes to market 3 dosage strengths: 25, 37.5, and 50 mg. The proposed dose range for risperidone long-acting injection (risperidone LA) is 25 to 50 mg every 2 weeks.

The rationale for this depot formulation is improved compliance, a problem with schizophrenic patients. There are currently two other depot antipsychotic formulations available, i.e., fluphenazine and haloperidol decanoate.

We held three meetings with the sponsor during the development of this product:

The first meeting **(6-19-97)** was held shortly after the submission of the IND (IND 52,982; submitted 3-18-97). The purpose of this meeting was to generally discuss what would be needed in a development program for this product:
-While we noted that a clinical trial showing a difference would be necessary, we agreed that a single positive trial would suffice. Since this formulation is generally used for maintenance treatment, we

strongly recommended a randomized withdrawal trial. However, even at this early point, they did not seem inclined toward a maintenance study.
-There was some preliminary discussion of what would be needed regarding carcinogenicity. We requested additional documentation from a 6-month IM dog study and a proposal for a study to document that there are no local injection site changes. Alternatively, they were invited to try to make a case that further testing was not needed.

An **EOP2 meeting** was held on **4-13-99**:
-The sponsor submitted protocols for study 121 (a 12-wk, placebo-controlled fixed dose acute study), study 61 (a noninferiority trial for European registration), and study 57 (a 12-month safety study).
-We again strongly encouraged a randomized withdrawal trial, but indicated that, in principle, study 121 would suffice, if positive.
-Since the plan for study 121 included oral supplementation during the early weeks of depot treatment, to prevent dropouts, we indicated that the drug would be recommended for use with early supplementation.
-We suggested that priority review would be unlikely.
-The required PK program was discussed in detail.
-A plan was discussed for further evaluation of excessive fluctuation of plasma levels that had been observed in a few patients.
-There was extensive discussion of the carcinogenicity requirements for this formulation. It was noted that the CAC had discussed the sponsor's proposed 24-month rat study, and that, due to concern regarding local changes observed in several species, they were not inclined to accept the plan for submission of the NDA with only 12-month interim sacrifice data. We also asked for documentation for their dose selection.

A **preNDA meeting** was held on **4-20-01**:
-We again discussed study 121, and indicated that, in principle, this was sufficient to show efficacy.
-The plan to analyze patients with schizophrenia and schizoaffective disorder separately was endorsed.
-We generally endorsed the adequacy of the expected exposure data for this formulation.
-It was again confirmed that the PK program, as described, appeared to be adequate.
-There was additional discussion of the concern about excessive fluctuation in plasma level observed in a few phase 1 subjects. The sponsor described a plan to fully explore this issue for the NDA, and this appeared to be adequate.
-There was discussion of what would be needed to support dosing recommendations for the elderly, namely, actual PK data.

This NDA required reviews by the CMC, pharmacology/toxicology, biopharmaceutics, and clinical groups. The CMC review was conducted by Gurpreet Gill-Sangha, Ph.D. The pharmacology/toxicology review was conducted by Lois Freed, Ph.D. The biopharmaceutics review was conducted by Maria Sunzel, Ph.D., with additional consultation by Vanitha Sekar, Ph.D. The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. Sharnon Yan, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

As noted, the studies supporting this supplement were conducted under IND 52,982, which was originally submitted 3-18-97. The original NDA was submitted 8-31-01.

We decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

3.0 PHARMACOLOGY

As noted, the sponsor was asked to conduct a 2-year carcinogenicity study in rats to further explore local changes observed in earlier studies. The rat study was conducted, and revealed several findings of concern (see review by Lois Freed, Ph.D., for details). Significant, dose-related effects were observed for 2 new tumor types in male rats, i.e., benign pheochromocytoma and renal adenoma. Neither tumor was observed to be dose-related in the oral studies with risperidone. In addtion, there was a substantial, dose-related occurrence of osteodystropy with risperidone LA, again a finding not observed with oral risperidone. This latter finding gives some credibility of this alternative route of administration being associated with a different profile of toxicity. It is further significant that the exposure levels in the rats at which these effects were observed are only slightly in excess of levels seen in humans at the recommended doses, and the exposures at the next lower dose at which the effects were not observed are well below human exposures. While the sponsor has made an effort to explain the findings as prolactin related, Dr. Freed has argued that a careful look at the actual prolactin data and the animals experiencing these effects does not support the sponsor's argument.

