

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-999

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-999

SUPPL # 000

HFD # 130

Trade Name Invega Extended-Release Tablets

Generic Name paliperidone

Applicant Name Johnson & Johnson

Approval Date, If Known December 20, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES NO

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

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

N/A

d) Did the applicant request exclusivity?

YES NO

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA#

NDA#

NDA#

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.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Keith Kiedrow, PharmD, LCDR USPHS
Title: Regulatory Project Manager
Date: 12/18/06

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Thomas Laughren
12/18/2006 03:17:52 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-999 Supplement Type (e.g. SE5): original Supplement Number:

Stamp Date: 10/20/06 Action Date: 12/20/06

HFD 130 Trade and generic names/dosage form: Invega (paliperidone) ER Tablets

Applicant: Janssen, L.P. C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

Therapeutic Class: Schizophrenia (code 2020200)

Indication(s) previously approved: Not applicable

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

Number of indications for this application(s): 1

Indication #1: Treatment of Schizophrenia

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Pediatric Written Request has been issued (IND 65,850; Robert Temple, MD, 11/2/06)

Date studies are due (mm/dd/yy): 12/2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-999
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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this page is the manifestation of the electronic signature.**

/s/

Keith Kiedrow

12/18/2006 01:01:25 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-999 Supplement Type (e.g. SE5): original Supplement Number:

Stamp Date: 11-30-05 Action Date: 9-30-06

HFD 130 Trade and generic names/dosage form: Paliperidone ER Tablets

Applicant: Janssen, L.P. C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Therapeutic Class: Schizophrenia (code 2020200)

Indication(s) previously approved: Not applicable

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

Number of indications for this application(s): 1

Indication #1: Treatment of Schizophrenia

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 13 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Application has not been approved/Pediatric Written Request has not been issued

Date studies are due (mm/dd/yy): N/A

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-999
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-999	Efficacy Supplement Type SE-	Supplement Number 000	
Drug: Paliperidone ER Tablets		Applicant: Janssen, L.P. C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.	
RPM: Keith Kiedrow		HFD- 130	Phone # 301-796-1924
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
<ul style="list-style-type: none"> • Review priority 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 		1	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		Not applicable.	
❖ User Fee Goal Dates		September 30, 2006	
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
<ul style="list-style-type: none"> • User Fee 		<input checked="" type="checkbox"/> Paid UF ID number 3006236	
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)			

• Applicant is on the AIP	() Yes (X) No
• This application is on the AIP	() Yes (X) No
• Exception for review (Center Director's memo)	Not applicable.
• OC clearance for approval	Not applicable.
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• 505(b)(2) status?	Not a 505(b)(2) application.
❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Not applicable.
❖ Actions	
• Proposed action	() AP () TA (X) AE () NA
• Previous actions (specify type and date for each action taken)	None. First Cycle.
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) 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)	Tab C and D
• Most recent applicant-proposed labeling	Tab D (May 31, 2006)
• Original applicant-proposed labeling	Not included.
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	See consult reviews and CMC, pharm/tox, biopharm, clinical reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Tab S; Risperdal, Abilify, Geodon
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Tab H; Tab M
• Applicant proposed	Tab H
• Reviews	Tab H; Tab M
• Post-marketing commitments	
• Agency request for post-marketing commitments	Tab C

<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	Has not occurred yet.
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See Tab O
❖ Memoranda and Telecons	See Tab O
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting 	Tab P
<ul style="list-style-type: none"> Pre-NDA meeting 	Tab P
<ul style="list-style-type: none"> Pre-Approval Safety Conference (approvals only) 	Not applicable.
<ul style="list-style-type: none"> Other 	(internal meetings) Filing meeting January 17, 2006 Mid-cycle meeting May 10, 2006 Update meeting September 8, 2006
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	Not applicable.
<ul style="list-style-type: none"> 48-hour alert 	Not applicable.
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Not applicable.
Summary	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Tab E, Tab F
Summary	
❖ Clinical review(s)	Tab G
❖ Microbiology (efficacy) review(s)	Not applicable.
❖ Safety Update review(s)	Tab G
❖ Risk Management Plan review(s)	Not applicable.
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Tab R
❖ Demographic Worksheet <i>(NME approvals only)</i>	Not applicable.
❖ Statistical review(s)	Tab I
❖ Biopharmaceutical review(s)	Tab K
❖ Controlled Substance Staff review(s) and recommendation for scheduling	Not applicable.
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> Clinical studies 	Tab L
<ul style="list-style-type: none"> Bioequivalence studies 	Not applicable.
Summary	
❖ CMC review(s)	Tab H
❖ Environmental Assessment	
<ul style="list-style-type: none"> Categorical Exclusion 	Tab H
<ul style="list-style-type: none"> Review & FONSI 	Tab H
<ul style="list-style-type: none"> Review & Environmental Impact Statement 	Tab H
❖ Microbiology (validation of sterilization & product sterility) review(s)	Not applicable.
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed

	(X) Requested () Not yet requested
Nonclinical	
❖ Pharm/tox review(s), including referenced IND reviews	Tab J
❖ Nonclinical inspection review summary	Not applicable.
❖ Statistical review(s) of carcinogenicity studies	Not applicable.
❖ CAC/ECAC report	Not applicable.
❖	
❖	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-999

Janssen, L.P.
C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Heddie Martynowicz, M.S., Director Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Martynowicz:

We acknowledge receipt on October 20, 2006 of your resubmission to your supplemental new drug application for Paliperidone 3, 6, 9, 12, [REDACTED] ER Tablets.

We consider this a complete, class 1 response to our September 29, 2006 action letter. Therefore, the user fee goal date is December 20, 2006.

If you have any question, call Keith Kiedrow, Pharm.D., Regulatory Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Keith Kiedrow, Pharm.D., LCDR USPHS
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Keith Kiedrow
11/3/2006 03:56:25 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-999

Janssen, L.P.
C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Heddie Martynowicz, M.S., Director Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Martynowicz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [REDACTED] (paliperidone ER) tablets, submitted November 30, 2005.

Please also refer to your submission dated August 2, 2006, in which you request for re-review of the proposed tradename [REDACTED] and review of the proposed tradenames, INVEGA and [REDACTED]. The Division of Medication and Technical Support (DMETS) and the Division of Psychiatry Products have the following recommendations/comments:

With regard to the re-review of [REDACTED] (*italicized sections were submitted by JJPRD*) –

- A. *As part of a multifaceted nomenclature study, the results of the verbal studies indicated that 100% (63 of 63 practitioners) of the interpretations of verbal [REDACTED] prescriptions from physicians, pharmacists and nurses did not result in the identification of a marketed brand/generic drug name. None of these healthcare practitioners identified Meridia or any variant close to Meridia as a potential problem.*

DMETS Response: DMETS acknowledges the independent name analysis conducted by DSI. DMETS also notes that the Agency takes a multifaceted approach when reviewing proprietary names; which includes verbal and written prescription studies, database searches, expert panel review, and analysis by a medication safety reviewer. However, with regards to DSI's verbal prescription results, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. DMETS utilizes the prescription studies as a tool in assessing the risk of confusion rather than an absolute means of identifying names. Proprietary names of currently marketed drug products not identified in the prescription studies does not necessarily mean that once widely prescribed, [REDACTED] will not be confused with them. Additionally, we were not provided with complete results from the [REDACTED] analysis. The results simply state "[REDACTED] was not misinterpreted for any existing brand/generic drug name". Results such as misspellings that are not an exact match (e.g. [REDACTED]) are an invaluable part of the analysis. Furthermore, our prescription studies revealed positive misinterpretations of the name [REDACTED] in

6 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

Thomas Laughren
11/1/2006 01:43:08 PM

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mailstop 4447)**

DATE RECEIVED: August 8, 2006	DESIRED COMPLETION DATE: November 1, 2006	OSE REVIEW #: 06-0024-2 and 06-0024-3
DATE OF DOCUMENT: July 31, 2006		

TO: Thomas Laughren, MD
Director, Division of Psychiatry Products
HFD-130

THROUGH: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Invega
(Paliperidone) Extended-Release Tablets
3 mg, 6 mg, 9 mg, and 12 mg

NDA#: 21-999

SPONSOR: Johnson & Johnson

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Invega. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Invega, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak Bldg #22, Mailstop 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 23, 2006

NDA#: 21-999

NAME OF DRUG: Invega
(Paliperidone) Extended-Release Tablets
3 mg, 6 mg, 9 mg, and 12 mg

NDA HOLDER: Janssen, L.P.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Psychiatry Products (HFD-130) for assessment of the proprietary name, Invega, regarding potential name confusion with other proprietary or established drug names. This is the alternate proprietary name submission by the sponsor. DMETS did not recommend the use of the previously submitted name, [REDACTED] because of orthographic similarity with [REDACTED] (see OSE Review 06-0024, dated February 8, 2006). Container labels and carton labeling were provided for review and comment.