At the time of completing this memo, this issue is not finally resolved and the primary and supervisory pharmacology reviews have not been finalized. However, it is my impression, based on data and arguments that I have heard thus far, that this is a significant problem for this drug. In a sense, this is a convenience form of this drug, and it is associated with a signal of risk in rats that is not observed with oral risperidone. Thus, I think it would not be unreasonable to not approve this NDA, pending a response from the sponsor to present a better argument, if possible, regarding why this signal may not be relevant for humans.

4.0 BIOPHARMACEUTICS

This depot formulation provides a small initial release of drug, followed by a lag time of about 3 weeks, and then continues for 4 to 6 weeks. With q 2weeks dosing, steady state is reached in 2 months. Oral supplementation is needed during the first 3 weeks to cover patients during the lag

phase. While there was some concern about excessive early release in an initial formulation, this was not seen with the TBM formulation in the phase 3 trial.

The pharmacokinetics of risperidone LA have been adequately characterized and I am not aware of any biopharmaceutics concerns that would preclude an approvable action on this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of study 121, a 12-week, acute study of 3 fixed doses of risperidone LA and placebo in patients with schizophrenia. The sponsor also submitted results of study 61, a noninferiority trial comparing risperidone LA and risperidone tablets, conducted for purposes of European registration. Since we have not accepted this approach to efficacy in this condition, this study was not reviewed with regard to efficacy. Efficacy data were also collected for a third study, i.e., 57, a 12 month, open safety study. Since the efficacy data from this trial are not interpretable from our standpoint, these data were also not reviewed.

5.1.2 Summary of Study RIS-USA-121

This was a randomized, double-blind, parallel group, 12-week, fixed-dose study comparing risperidone LA (25, 50, or 75 mg, q2wks, IM) and placebo in adult inpatients or outpatients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder. Patients selected for this study were discontinued from their current antipsychotic medications and switched to oral risperidone 4 mg/day during a 1-week run-in period. Only patients who successfully completed this open run-in were randomized. Randomization was stratified based on inpatient/outpatient status and on baseline PANSS total score ($>$ or ≤ 80). Patients randomized to risperidone LA were given supplemental oral risperidone during the first 3 weeks of the trial (with dose depending on risperidone LA dose, i.e., 2 mg/day for 25 mg group, 4 mg/day for 50 mg group, and 6 mg/day for 75 mg group). During the trial, a decision was made to stop recruiting patients with schizoaffective disorder, and thus, the patients were roughly 90% schizophrenic. The analysis will focus only on patients with schizophrenia. There were roughly 90 patients per each of the 4 groups in the sample analyzed (n=370). There were substantial dropouts before reaching the 12 week endpoint, with the % completing to 12 weeks ranging from 32 (for placebo) to 48% (for all 3 drug groups). [Note: The dropout rate of 52% for drug patients is quite high, but not too surprising, given that this was a 12-week trial, with a placebo arm, so that clinicians may have been more inclined to drop patients who were not optimally controlled. This high dropout rate is also balanced by the fact that the OC analyses were also significantly in favor of drug.] The patients were about 3/4 male, mostly black or Caucasian, and the mean age was about 38 years.

Assessments included the PANSS and CGI, at baseline and q2 weeks. The primary outcome was change from baseline to endpoint in PANSS total score, and I will focus on that outcome. As is usually the case, the ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup PANSS assessment. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. If the overall analysis was significant, pairwise comparisons of active drug groups with placebo were made. The overall analysis for PANSS was highly significant ($p<0.0001$), as were all the pairwise comparisons of active drug vs placebo (in both LOCF and OC analyses):

Efficacy Results on PANSS Total Score for RIS-USA-121 (LOCF)

	Baseline PANSS	**Δbaseline PANSS**	**[P-value(vs pbo)]**
Ris LA 25 mg (n=93)	**81.7**	**-6.1**	**p<0.002**
Ris LA 50mg (n=98)	**82.3**	**-8.7**	**p<0.002**
Ris LA 75 mg (n=87)	**80.1**	**-5.6**	**p<0.002**
Placebo (n=92)	**82.0**	**+2.6**	

While not described here, results on the 5 subscales of the PANSS (including positive and negative symptoms), the CGI, and OC analyses, generally favored all 3 risperidone groups over placebo. Subgroup analyses based on age, gender, and race suggested some possible differences, however, overall, the effect appeared to be preserved regardless of demographic subgroup, at least numerically.

Comment: Both Drs. Hearst and Yan considered this a positive study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Risperidone LA Schizophrenia

Evidence Bearing on the Question of Dose/Response for Efficacy

All 3 dose groups beat placebo, and the 50 mg group was numerically the best. Labeling should reflect this finding of no clear evidence of an advantage of the higher dose groups over the 25 mg group, and this should be the target dose.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, age, and race. While there were some differences suggested in responsiveness in different subgroups, I do not feel the data are sufficient to be the basis for any labeling statements suggestive of differences.

Size of Treatment Effect

-CVA: Given recent interest in looking at the occurrence of cerebrovascular accidents (CVAs) in patients with vascular dementia taking atypical antipsychotics, it was noteworthy that there were 4 reports of "CVA" among patients receiving risperidone in this program. Two of these involved oral risperidone and two were taking risperidone LA.

-A30860 (RIS-INT-63): 38 y/o male; taking risperidone LA 75 mg IM q2wks for approximately 8 months; experienced increase in psychotic symptoms and also "concentration problems, was easily irritated, had a sleep disorder, and could not find the right words." He was discontinued from risperidone LA and hospitalized. An MRI revealed a "probable cerebral aneurysm." Folowup information was not available.

-A30050 (RIS-INT-57): 54 y/o male; taking risperidone LA 75 mg IM q2wks for approximately 10 weeks; he was hospitalized with a pulmonary embolism, and was also noted to have "anoxic brain injury," that was judged to have occurred during transport to the hospital; few details are avaiblable; apparently discharged to a nursing home.

-A30146 (RIS-USA-121): 44 y/o male; taking oral risperidone LA 2-4 mg/day for approximately 9 days; at that time he was hospitalized and diagnosed with metastatic lung cancer, but also noted on MRI to have "multiple CVAs that were felt to be embolic and not due to metastases." He had expressive aphasia, dysarthria, and right handed weakness.

-A30015 (RIS-INT-61): 44 y/o female; taking oral risperidone LA 2 mg/day for approximately 6 months; experienced right handed numbness and some loss of strength in her right hand; she was diagnosed with "possible stroke."

These cases all seem very different, with clear alternative explanations for the CVAs in 3 of the cases; the fourth case is unclear as to diagnosis or cause. Thus, I don't view this as a signal of risk for risperidone, but rather, as events most likely unrelated to taking risperidone in either form.

5.2.2 Conclusions Regarding Safety of Risperidone LA in Schizophrenia

There were no new safety findings to suggest a substantially different safety profile for risperidone LA compared to that observed for oral risperidone, and no basis for substantially different labeling for risperidone LA compared to that for oral risperidone.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

There was no literature to review in this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, risperidone LA is not approved for the treatment of schizophrenia anywhere at this time. We will ask for an update on the regulatory status of risperidone LA for the treatment of schizophrenia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Three sites were inspected and found to be satisfactory.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 8-31-01.

10.2 Foreign Labeling

Risperidone LA is not approved for the treatment of schizophrenia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Janssen has submitted sufficient data to support the conclusion that risperidone LA is effective and acceptably safe in the treatment of schizophrenia, with the exception of the rat carcinogenicity data. This concern regarding a signal for carcinogenicity is discussed under 3.0 (Pharmacology). The sponsor needs to make a stronger case that this signal is not of sufficient relevance to humans before we could consider the final approval of this product. [redacted] However, I would also not object to

a nonapproval action, based on these findings.

cc:
Orig NDA 21-346
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/EHearst/SHardeman

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/s/

Thomas Laughren
6/21/02 09:50:16 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED: 09/18/01	DUE DATE: 05/20/02	ODS CONSULT #: 01-0207

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

THROUGH:
Steven D. Hardeman, R.Ph
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

PRODUCT NAME:	**NDA SPONSOR:** Janssen Pharmaceutical
Risperdal Consta™ (Risperidone for Injection) 25 mg, 37.5 mg and 50 mg **NDA:** 21-346	

SAFETY EVALUATOR: David Diwa, 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 performed a review of the proposed proprietary name *Risperdal Consta™* to determine the potential for confusion with approved proprietary and established names as well as pending drug names.