PRODUCT INFORMATION

Invega (paliperidone) is a psychotropic agent indicated for the treatment of schizophrenia. The recommended dose is 6 mg once daily in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 mg to 12 mg once daily. Invega will be available as 3 mg, 6 mg, 9 mg, and 12 mg extended-release tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to a degree where potential confusion between drug names could occur under the 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 conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Invega. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This 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 and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Invega, acceptable from a promotional perspective.
2. The Expert Panel identified eight proprietary names that were thought to have the potential for confusion with, Invega. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

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

Product Name	Dosage form(s), Strength(s)	Indication	Other**
Invega	Paliperidone Extended-release oral tablets 3 mg, 6 mg, 9 mg, and 12 mg	Schizophrenia. Once daily. Some patients may benefit from lower or higher doses than the recommended range of 3 mg to 12 mg once daily.	N/A
Integra Dermal Regeneration Template	Not applicable. Integra is a synthetic dermal substitute.	Not applicable.	LA
Invanz	Ertapenem Powder for injection 1 gm vial	<u>Treatment of moderate to severe infections of the pelvis, lungs, urinary tract, abdomen, skin and skin structures due to susceptible isolates:</u> <i>Intravenous:</i> 1 gm once daily for up to 14 days. <i>Intramuscular:</i> 1 gm once daily for up to 7 days.	LA
“Omega-3” products (There are multiple OTC products that use the name “Omega-3”, one such product is listed below)	Multiple omega-3 fish oil products are available over-the-counter and the strengths vary by product. (Strengths identified: 1 gm and 1.2 gm)	Doses vary depending on the product being used. (Dosage range identified: 2 gm to 4.8 gm per day)	LA/SA
Omega-3 Purified Fish Oil Softgels	Omega-3 fish oil Softgel capsule 1 gm	<u>Dietary supplement used to help maintain normal heart and cardiovascular function and to support immune health:</u> 2 capsules with a meal daily. Up to 4 capsules may be taken daily.	
Inspra	Eplerenone Tablets 25 mg and 50 mg	<u>Congestive heart failure post-MI:</u> Start with 25 mg once daily and titrate to 50 mg once daily. <u>Hypertension:</u> 50 mg once daily; may increase to 50 mg twice daily if response is not adequate.	LA

Integra (Foreign product, Germany)	Collagen (Additional product information not available)	Product information not available.	LA
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Product Name	Dosage form(s)	Indication	Other**
Invega	Paliperidone Extended-release oral tablets 3 mg, 6 mg, 9 mg, and 12 mg	See package insert for full prescribing information. Some patients may benefit from lower or higher doses than the recommended range. Some patients may benefit from once daily dosing.	N/A
Invigan <i>(Foreign product, Chile)</i>	Ornidazole Tablets 500 mg	<u>Anaerobic bacterial infections, dracunculiasis, protozoal infections:</u> Dosing information not available.	LA
Invigan <i>(Foreign product, Spain)</i>	Famotidine (Additional product information not available)	Product information not available.	LA
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Invega with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study employed a total of 126 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Invega (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	"Invega 6 mg #60 One tablet every morning"
<u>Inpatient RX:</u> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A (page 12) for the complete listing of interpretations from the verbal and written studies.

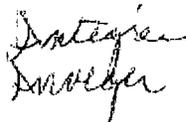
C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Invega, the primary concerns relating to look-alike and sound-alike confusion with Invega are: Integra Dermal Regeneration Template, Invanz, Omega-3, Inspra, ████████ Integra (collagen in Germany), Invigan (ornidazole in Chile), and Invigan (famotidine in Spain). Upon further review, the foreign names Integra and Invigan were not reviewed further because they are foreign names that are not exact matches, have different product characteristics (such as strength and indication of use) and/or there is a lack of product information available.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Invega.

1. Integra (the root name of "Integra Dermal Regeneration Template") was identified as a name with similar appearance to Invega. Integra is a bilayer membrane system for skin replacement. It is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.

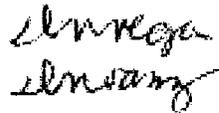
The orthographic similarities between the names are due to the fact that both names begin with the letters "In" and end with the letter "a". Additionally, both names share five overlapping letters (Integra vs. Invega) which contributes to their look-alike similarity. However, the letter "t" in Integra contains an upstroke which may help to differentiate the names. Moreover, the context of use and different product characteristics between the two products will help to minimize the potential for confusion. For example, Integra is a synthetic dermal substitute applied during burn surgery and, therefore, it is not likely to get ordered from a pharmacy. Thus, despite some look-alike similarities between this name pair, the different context of use and different product characteristics will minimize confusion.



NOTE: This review contains proprietary and confidential information that should not be released to the public.

2. Invanz (ertapenem) was identified as a name with similar appearance to Invega. Invanz is an antibiotic used to treat moderate to severe infections of the abdomen, skin and skin structures, urinary tract, pelvis and lungs caused by susceptible isolates. The recommended dose for intravenous (IV) administration is 1 gram once daily for up to 14 days and for intramuscular (IM) administration, 1 gram once daily for 7 days.

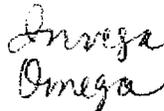
The orthographic similarities between the names are due to the fact that both names contain six letters of which the first three letters are identical (“Inv”). Additionally, the latter portion of the names contain letters that have the potential for downstroke characteristics (“z” vs. “g”) which may contribute to their look-alike similarities. However, these products differ in route of administration (intravenous or intramuscular vs. oral), and strength (1 gm vs. 3 mg, 6 mg, 9 mg, and 12 mg) which may help to differentiate the names. For example, a prescription for Invega would have to specify a strength since multiple strengths are available. Similarly, a prescription for Invanz would have to specify the route of administration since it can be administered intravenously or intramuscularly. Although there are some orthographic similarities, the different product characteristics minimize the potential to confuse Invanz with Invega.



The image shows two lines of handwritten cursive text. The top line reads "Invega" and the bottom line reads "Invanz". The letters are slanted and connected, with a prominent downstroke on the 'v' in both words, which is a key similarity noted in the text.

3. The root name, “Omega”, of “Omega-3” product lines was identified as a name that may look and sound similar to Invega. Omega-3 product lines are over-the-counter (OTC) dietary supplements used to help maintain normal heart and cardiovascular function and to support immune health. The products are typically available in 1 gm or 1.2 gm strengths and the dosage range is 2 gm to 4.8 gm per day. One such product is Omega-3 Purified Fish Oil which is available in a 1 gm strength with a recommended dosage of 2 capsules with a meal once daily; up to 4 capsules may be taken daily.

The root name “Omega” may look similar to Invega especially when the modifier “3” is omitted from the name “Omega-3”. The orthographic similarities between the names are due to the fact that the letter “m” in Omega may look similar to the letters “nv” in Invega when the names are scripted. Additionally, both names contain the same three ending letters “ega” which contributes to their look-alike and sound-alike similarities. The names may also sound similar because the second and third syllables of the names have a rhyming sound (Ō-MĔ-GĀ vs. ĪN-VĔ-GĀ). Additionally, these products have strengths with numbers that may potentially overlap (Omega-3 1.2 gm vs. Invega 12 mg). However, the beginning letters (“I” vs. “O”) look different when scripted and the different first syllable sound (“IN-” vs. “O-”) will help to distinguish the name pair phonetically.