DMETS RECOMMENDATION: DMETS has no objections to use of the proposed proprietary name *Risperdal Consta™*. In addition, we recommend revising the labels and labeling as outlined in section III of this review in order to minimize potential errors with the use of this product.

DMETS' decision is considered tentative. The firm should be notified that this name, and 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 names, and established names from the signature date of this document.

Carol Holquist, R.Ph
Deputy Director
Division of Medication Errors & Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 480-8173

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

Consulted use of "Long Acting" to Dan Boring of LNC to get comment on the correct nomenclature of the established name. No response to date.

Steve Hardeman, RPh /HFD-120

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
HFD-400; ROOM 15B32
CENTER FOR DRUG EVALUATION AND RESEARCH

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 05/3/02

NDA: 21-346

NAME OF DRUG: Risperdal Consta™ (Risperidone for Injection) 25 mg, 37.5 mg and 50 mg

NDA HOLDER: Janssen Pharmaceutical

I. INTRODUCTION

This consult was written in response to a September 18, 2001, request from the Division of Neuropharmacological Drug Products (HFD-120) for an assessment of the proposed proprietary drug name, *Risperdal Consta™*, regarding potential name confusion with other proprietary and established drug names. In addition, the container label, carton labeling and insert labeling were also submitted for review and comment.

The sponsor, Janssen Pharmaceutical, currently markets Risperdal (risperidone) as a 1 mg/mL oral solution as well as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg oral tablets.

PRODUCT INFORMATION

Risperdal Consta (Risperidone for Injection) is a combination of extended release microspheres for injection and a diluent for parenteral use. The product is an antipsychotic agent indicated for the treatment of schizophrenia. The extended release microspheres formulation is a white to off-white powder, which will be available in strengths of 25 mg, 37.5 mg and 50 mg risperidone per vial. The diluent for parenteral use is a clear, colorless solution in which the microspheres will be suspended prior to injection. The recommended dose of Risperdal Consta is 25 mg every two weeks by deep intramuscular (IM) gluteal injection. The maximum dose should not exceed 50 mg every two weeks. Oral Risperdal should be given with the first injection and continued for 3 weeks to ensure that adequate plasma concentrations are maintained prior to the release phase of risperidone from the injection site. Injections should be alternated between the two buttocks. Two different dosing strengths of Risperdal Consta should not be combined in a single administration. The product should be stored in the refrigerator at temperatures between 2°C to 8°C (36°F-46°F). If refrigeration is unavailable, the product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration.

Risperdal Consta will be provided in [redacted] The Alaris system will contain a vial of microspheres, a pre-filled syringe of 2 mL diluent, one SmartSite Needle-Free Vial Access Device, and one NeedlePro 20 gauge safety needle [redacted]

II. RISK ASSESSMENT

The DMETS medication error staff conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] and SAEGIS™ Pharma-In-Use database[v] for existing drug names which sound-alike or look-alike to *Risperdal Consta* to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[vi]. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

Information was gathered from the DMETS Expert Panel regarding their professional opinions on the safety of the proprietary name *Risperdal Consta*. This included potential concerns regarding drug marketing and promotion relating to the proposed name. The group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical experience, other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel was concerned about the potential risk of sound-alike/look-alike name confusion between the proposed name and the proprietary names *Concerta, Constilac* and *Constulose*. These products are listed in Table 1 below, along with the dosage forms available and usual dosage.

DDMAC did not have any concerns with the name *Risperdal Consta* in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Risperdal Consta	Risperidone for Injection 25 mg, 37.5 mg, 50 mg	25 mg IM every 2 weeks	
Concerta	Methylphenidate Extended Release Tablets 8 mg, 36 mg	Children (≥6 yrs): 5 mg twice daily . Adults: 20 mg to 30 mg daily in 2 to 3 divided doses	SA/LA
Constilac	Lactulose Syrup 8 oz and 16 oz bottles, and 30 mL unit dose.	15 to 30 mL or 10 g to 20 g of lactulose daily	SA/LA
Constulose	Lactulose Oral Solution; 237 mL, 946 mL		

*Frequently used, not all-inclusive. **LA: look-alike, SA-sound-alike.

[i] MICROMEDEX Healthcare Intranet Series, 2000, 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, 2000).

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson

[iv] New Drug Approvals 98-01, and the electronic online version of the FDA Orange Book.

[v] Data provided by T&T's SAEGIS ™ online service available at www.thomson-thomson.com

[vi] WWW location http://www.uspto.gov/tmdb/index.html.

B. AERS DATABASE SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database for all postmarketing safety reports of medication errors associated with the name Risperdal. The MedDRA Preferred Term (PT) "Medication Error," 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, 6 accounts involved the misinterpretation of Risperdal. All 6 events pertained to *actual* occurrence of medication errors. Results are listed in attachment A on page 10.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. 3-Needle and Alaris System

2. Diluent (——— Alaris System)

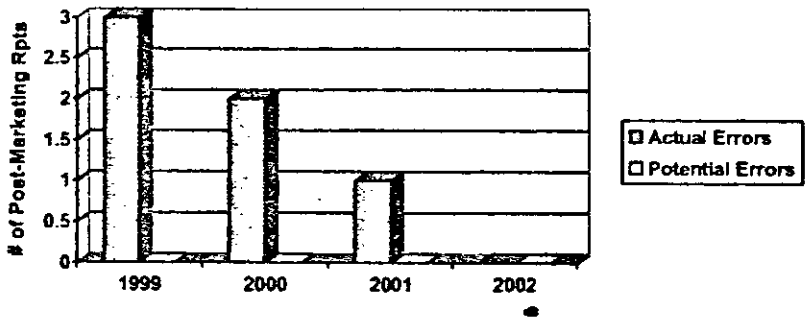
DMETS has concerns with the proposed packaging configuration for the diluent. By providing a —— ——— there is potential risk that the diluent may be injected in error instead of the active ingredient. Post-marketing experience has demonstrated errors occurring with the inadvertent administration of diluent as a result of the diluent being provided in a ——— Therefore, we recommend supplying the diluent in a vial ———

3. AERS Database results

DMETS identified six (6) post-marketing reports of medication error relating to the use of 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, we identified six (6) medication error reports between Risperdal and various drug products, which were randomly received by the Agency. The number and year in which the post-marketing reports were received by the agency is shown in figure 1 on page 5. These reports did not show any specific pattern of name and packaging similarity with the drugs dispensed in error (see attachment A). 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 Risperdal.

Figure 1

Medication Error Reports Related to Risperdal



4. Established name

The term "Long Acting" in the established name of this product is not an officially recognized dosage form. We recommend that the Division consult Don Boring of the CDER Labeling and Nomenclature Committee (LNC) for comment on the correct nomenclature of the established name.

5. Look-alike and sound-alike names

In reviewing the name, "*Risperdal Consta*," the proprietary drug names *Concerta, Constulose, and Constilac* were identified as having the most potential for name confusion with the proposed modifier "*Consta*".

Concerta (methylphenidate extended release tablets) is a CNS stimulant and schedule II controlled substance used in the management of attention deficit hyperactivity disorder. It is available as 18 mg extended release oral tablets. The recommended starting dose is 18 mg once daily. The dose may be individually adjusted in 18 mg increments up to a maximum of 54 mg a day. Certain aspects of the proposed name raise some concern. *Concerta* and the proposed modifier *Consta* sound somewhat similar. They also look similar, both sharing the prefix "*Con*" and the suffix "*ta*". However, *Risperdal Consta* is an injectable product that will be administered once every two weeks as compared with *Concerta,* which is administered by mouth every day. In addition, the proposed modifier will be used in conjunction with the proprietary name Risperdal. The risk of selecting a wrong product from storage shelves is minimal since Risperdal *Consta* will be refrigerated and *Concerta* is stored at room temperature. Moreover, *Concerta* is a schedule II controlled substance with more prescribing and dispensing restrictions that will further decrease the risk of confusion with Risperdal *Consta.* Therefore, based on information currently available, the risk of name confusion between *Concerta* and Risperdal *Consta* is minimal.