The image shows two lines of handwritten cursive text. The top line reads "Invega" and the bottom line reads "Omega". The 'v' in Invega and the 'm' in Omega are written in a similar slanted, connected style, illustrating the orthographic similarity mentioned in the text.

Although Omega product lines are available over-the-counter, an order could potentially be written or called into the pharmacy. However, an order for an “Omega” product would not likely just state “Omega” without the modifier since products are available that contain Omega-6 fatty acids as well. Additionally, since there are multiple formulations of Omega-3 products, it would seem likely that the specific brand may be indicated on a

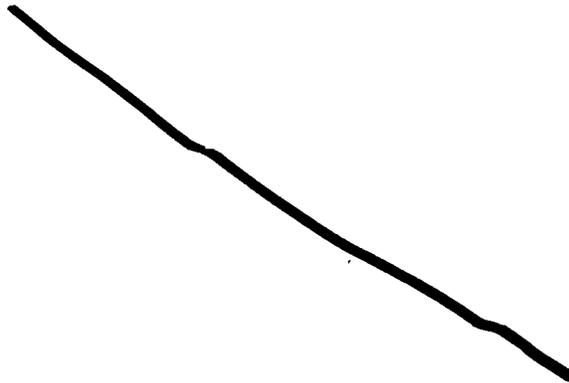
prescription in order to decrease confusion. Therefore, because of the different product characteristics, the potential to confuse Omega-3 with Invega is minimal.

4. Inspra was identified as a name with similar appearance to Invega. Inspra is indicated for the treatment of congestive heart failure post-myocardial infarction and for hypertension. The recommended doses are: for congestive heart failure, start with 25 mg once daily, then titrate to 50 mg once daily; for hypertension, 50 mg once daily, may increase to 50 mg twice daily if response is not adequate. Inspra is available in 25 mg and 50 mg tablets.

The names are orthographically similar because they begin and end with the same letters, "In" and "a", respectively. Additionally, they both contain the same number of letters, six, which makes the names look similar in length. However, the middle portion of the names appear different orthographically ("spr" vs. "veg") which may help to differentiate the names. Inspra and Invega have some overlapping product characteristics such as dosage form (tablet), route of administration (oral) and frequency of administration (once daily). On the other hand, they differ in product strength (25 mg and 50 mg vs. 3 mg, 6 mg, 9 mg, and 12 mg) which may help to differentiate the names. For example, an outpatient prescription for either of these products would have to specify the strength since both products are available in multiple strengths. Although there are some orthographic similarities between Inspra and Invega, the different product characteristics such as the strength will minimize the potential to confuse the name pair.

Invega
Inspra

5.



NOTE: This review contains proprietary and confidential information that should not be released to the public.

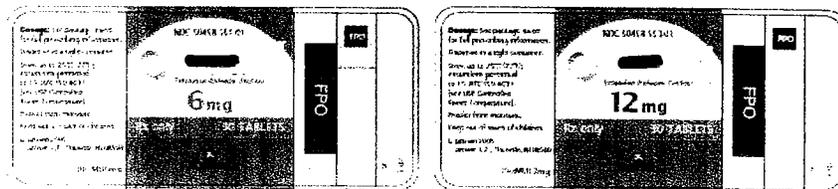
III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Invega will be available in 3 mg, 6 mg, 9 mg and 12 mg strengths. However, the container labels and carton labeling that have the name Invega imprinted were submitted for the 3 mg strength only in the EDR. The container labels and carton labeling for the 6 mg, 9 mg and 12 mg strengths have the previously proposed name **_____** imprinted on them. However, per email correspondence with the project manager on September 18, 2006, the Division has instructed DMETS to review the labels and labeling for these strengths.

In the review of the container labels and carton labeling of Invega, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified areas of improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. The sponsor uses color to help distinguish the product strengths by imprinting the different strengths in a different color, for example, green for the 3 mg strength, orange for the 6 mg strength, blue for the 9 mg strength, and red for the 12 mg strength products. However, the labels for all strengths look similar when compared side by side because of the predominant orange color used on the labels that arches over the name and highlights the company name. Because of this overwhelming color, the colors used to highlight the different strengths are not distinguishable. We recommend removing the large orange area from the label and highlight the strengths only or use the same color as the strengths to highlight the area that is now orange.



2. Remove the circle graphic as it is more prominent than the tradename and the established name.
3. Increase the size of the statement "Extended-Release Tablets" so that it is commensurate with the size of the established name.
4. Ensure that the established name is at least 1/2 the size of the proprietary name in accordance with 21 CFR 201.10 (g)(2).

B. CONTAINER LABEL (3 mg, 6 mg, 9 mg, and 12 mg; 30-count and 350-count bottles)

1. See General Comments, A-1 through A-4.
2. Relocate the net quantity statement so that it is not in close proximity to the product strength in order to prevent potential confusion between the net quantity with the product strength. For this same reason, dehighlight the net quantity statement.
3. If the 30-count bottles are unit-of-use containers, ensure that the containers have child-resistant closures in accordance with the Poison Prevention Act.

C. BLISTER LABEL (3 mg, 6 mg, 9 mg and 12 mg; hospital unit-dose, 100-count)

1. See General Comments, A-3 and A-4.
2. The different product strengths are printed in the same color (i.e., black typeface on a white background). Please use a different color scheme, boxing, highlighting or other means to distinguish the different strengths in order to avoid selection errors due to the products similar appearance.



D. PROFESSIONAL SAMPLE BLISTER LABEL (7-count)

1. It appears from the labels/labeling provided that the professional sample pack contains 7 tablets. What is not clear is if the blister provided contains a single tablet or all 7 tablets. If all 7 tablets are packaged in a single cell, we do not recommend this presentation. Placing 7 tablets in a single blister may cause confusion to the patient because, as labeled, it appears all 7 tablets constitute the 6 mg when, actually, 6 mg is contained in each tablet (see below).

NDC 50458-551-99

PALIPERIDONE
Extended-Release Tablets

6mg

Rx only.

Store up to 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature). Protect from moisture. Pack contains seven tablets.

Professional sample. Not to be sold.

PACKAGING NOT CHILD RESISTANT

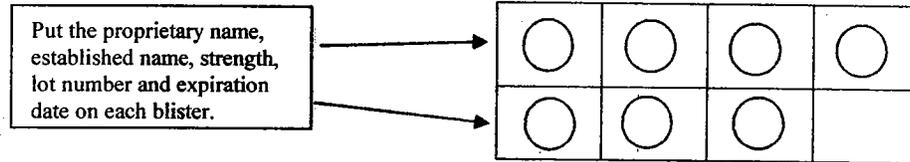
Janssen
Janssen, a Division of Janssen Pharmaceutica

Sample Blister M66mg

EXP: ANVAX

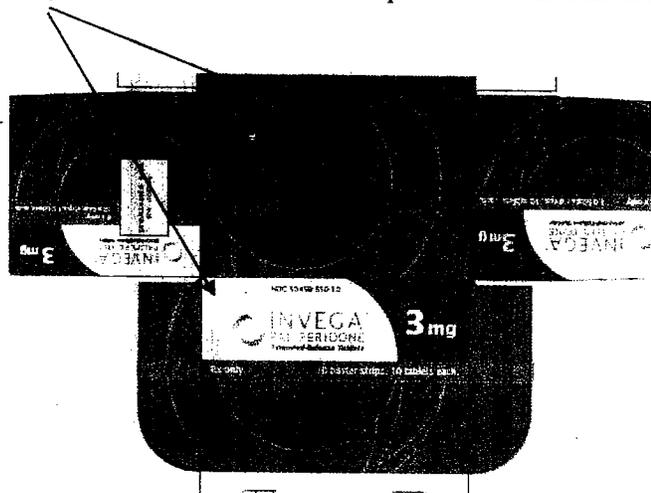
LOT: XXXXXXXXX

Even if a patient doesn't get confused by this presentation, it is still not a good design. Once the tablets are punched out, you lose the important information printed on the reverse side. Each tablet should be labeled with the proprietary name, established name, strength, lot number and expiration date. For example:



D. **CARTON LABELING (3 mg, 6 mg, 9 mg and 12 mg; hospital unit-dose carton, 100-count; professional sample carton, 7-count; and professional sample box, 35-count)**

1. See General Comments, A-1 through A-4.
2. Remove the thin white/orange halo graphics that appear throughout the labeling as they are distracting and make the information presented difficult to read (see sample below).



Appendix A. Prescription Study Results For Invega

Inpatient	Outpatient	Verbal
Invega	Invega	Envega
Invega	Invega	Envega
Invega	Invega	Invaega
Invega	Invega	Invega
Invega	Invega	
Invega	Invega	
Invega	Invega	
	Invega	

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

/s/

Loretta Holmes
10/27/2006 09:32:18 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
10/27/2006 12:36:58 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/27/2006 01:13:15 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director in her
absence



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-999

Janssen, L.P.
C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Heddie Martynowicz, M.S., Director Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Martynowicz:

Please refer to the teleconference between representatives of your firm and FDA on October 13, 2006. The purpose of this meeting was to discuss in vitro release specifications for paliperidone ER tablets.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING
NDA 21-999; Paliperidone ER Tablets
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Type A meeting
October 13, 2006

Participants –

FDA

Ramesh Sood, PhD	Interdisciplinary Supervisor, ONDQA
Thomas Oliver, PhD	Chemistry Team Leader, ONDQA
Chhagan Tele, PhD	Chemistry Reviewer, ONDQA
Ray Baweja, PhD	Biopharmaceutics Team Leader, OCPB
Ron Kavanagh, PhD	Biopharmaceutics Reviewer, OCPB
Keith Kiedrow, PharmD	Regulatory Project Manager

Attendees Representing the Sponsor

Dawn Kracht	Associate Director, Chem Pharm Regulatory Affairs
Hans Vermeersch, PhD	Chem Pharm Team Leader
Noymi Yam, MS	Chem Pharm Team Leader, ALZA
Heddie Martynowicz, MS	Director, North America Region, Regulatory Affairs
Stan Altan, PhD	Senior Research Fellow, Biostatistics
Adriaan Cleton, PhD	Assistant Director, Clinical Pharmacology
George Finley	Senior Director, Technical Services, Global Pharmaceutical Sourcing Group
Maureen DiIorio	Manager, Quality Assurance, Global Pharmaceutical Sourcing Group
Koen Iterbeke, PhD	Principal Scientist, Analytical Development
Besaint Sahni	Stability Technical Team Leader, ALZA
Linda Carter	Senior Director, FDA Liaison

A teleconference was held on 13 October 2006 with representatives of the Division of Psychiatry Products, Office of New Drug Quality Assurance and the Office of Translational Sciences to discuss the *in vitro* release specifications for paliperidone ER Tablets proposed by FDA in the 29 September 2006 Approvable Letter.

Summary

FDA acknowledged the background package submitted by J&JPRD on October 6, 2006, and stated that the assessment of the appropriate *in vitro* release specifications is a review issue. To assist in the review, the following information was requested by Drs. Kavanagh and Oliver to be included in the complete response:

- *in vitro* results of individual tablets (14, 16, 18, 20, 22 and 24 hours), at release, for the phase 3 clinical lots, _____
- *in vitro* results of primary stability batches (14, 16, 18, 20, 22, and 24 hours)
- Scientific rationale for each of the proposed time points, including the information provided in the background document

J&JPRD agreed to provide the requested information as part of the complete response.

Drs. Kavanagh and Oliver confirmed their willingness to work with J&JPRD during the review of the Complete Response in order to come to an agreement on proposed specifications, and to facilitate approval of the application. J&JPRD will contact Keith Kiedrow after submission of the complete response to schedule a follow-up teleconference to discuss the specifications.

Detailed discussions

Agreement between FDA and J&JPRD was confirmed on the 0-2 hour and 0-8 hour proposed specifications.

With regard to the 0-14 and 0-18 hour specifications, Dr. Kavanagh requested the individual tablet data (upon release) for the phase 3 batches [REDACTED] (time points 14, 16, 18, 20, 22 and 24 hours). He informed J&JPRD that he will not use the primary stability data in his analysis of the specifications. However, Dr. Oliver requested these same time points be provided for the primary stability batches. J&JPRD agreed to provide the requested data in the complete response.

Regarding the 0-18 hour specifications, Dr. Kavanagh acknowledged J&JPRD's correlation of the 14-hour to 18-hour release profiles provided in the background package, and stated that if the company proposes to use these data to support the proposed specifications, they should be included in the complete response.

Dr. Kavanagh explained that the 18-hour time point was to address the late-stage release and to assure that complete dissolution did not occur too early in the release profile.

The 0-24 hour time point was requested to assure complete release over the 24-hour period. Dr. Kavanagh did not agree with J&JPRD's statement that the specifications at this time point cannot be tighter than allowed USP <905> Uniformity of Dosage Units – Content Uniformity limits of [REDACTED]

J&JPRD requested that FDA accept the proposed specifications on an interim basis, while reviewing the requested data sets. After some discussion, FDA was not in agreement with this approach. In addition, J&JPRD requested agreement for acceptance of the FDA specifications at the 0-14 hour time point for release, and the J&JPRD specification for this time point on stability. FDA was also not in agreement with this approach.

Finally, J&JPRD requested confirmation that submission of the requested information would not result in a Class 2 review. FDA stated that they did not think the additional information requested would require a Class 2 review, but could not confirm until they had the opportunity to review the information submitted.

Revised Drug Product Specifications

Revised drug product specifications, which reflect proposed specifications for cumulative drug release, will be provided in Module 3.2.P.5.1 and Module 3.2.P.8.1 of the complete response.

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Johnson & Johnson Pharmaceutical Research & Development, L.L.C., is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Keith Kiedrow, Pharm.D.
Regulatory Project Manager

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

/s/

Thomas Laughren
10/27/2006 02:33:18 PM

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

REQUEST FOR CONSULTATION

TO (Division/Office): **HFD- 860/Biopharm / Ray Baweja**

FROM: **HFD-130 (Division of Psychiatry Products);
Kim Updegraff**

DATE
October 23, 2006

IND NO.

NDA NO.
21-999

TYPE OF DOCUMENT
Response to AE Letter

DATE OF DOCUMENT
October 20, 2006

NAME OF DRUG
**Paliperidone Extended-Release
Tablets**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
11/2/06

NAME OF FIRM: **J&J**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

J&J has submitted a response to our 9-29-06 AE letter in a submission dated & received 10-20-06. They are requesting a class 1 resubmission coding. The submission is in the EDR under the following path:

\\CDSESUB1\EVSPROD\NDA021999\0014

SIGNATURE OF REQUESTER

Kim Updegraff, BSP, MS, RPh
Regulatory Project Manager
301-796-2201
Kimberly.updegraff@fda.hhs.gov

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Kimberly Updegraff
10/23/2006 04:15:14 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM:
**Division of Psychiatry Products, HFD-130
WO22, RM 4390**

DATE 8/8/06	IND NO.	NDA NO. 21-999	TYPE OF DOCUMENT	DATE OF DOCUMENT 7/31/06
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NAME OF DRUG Paliperidone Extended Release Tablets	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Schizophrenia	DESIRED COMPLETION DATE ASAP - PDUFA due date is 9/30/06, package due to Bob Temple 9/1/06
--	------------------------	--	--

NAME OF FIRM: **Johnson & Johnson**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review. |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS: The sponsor has proposed the alternative tradenames INVEGA and in order of preference. Their submission is entirely electronic. The network path location is:
\\CDSESUB1\EVSPROD\N021999\021999.ENX (select amendment #009)

PDUFA DATE: 9/30/06
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 21-999
HFD-130/Division File
HFD-130/RPM
HFD-130/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER Steven D. Hardeman, R.Ph. 6-1081	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
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SIGNATURE OF RECEIVER

**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
8/8/2006 09:55:47 AM

The following are various e-mail communications regarding NDA 21999 N000

Questions Conveyed to the Sponsor

**(a response to Question 1 was e-mailed, pending submission under the NDA) and
Outstanding Questions**

(responses to Question 2-4 are pending at the time of this writing)

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

From: Brugge, Karen [mailto:karen.brugge@fda.hhs.gov]

Sent: Wednesday, June 28, 2006 10:46 AM

To: Martynowicz, Jadwiga [PRDUS]

Cc: sochalsk@prdus.jnj.com; Khin, Ni Aye; Kiedrow, Keith

Subject: RE: Outstanding SCH-1009 Qs & Miscellaneous

Hi Heddie,

Thanks for your responses and we look forward to your response to the syncope-related Q.

This e-mail is a follow-up to your last response regarding SCH-1009 (see Q1 below), 2 new questions that we were hoping you could help us with (see Q 2 and 3), and examples of dropouts that we said we would be sending you (Q 4). Q 5 below is related to our examples of dropouts but is regarding subject 100057 who had adverse events ("muscle stiffness over the entire body" and other AEs during treatment that were followed by a serious adverse event (SAE) of neuroleptic malignant syndrome within days of treatment cessation that was not captured in the SAE database. Thanks for your assistance on getting the answers to our questions.

1. We received the most recent response about Study -1009-related Qs (forwarded with this e-mail). Just to be sure we don't miss anything, it looks like there is only 1 outstanding Q on this study which is the following about gender (we recently discussed this outstanding Q with you and I then sent you a follow-up e-mail from which I've copied key sections below for your convenience).

The raw mean QT and QTc values (for each method except for Bazett's) of each treatment condition by gender over time (similar to how results are presented in Tables 108 and 109 in the CSR but with groups subdivided by gender and including results of all treatment conditions in both tables). Would you provide these results? It would also be helpful to do the same using the least square mean results for QTcLD based on the analyses that was conducted in reply to our inquiry. Would you also conduct a similar analyses with least square mean results for QTcF and provide the results?

2. We would like to verify if all Phase III trials (-303, -304, -305, -302 and open label trials -702, -703, -704 and -705) used the to-be-marketed formulation. If not please clarify.

3. Would you send us more information about the following subjects that would be helpful regarding potential etiologies of these events?

- a) Subject 300541 was described in the Clinical Study Report for Study -304 section of the submission as having "pauses" on holter monitor after presenting with syncope, hypotension and bradycardia. Please provide more complete information on this subject (include a description of the actual syncope that

occurred and other relevant information that may help to determine the etiology).

b) A safety alert report submission N182 under IND 65850 for oral ER tablets (OROS) dated 4/3/06 was a description of a sudden death (after at least 3 months of 12 mg Pal daily in the OL study -701, and was receiving trihexyphenidyl, 2 mg given as needed) in a healthy 24 year old female (subject ~~_____~~). Please provide more complete information on this subject (include relevant information that may help to determine the etiology). Please also provide a hospital report (e.g. discharge summary) on this subject who died in transit to another hospital and any autopsy report (if one was performed). We are also wondering why this subject was prescribed trihexyphenidyl (e.g. "as needed" for what)?

4. The following paliperidone subjects are some examples which lead us to wondering if we are missing subjects who were adverse dropouts (ADOs), such as subjects who withdrew from the study for reasons related to AEs or due to clinical abnormalities (e.g. subjects who withdrew consent due to AEs, subjects who were withdrawn due to noncompliance in which their noncompliance was due to AEs or subjects that withdrew early for other reasons related to AEs)?

a) Subject 503018 in Study -305 in the original NDA submission was withdrawn due to noncompliance" after 4 days of stopping the study drug (drug stopped on Day 20 and withdrew "due to noncompliance" on Day 24) who had abnormal LFTs on Day 15 and "onward" (elevations of up to approximately 5 times the ULN, first observed on Day 15). Values normalized on Day 29 (9 days post-treatment cessation). This subject was found in the narrative section of subjects but was not checked off in the narrative summary table (preceding the narratives) as having either an SAE or as "premature discontinued." This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.

b. Subject 201803 in Study -303 (33 year old male) had a serious adverse event of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values. His baseline supine and standing heart rate values (HR) were 72 and 76 bpm, respectively compared to supine and standing HRs of 106 bpm and 130 bpm, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days. The subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG HR of 73 bpm on that day. Why did this subject withdraw consent? This subject was also not checked off under the "premature discontinued" column in the narrative summary table (preceding the narratives) and could not found in the line listings for premature discontinuations in Appendix 2.7.4.3.8.2.1 in the original NDA (in the SCS).

c. Subject 100232 (an ADO due to prolonged QT) is described in the narrative (page 1790 of the SUR) as not being included in the "interim analyses." Please clarify this comment and if this pertains to how this subject was captured in the safety database (e.g. in enumerating ADOs in SUR summary tables or line listings).

d. Subject 300011 withdrew "due to lack of efficacy" and is described in the narrative of the N000 submission as follows:

The subject received paliperidone 12 mg/day; she was discharged from the inpatient hospitalization portion of this study on Day 12 (source: CIOMS). Her symptoms had significantly improved and she was eager to be discharged. At her outpatient therapy on Day 15, she reported that the voices had returned on Day 13 and that she wanted to kill herself (source: follow-up SAE reports). The serious adverse event schizophrenia (increase of symptoms of schizophrenia verbatim) was reported on Day 15; the serious adverse event suicidal ideation (suicide ideation-verbatim) was reported on Day 17 (source: SAE follow-up forms). She went to the emergency room after experiencing a return of hallucinations and wanting to "kill herself." She was admitted to an adult psychiatric unit (source: CIOMS). She took paliperidone 12 mg/day on Day 15 but admitted that there may have been times that she forgot to take the medication (source: SAE follow-up forms). Study medication was held on Day 16, given on Day 17 and then permanently stopped.

She is not checked off in the narrative summary table under "premature discontinued." Was this subject captured in the line listings and summary tables enumerating ADOs (e.g. in Table 34 of the SCS)? If not why and how is this subject different that other subjects with psychotic-related events that were captured in Table 34? Please clarify.

e) Subject 100057 also had AEs that he could not tolerate on the same day of having study medication stopped "permanently on Day 22 as the subject withdrew consent." Refer to the narrative on page 1815. The following are excerpts from the narrative (also see Item II below describing this subject as well):

The subject was discharged from the hospital portion of the study on Day 20. At the scheduled Day 22 visit, he reported side-effects that he "could not tolerate" (restlessness and inability to sleep) (source: CIOMS). Study medication was permanently stopped on Day 22 as the subject withdrew consent. Vital signs were within normal limits but slightly higher than at earlier readings (138/91 mmHg standing; 141/72 mmHg supine); temperature was 36.4 degrees. Laboratory analyses on Day 22 (end of study) revealed a creatine kinase (CK) of 2201 U/L (reference range: 18-198 U/L); all other laboratory values were reported within the normal range. At baseline (Day -2), the baseline creatine kinase value was 186 U/L. The serious adverse events "elevated CK" and "neuroleptic malignant syndrome (acute EPS side effects)" were reported on Day 24 and Day 25, respectively; the elevated CK was considered life threatening.

This subject is recorded on the narrative summary table as only having an SAE and is not checked off as being an adverse dropout but is checked off as an SAE (see the "premature discontinued" column on page 1773)? Please clarify why this subject was not considered an ADO.

Q 5. Why is subject 100057 (an SAE during run-in phase of study -301 found in the narratives) not listed in line listings of

SAEs for this study (Appendix 3.5.1) and does not appear to be included in the in-text summary tables of SAEs in the SUR (e.g. Table 31)?

We note a comment about the reason provided as a footnote in the narrative summary table (on page 1773 of the SUR) yet it is still confusing for the following reasons. The subject had SAE of neuroleptic malignant syndrome reported only 2 days study after the drug was stopped, but was preceded by related AEs that included "muscle stiffness over the entire body" that the subject "could not tolerate" on Day 22. The subject withdrew consent on this same study visit (Day 22). Please clarify why this SAE was not captured in the database. :

Are there any other SAEs that occurred after treatment cessation that were preceded by AEs that lead to the SAE that were not captured in the Phase III database (of double-blind and open-label drugs)?

**Appears This Way
On Original**

Questions Conveyed to the Sponsor (some responses were received by e-mail and are pending submission to the NDA at the time of this writing)

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

From: Geter-Douglass, Beth [PRDUS]

Sent: Thursday, June 29, 2006 2:56 PM

To: Karen. Brugge (E-mail)

Cc: Ni. khin (E-mail); Ochalski, Stefan [PRDUS]; Martynowicz, Jadwiga [PRDUS]; Keith. Kiedrow (E-mail)

Subject: RE: Outstanding SCH-1009 Qs & Miscellaneous --EMAIL #1a of 2

Dear Dr. Brugge,

On behalf of Heddie Martynowicz who is on vacation this week, I am acknowledging receipt of your June 28 e-mail with additional questions regarding NDA 21-999.

I am also providing J&JPRD's response to the outstanding question "b" regarding SCH-1009 that was originally sent on June 21 and referred to below as Question #1. Responses to the new questions will be provided to you shortly.

Please find attached the following tables for question "b":

- tecg05b: equivalent for table 108 for each QTc parameter with raw means (descriptive statistics) by gender **Given that this file is too large to send with the others, I will send separately]**
- tecg06b: equivalent for table 109 for each QTc parameter with raw means (descriptive statistics) by gender[Geter-Douglass, Beth [PRDUS]] **Given that this file is too large to send with the others, I will send separately]**

In addition we have for completeness:

- tecg05a: table 108 for each QTc parameter (LSMeans) **[attached]**
- tecg06a: table 109 for each QTc parameter (LSMeans) **[attached]**

Lastly, the LS mean results by gender **[Given that this file is too large to send with the others, I will send separately]**

- tecg06c

Best Regards,
Beth

*Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs
J&J Pharmaceutical Research and Development
609-730-4409 (phone)
609-730-2069 (fax)
609-369-0743 (cell)*

Initial Set of Questions Sent to the Sponsor in May of 2006 (See Sponsor's Teleconference Meeting minutes on the following pages that followed this initial request)

We are moving along on the paliperidone review and we also recently received the safety update. We have run into a fairly time-consuming search problem that we were hoping you could help us with. In the original submission there is a line listing of patients with Deaths, Serious Adverse Events (SAE) and Discontinuations due to Adverse Events (DAE) that we found in an appendix to the Summary of Clinical Safety section (SCS). The listing does not provide page numbers or hyperlinks to the exact location for each subject. In-text sections of the SCS sometimes refers to subjects having potentially remarkable safety findings but often does not provide subject numbers and/or exact locations to narratives. Sometimes a hyperlink is provided but it generally goes to a summary table or listing (often a lengthy appendix to the SCS) in which we cannot find the subject number and/or exact location of a narrative of the specific subject in the hyperlinked section.

- So, for the open-label combined-trials safety-dataset, study 301, study 701, would it be possible for you to generate a list of the patients with Deaths, SAE, and DAE along with their verbatim and thesaurus term with a page number reference to the narrative (please make the listing comprehensive to include all deaths, SAEs, DAEs through the cut-off date used for the safety update report submission)?

We also are having trouble reconciling the cases described in the narrative text of the Safety summary with the cases in the datasets. It is common for the cases to be briefly described and enumerated, but there is no way for us to reconcile the descriptions with the actual cases. We are looking at liver effects and syncope and need some help.

- Drug effects on the liver is something that we always look closely at and we have a case that appears to be significant that we could not find described in in-text sections of the SCS (Subject 503018 in the 15 mg Pal group was a 44 year old male with no history or abnormal baseline values suggestive a pre-existing liver disorder who developed approximately 8 times the ULN of ALT and approximately 5 times the ULN of AST with about almost 4 times the ULN of GGT on Day 15 of Pal that resolved to normal values after 9 days (on Day 29) following Pal cessation on Day 20.)

There are also several patients who had elevated LFTs at baseline and it is difficult to dissect those away from patients who had normal LFTs at baseline and elevations. Would you be able to provide a listing of patients who had normal ALT, AST and bilirubin at baseline who went on to have AST or ALT of >3x and >8X normal along with their bilirubin values when these elevations occurred?

- Syncope and potential pro-arrhythmic effects: Patient 300541 in study 304 is described as having sinus pauses of up to 8 seconds but a description of this

subject could not be found in the pro-arrhythmic section of the SCS or in any other in-text section of the SCS.

Subject 201805 in Study -303 (a 33 year old male) had 12 mg daily Pal treatment discontinued on Day 7 who had an SAE of tachycardia that was first noted on Day 4 and reached a HR of 120 bpm supine (124 bpm standing) compared to 71 bpm (per ECG) at baseline (84 bpm supine at baseline). The subject also developed "hypotension" in which Day 4 BP was 100/65 mmHg, supine (115/75 standing) compared to 135/65 mmHg, supine at baseline and decreased further to 85/55 mmHg, supine, on Day 6 (80/50 standing). Supine BP of 115/80 mmHg and HR of 93 bpm on day 7. The tachycardia prolonged his hospitalization. Tachycardia was reported to resolve by 12 days and hypotension by 3 days without treatment. ALT was also reported to be "increased" during the study.

Subject 201803 in Study -303 (33 year old male) had a SAE of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values while BP generally did not change from baseline values. This subject was not described as having orthostatic hypotension (on page 146 of the CSR). His baseline supine and standing heart rates were 72 and 76 bpm, respectively compared to supine and standing heart rates of 106 and 130, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days, then the subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG heart rate of 73 bpm on that day.

We are interested in a listing of patients that were asymptomatic at baseline but who went on to have syncope, symptomatic bradycardia or tachycardia or symptomatic hypotension. Would it be possible for you to make a listing of these patients (with whether they were SAE, DAE or both along with their verbatim and thesaurus term) and a page number reference to the narrative?

Follow-up Teleconference Minutes (Sponsor's Version) of a 5/15/06 Teleconference between the Sponsor and Team Leader Dr. Paul Andreason and Reviewer Dr. Karen Brugge (with some Responses in a N005 6/15/06 Submission)

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

From: Martynowicz, Jadwiga [PRDUS] [<mailto:JMartyn1@PRDUS.JNJ.com>]
Sent: Monday, May 15, 2006 9:23 PM
To: Kiedrow, Keith
Subject: NDA 21-999: Summary of 15 May 2006 Teleconference

Dear Keith,

Thank you for arranging this teleconference. As promised, here is our summary of key outcomes from the meeting. Please share with Drs. Brugge and Andreason and let me know if there are any differences in understanding.

Attendees from FDA: Paul Andreason, MD; Karen Brugge, MD; Keith Kiedrow, PharmD.

Attendees from J&JPRD: Peter Briscoe, MD; Denise Brown; Jackie Brown; Linda Carter; William Clayton; Joseph Donato, Beth Geter-Douglass, PhD, Michelle Kramer, MD, Pilar Lim, PhD; Heddie Martynowicz, MS; Anna Mendlin, PhD; Wayne Napolliello, Paul Sokol.

* We agreed that FDA Medical Reviewers may contact J&JPRD at anytime with further questions resulting from their ongoing review of the NDA. The primary contact will be Heddie Martynowicz. Contact information for Heddie is provided below:

Tel: 609-730-7028
Cell: 609-509-1043
Fax: 609-730-3091
Email: jmartyn1@prdus.jnj.com

* J&JPRD will update and combine the tables currently provided in front of the narrative sections of the 4-month Safety Update to add the following information for each subject: verbatim and thesaurus terms and page numbers for each narrative included in the 4-month Safety Update through the cut-off date of November 1, 2005. The resulting comprehensive table will be organized as follows:
R076477-SCH-R076477-301, R076477-SCH-701 and followed by pooled open-label trials (R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705).

* FDA clarified that the data displays requested below are needed to complete their standard safety assessment:

* An incidence table by treatment group will be provided for subjects in the double-blind studies that were included in the original NDA (R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305) with ALT and/or AST values >3 times the upper limit of normal (who had normal AST, ALT and bilirubin values at baseline). A separate incidence table will be provided for the elderly study (R076477-SCH-302).

* A listing of subjects with ALT and/or AST values >8 times the

upper limit of normal (who had normal AST, ALT and bilirubin values at baseline) and existing narratives previously submitted to the NDA will be provided for all safety datasets including those submitted in the original NDA as well as those included in the 4-month Safety Update through the November 1, 2005 cutoff date.

* A listing of those subjects with syncope, symptomatic bradycardia, symptomatic tachycardia or symptomatic hypotension (asymptomatic at baseline) will be provided for all safety datasets including those submitted in the original NDA as well as those included in the 4-month Safety Update through the November 1, 2005 cutoff date. For those subjects with SAE's, deaths or discontinuations due to adverse events, existing narratives previously submitted to the NDA will be provided for ease of review. The methodology used for selecting subjects for this listing will be described.

* The above items will be provided to FDA as soon as each response becomes available and will be submitted as Review Aides. The timelines for providing FDA responses to these requests are in preparation.

* The same requests will be applied to the 7-month Safety Update. However, the information will be limited to only the new safety data available after the cutoff date of the 4-month Safety Update.

Thank you for a very informative and productive discussion. I am looking forward to working with you, Dr. Brugge and Dr. Andreason in addressing any further questions/requests and facilitating completion of FDA's review of this NDA. In addition, please note that J&JPRD is willing to assist in addressing questions as they arise from any of the other FDA Review Teams.

Best regards,

Heddie

Heddie Martynowicz, M.S.
Director, Regulatory Affairs
Johnson & Johnson
Pharmaceutical Research & Development L.L.C.
Tel: 609-730-7028
Cell: 609-509-1043
Fax: 609-730-3091
Email: jmartyn1@prdus.jnj.com

**The Sponsor's Minutes of 5/23/06 Teleconference with
Some Responses in a N005 6/15/06 and Submission**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Regulatory Affairs

Record of Contact

EDMS-PSDB-5573941

Date of Contact: 23 May 2006

Date of Report: 25 May 2006

Health Authority/Division:
Center for Drug Evaluation and
Research/Division of Psychiatry Products

Product: R076477 (RWJ16232411)
(paliperidone)
NDA No.: 21-999

Health Authority Contact:
Name: Keith Kiedrow, Ph.D.
Title: Project Manager

Prepared by:
Name: Heddie Martynowicz, MS
Title: Director, Regulatory Affairs

Health Authority Attendee(s):
Name: Paul Andreason, MD
Title: Psychopharmacology Team
Leader

Company Attendee(s):
Name: Heddie Martynowicz, MS
Title: Director, Regulatory Affairs

Name: Karen Brugge, MD
Title: Medical Reviewer

Subject: QUESTIONS RECEIVED VIA TELEPHONE FROM DRS.
ANDREASON AND BRUGGE ON 23 May 2006 REGARDING
NDA 21-999 AND FOLLOW-UP E-MAIL FROM DR. BRUGGE

1. **Vital signs:** Study 1009: Did you collect vital signs at Tmax in this study? If no, do we have information from any other Ph 1 study (preferably with the to be marketed formulation) where we may have collected vital signs and EKGs at Tmax.

2. **Confounding factor analysis:** Study 1009: Looking for role of confounding variables, such as gender, concomitant medication or pre-existing cardiac condition. This info is not found in SCS. Also would like to see raw mean results presented in Table 109 in SCS.

3. **Logic for laboratory data displays in the SCS:** We provide in the SCS incidence of outliers for a variety of laboratory parameters. However, this list is not comprehensive. FDA wants to understand why we chose to present only those and not the other laboratory parameter in the SCS. Is it because there were no outliers in those parameters? If this is not the case where can they find the rest of the data?

4. **Suicidality:** SCS Section 2.1.6.1.1 provides a search of all terms that may be indicative of suicidality. FDA is having a hard time reconciling this list with cases included elsewhere. They want to understand what patients were excluded and why. They make references to cases described on p. 109, 104, 96, 95 and specific references to patients from 304 study: 300397 and 300301. They don't understand why these cases should be excluded from list and dismissed, as terms are suggestive of suicidality. And they don't see info of any pre-existing suicidality at study entry.

5. **CPK:** We mention in the SCS that we have observed inconsistent elevations in CPK in our Ph 3 schizophrenia data. We also offer an explanation that this is indicative of the

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

EDMS-PSDB-5573941

schizophrenia population (not due to extra pyramidal effects of the drug or other effect of the drug). However, when looking at the Ph 1 data, FDA notes that there are also elevations in healthy subjects and that the greatest increases in CPK occur in the paliperidone high dose group. FDA is looking at the SCS, which includes information from 17 pooled phase 1 studies. In this section, there are various subgroups within that data set, including placebo, low dose OROS, high dose OROS and other. FDA wants to understand why there are elevations in healthy subjects? They are looking for pooled information (a) descriptive statistical results and (b) incidence of outliers for these subgroups from the pooled data set. FDA is particularly interested in seeing results for the placebo group.

Follow-up e-mail from Dr. Brugge to Ms. Martynowicz on 23 May 2006:

I just found a few examples in which I cannot find results in summary tables on a clinical parameter for a given treatment condition (in this case it's the IR Paliperidone treatment condition) for the Phase I healthy subject (pooled) safety dataset. See appendix 2.7.4.3.1 as an example on page 3611 in which creatine kinase results are not shown for placebo treatment condition/group and also for some other treatment conditions/groups. Note that these groups have results for other parameters but not for all parameters. Look at page 3627 in Appendix 2.7.4.3.2 for another example where creatine kinase and other parameters are not shown for the "Pali IR" subgroup but results on some other parameters are shown.

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A Question to Which a Response was Submitted (N007 6/27/06)

During the 15 May 2006 teleconference, the FDA requested the following information:

Please provide a listing of subjects with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension, and syncope (asymptomatic at baseline) for all safety datasets through November 1, 2005. For those subjects with serious adverse events, deaths, or discontinuations due to adverse events, it was agreed that existing narratives previously submitted to the NDA would be provided with the response to this request.

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/s/

Karen Brugge
8/1/2006 03:04:13 PM
MEDICAL OFFICER

This is to document all our Qs on the
NDA, as you requested me to do

Ni Aye Khin
8/2/2006 03:12:06 PM
MEDICAL OFFICER

NDA 21999 N000

The following summarizes meeting notes by the undersigned (Team Leader, Dr. Ni Khin concurred on the minutes below) in which the sponsor provided further clarification on their methods in finding uncpatured subjects in the results on suicidality (after the undersigned reviewer reviewed their N005 response to our question related to this topic):

In our Tcon today at 1:30 pm with Dr. Michelle Kramer and Heddie, Dr. Kramer explained to us (Drs. Ni Khin, Team Leader and Dr. Karen Brugge, reviewer) that all CIOMS forms (so any and all SAEs) of the Phase III trials were reviewed for any comments of suicidality, aggression or agitation that may have been written on the CIOMS forms by the investigator. If such comments were found in a given CIOMS but were not coded in the CRFs as suicidality-related AEs or SAEs, then the investigator was asked why (by the sponsor). If the investigator did not think it should be coded as a separate AE or SAE, then comments were transferred over to the comment section of the CRFs but were not coded as AEs or SAEs and were therefore not captured in their AE, ADO or SAE database. Therefore, if for example a given patient had suicidality related events (e.g. complained of suicidal thoughts) but the investigator thought it was part of there overall clinical condition or that it was adequately captured by another SAE term (e.g. exacerbation of schizophrenia) then suicidality was not coded and captured in the database as an SAE or AE of suicidality.

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/s/

Karen Brugge
7/21/2006 07:55:31 PM
MEDICAL OFFICER

Ni Aye Khin
7/24/2006 12:20:42 PM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 6, 2006

TO: Keith Kiedrow, Pharm.D., Regulatory Project Manager
Karen Brugge, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-999

APPLICANT: Johnson and Johnson

DRUG: ██████████ (Paliperidone)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of schizophrenia.

CONSULTATION REQUEST DATE: February 14, 2006

DIVISION ACTION GOAL DATE: July 8, 2006

PDUFA DATE: September 30, 2006

I. BACKGROUND:

Paliperidone was studied to evaluate its safety and efficacy, relative to placebo, in the treatment of subjects with schizophrenia. Dr. Himasiri DeSilva and Dr. Gregory Kaczynski's sites were selected for inspection due to large enrollment in protocols R076477-SCH-304 and R076477-SCH-305 respectively. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The following protocols were audited: R076477-SCH-304 entitled "A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Extended Release OROS® Paliperidone (6 and 12 mg/day) and Olanzapine (10 mg/day), with Open-label Extension, in the Treatment of Subjects with Schizophrenia" and # R076477-SCH-305 entitled "A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages

of Extended Release OROS® Paliperidone (3, 9 and 15 mg/day) and Olanzapine (10 mg/day), with Open-label Extension, in the Treatment of Subjects with Schizophrenia.”

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Dr. Himasiri DeSilva	Santa Ana, CA	R074677-SCH-304	Mar. 22-Apr.3, 2006	5/10/06	NAI
Dr. Gregory Kaczinski	Little Rock, AR	R074677-SCH-305	Apr. 7-19, 2006	Pending	Pending-NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations fro regulations. Data unreliable.

A. Protocol # R076477-SCH-304

1. Dr. Himasiri DeSilva
Clinical Innovations
801 N. Tustin Ave., Suite 600
Santa Ana, CA 92705

a. What was inspected: Dr. DeSilva enrolled 32 subjects. The inspection encompassed an audit of 16 subjects' records. Primary endpoint efficacy data were verified for 22 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data from this site are acceptable.

B. Protocol # R076477-SCH-305

1. Dr. Gregory Kaczinski
801 Scott Street
Little Rock, AR 72201

The following information for Dr. Kaczinski is based on communication from the field investigator. The establishment inspection report (EIR) for Dr. Kaczinski's site has not yet been received. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. What was inspected: Dr. Kaczinski enrolled 19 subjects. The inspection encompassed an audit of all 19 subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: none

c. General observations/commentary: No deviations from FDA regulations were observed.

d. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, inspection of Drs. DeSilva and Kaczinski revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Data from these three clinical investigators are acceptable in support of NDA 21-999.

Note: The information noted above for Dr. Kaczinski's site is based on communication from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Sherbert Samuels
7/7/2006 12:13:15 PM
CSO

Constance Lewin
7/7/2006 01:13:21 PM
MEDICAL OFFICER

Meeting Minutes

Meeting Date: 5-17-04
Location: WOCII - Rm 4028
IND: 65,850
Drug: Paliperidone Oros
Sponsor: J&J
Type of Meeting: With Sponsor
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Steven D. Hardeman, R.Ph.

Participants: see attached.

Discussion Points (bullets):

The following minutes were prepared by J&J and will be archived as official minutes of this meeting.

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Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Regulatory Affairs

Record of Contact

EDMS-PSDB-3599582

Date of Contact: 17 May 2004

Date of Report: 28 June 2004

Government Agency/Division:
Center for Drug Evaluation and
Research/Division of
Neuropharmacological Drug Products

Product: Extended-Release OROS®
Paliperidone
Reference No: R076477
IND No.: 65,850

FDA Contact:
Name: Stephen Hardeman, R.Ph.
Title: Sr. Regulatory Project Manager

J&JPRD Representative:
Name: Beth Geter-Douglass, Ph.D.
Title: Associate Director, Regulatory
Affairs

Subject: Minutes of the May 17, 2004 hepatic/drug-drug interaction
meeting

J&JPRD Participants:

Global Regulatory Affairs:	Kathleen Basmadjian, Ph.D.
US Regulatory Affairs:	Beth Geter-Douglass, Ph.D.
Pharmacokinetics:	Sandra Boom, Ph.D.
Global Preclinical Development:	Patrick Sterkens, I.R.
Global Clinical Development:	Marielle Eerdeken, M.D.
FDA Liaison:	Toni Marie Nearing-Crowley

FDA Participants:

Division Director:	Russell Katz, M.D.
Biopharmaceutics Team Leader:	Ray Baweja, M.D.
Psychopharmacology Team Leader:	Paul Andreason, M.D.
Senior Regulatory Project Manager:	Steve Hardeman, R.Ph.

Meeting Objective:

The objectives of the meeting were to reach consensus on:

- the proposal to continue the analysis of paliperidone using nonenantioselective bioanalysis methods for the plasma samples collected during phase 3 efficacy studies.
- the interpretation of newly generated data on the absorption, metabolism and excretion of paliperidone in addition to the risperidone data to support our proposals for labeling and for concluding that individual metabolic drug-drug interaction studies are not necessary for registration.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

EDMS-PSDB-3599582

- the appropriateness of the previously conducted study in subjects with hepatic impairment administered risperidone to support paliperidone product labeling.

Executive Summary:

FDA agreed with our proposal to use achiral bioanalytical methods for the phase 3 studies.

FDA requested that we conduct in vitro cytochrome interaction studies including paliperidone concentration to a maximum of 20 times the therapeutic concentration. If these in vitro studies do not show interactions at paliperidone concentrations up to 20 times the therapeutic concentration, then in vivo studies are not necessary.

FDA stated that the risperidone hepatic impairment study does not meet the current guidance and a specific paliperidone study is recommended using a reduced study design.

Minutes:

FDA agreed with our proposal to use achiral bioanalytical methods for the Phase 3 studies.

We discussed the interpretation of the absorption, metabolism and excretion of paliperidone data in addition to relevant risperidone data. FDA commented on the following points:

- FDA noted that the in vitro cytochrome interaction studies were all conducted at supra-therapeutic concentrations. FDA requested that we conduct in vitro cytochrome interaction studies including paliperidone concentration up to a maximum of 20 times the therapeutic concentration. If these in vitro studies do not show interactions at paliperidone concentrations up to 20 times the therapeutic concentration, then in vivo studies are not necessary.
- FDA queried whether the presented human data on the relationship between paliperidone pharmacokinetics and CYP2D6 pheno/genotype was sufficiently robust to rule out clinically significant CYP2D6 involvement in the overall pharmacokinetics of paliperidone.
- We discussed with the agency the population pharmacokinetic analysis from the RISPERDAL bipolar filing related to the interaction between carbamazepine and risperidone and paliperidone. The data suggest the lack of interaction between paliperidone and carbamazepine. The agency was not in the position to discuss that data at the meeting given that in the previous submission, they had not reviewed it with paliperidone in mind. Our proposed approach seemed reasonable to FDA. FDA requested that we submit the data

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EDMS-PSDB-3599582

in the paliperidone registration file if we want to use it to support the paliperidone labeling. FDA will then review as part of the NDA review our argumentation for the use of the study and the study data to support paliperidone labeling.

- FDA queried the relevance of drug interaction studies conducted with 1 mg of risperidone given that the exposure anticipated with ER OROS paliperidone is greater than that obtained after the 1 mg dose of risperidone. J&JPRD emphasized that the greatest test sensitivity is observed when in vivo drug interaction studies are conducted with the enzyme inhibitor/inducer at high therapeutic doses and the test drug at a low dose. Using this paradigm allows the maximum percent change in the metabolism of the test drug to be observed. FDA accepted this logic. They requested to submit all risperidone interaction studies that we want to use to support the paliperidone labeling in the paliperidone registration file with our interpretation of the data and rationale for its applicability to paliperidone. FDA will then review our proposed use of these studies to support paliperidone labeling as part of the NDA review.
- FDA referred to the drug-drug interaction guidance for the appropriate language to be used in product labeling based on in vitro data only.

With respect to the need for conducting interaction studies between paliperidone and other drugs on protein binding, the FDA requested that we sub-fractionate paliperidone binding to individual plasma proteins (specifically to alpha₁ acid glycoprotein) at three paliperidone concentrations.

For the renal interaction study, FDA accepted trimethoprim as an appropriate organic cation transport inhibitor. FDA mentioned that we could consider the use of lithium although they are aware of the limitations of the use of this cation transport inhibitor.

FDA stated that they consider hepatic metabolism important for paliperidone. Therefore, they recommended that we conduct a hepatic impairment study using a reduced design (per FDA guidance, "Guidance for Industry: *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*", May 2003) with paliperidone given that the previously conducted risperidone study does not meet current standards with respect to the classification of hepatic impairment according to Child-Pugh. FDA agreed with our proposal