Constulose is a hyperosmotic laxative used in the treatment of constipation. It is Alpharma's proprietary name for lactulose oral solution and is available in a concentration of 10 g lactulose per 15 mL. The product is packaged in 237 mL and 946 mL containers. Although *Constulose* and the proposed modifier *Consta*, share the prefix "*Const*", *Constulose* contains 10 letters while *Consta* contains only six. The suffix "*lose*" in *Constalose* is distinguishable from *Consta* in script and sound. In addition, the proposed modifier "*Consta*" will be used in conjunction with the proprietary name Risperdal. These

products are also different because *Constulose* is orally administered whereas Risperdal *Consta* will be administered intramuscularly. While *Constulose* is usually dosed 15 to 30 mL daily, the recommended dose of Risperdal *Consta* is 25 mg every 2 weeks. Moreover, the risk of selecting a wrong product from pharmacy storage shelves is minimal since *Risperdal Consta* will be refrigerated and *Constulose* is stored at room temperature. Therefore, the potential risk of name confusion between *Constulose* and Risperdal *Consta* appears to be minimal.

Constilac, a product manufactured by Alra Laboratories, is another proprietary name for lactulose syrup. It is used in the treatment of constipation and is available in a concentration of 10 g of lactulose per 15 mL. The product is packaged in 8 oz and 16 oz bottles, and unit dose packages of 30 mL. Although *Constilac* and the proposed modifier *Consta* share the prefix "*Const*", *Constilac* contains 9 letters while *Consta* contains only 6 letters. The suffix "*lac*" in *Constilac* is distinguishable from the modifier *Consta* in script and sound. Moreover, a prescription for Risperdal *Consta* will contain both the proprietary name and the modifier *Consta*. *Constilac* is orally administered whereas Risperdal *Consta* will be administered intramuscularly. In addition, *Constilac* is usually dosed 15 to 30 mL daily, while the recommended dose of *Risperdal Consta* is 25 mg administered every 2 weeks. Furthermore, the risk of selecting a wrong product from pharmacy storage shelves is minimal since *Risperdal Consta* will be refrigerated and *Consilac* is stored at room temperature. Based on information currently available, the potential risk of name confusion between *Constilac* and *Consta* appears to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In reviewing the container label, carton labeling and the package insert labeling for *Risperdal Consta*, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. 2 mL DILUENT (Pre-filled Syringe: [redacted]

1. We note that recent revisions to the container labels and carton labeling dated March 29, 2002, did not include the diluent label. The following comments refer to the old pre-filled syringe label. The statement identifying the diluent content should be listed first so that it is more prominent. In addition, a statement should be provided identifying the pre-filled syringe contents as a diluent for *Risperdal Consta*.

2. DMETS recommends providing the diluent in a vial rather than a pre-filled syringe in order to prevent the inadvertent administration of diluent without active ingredient.

B. THE ALARIS SMARTSITE ACCESS DEVICE DOSE-PACK

1. CONTAINER LABEL

   a. Provide a statement indicating that the vial of microspheres is for single use only.

   b. Provide a statement indicating that the product is for glutteal intramuscular injection only.

   c. Express the strength as milligrams per vial for all strengths. For example, the label should read "25 mg/vial."

d. We notice that information relating to the NDC number, active ingredients and storage has been repeated on two separate panels. Delete the duplicate information.

e. Provide information indicating that the product should be reconstituted prior to use.

f. Provide space between the strength and "mg". In addition, increase the prominence of the expression "mg".

2. CARTON LABELING

a. Provide a statement indicating the strength of the reconstituted product. For example: once reconstituted each mL contains XX mg of risperidone.

b. Relocate information about the dose pack contents from the side panel (Panel 3) to the principal display panel (Panel 1).

c. See comment B1f.

d.

3. PACKAGE INSERT LABELING

Dosage and Administration

a. The statement "Do not administer intravenously" found in the second paragraph of the Dosage and Administration section should be emphasized in the Instructions for Use section.

c. The statement ' ——— should be revised to include the meaning of the For example the above statement should read

C. THE 3-NEEDLE SYSTEM

1. CONTAINER LABELS

See statements B1a through B1e.

2. CARTON LABELING

a. See comments under B1a, B2a, and B3c.

b. The content list, storage temperature directions and the cautionary statement "keep out of the reach of children" printed in white appear illegible against the green background. Increase the font size and/or use contrasting colors to increase the prominence.

c.

d.

f. Provide a statement indicating the strength of the reconstituted product. For example: once reconstituted each mL contains XX mg of risperidone.

g. Provide space between the strength and "mg".

h. Increase the prominence of the statement "for gluteal intramuscular injection only" on panel 3.

i.

3. PACKAGE INSERT LABELING

a. The statement "Do not administer intravenously" found in the second paragraph of the dosage and Administration section should be emphasized in the Instructions for Use section.

b. See comment B3c.

IV. RECOMMENDATIONS:

1. DMETS has no objection to the use of the proposed proprietary drug name *Risperdal Consta.*

2. We recommend implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3 In addition, we recommend that the Division consult Don Boring of the CDER Labeling and Nomenclature Committee (LNC) for comment on the correct nomenclature of the established name.

We 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 the project manager, Sammie Beam, R.Ph. at 301-827-3242.

_____

David Diwa, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Concur:

_____

Alina Mahmud, R.Ph.
Team Leader
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APPEARS THIS WAY
ON ORIGINAL

ATTATCHMENT A

Table of Pertinent Medication Errors from the AERS Database

	AERS/DQRS /USP #	DATE OF EVENT/ REPORT	INTENDED PRODUCT	DISPENSED PRODUCT	ABBREVIATED NARRETIVE/OUTCOME
1	3274299-1		Relafen 500 mg	Risperdal 1 mg	A pharmacy technician filled Risperdal 1 mg instead of Relafen 500 mg for a long-term-care (LTC) patient. According 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		Remeron 30 mg	Risperdal 3 mg	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 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		Rocaltrol 0.25 mcg	Risperdal 0.25 mg	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		Dostinex 2 mg (Carbergoline)	Risperdal 2 mg	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		Requip	Risperdal	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		Requip 0.5 mg (ropinirole)	Risperdal 0.5 mg	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.

APPEARS THIS WAY

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/s/

David Diwa
5/17/02 10:57:27 AM
PHARMACIST

Alina Mahmud
5/17/02 11:00:19 AM
PHARMACIST

Carol Holquist
5/17/02 11:07:53 AM
PHARMACIST

Jerry Phillips
5/17/02 11:29:54 AM
DIRECTOR

Executive CAC
Date of Meeting: 4/23/02
Rat Carcinogenicity Study

Committee: Joseph Contrera, Ph.D., HFD-900, Acting Chair
Jeri El Hage, Ph.D., HFD-510, Alternate Member
Robin Huff, Ph.D. HFD-570, Alternate Member
Barry N. Rosloff, Ph.D., HFD-120, Supervisory Pharmacologist
Lois M. Freed, Ph.D., HFD-120, Presenting Reviewer

Author of Draft: Lois M. Freed, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #**21-346**
Drug Name: risperidone i.m. depot
Sponsor: Janssen Pharmaceutica

Rat Carcinogenicity Study: a 2-yr carcinogenicity study was conducted in Wistar rats at doses of 0, 5, and 40 mg/kg. The study included both saline and vehicle controls. The following tumors were identified by the sponsor as significant drug-related findings: (a) increase in mammary adenocarcinomas in LDF, (b) increase in pancreatic islet cell tumors (particularly adenomas) in HDM and HDF, (c) increase in pituitary adenomas and adrenomedullary pheochromocytomas in HDM, (d) increase in mammary gland tumors (particularly adenocarcinomas) in HDF, (e) decrease in ovarian polyps and absence of ovarian tumors in females, (f) "marginal" increase in solid renal corticotubular tumors in HDM, (g) a significant trend in mammary gland tumors in males (compared to SC), (h) a significant trend in adrenal pheochromocytoma in females (compared to SC). No vehicle- or drug-related findings were detected at the injection site.

Executive CAC Recommendations and Conclusions: the ExeCAC concurred with the following tumor findings: (a) mammary gland adenocarcinomas in LDF and HDF, (b) pancreatic islet cell tumors [adenoma, combined adenoma/carcinoma] in HDM and pancreatic islet cell adenomas in HDF. (c) adrenal pheochromocytomas [benign, combined benign/malignant] in HDM, (d) renal tubular tumors [adenoma, combined adenoma/adenocarcinoma] in HDM, (e) pituitary adenomas in HDM. The Committee noted that the HD may have exceeded the MTD in males, based on body weight/clinical signs data.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

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/Division File, HFD-120
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Joe Contrera
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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling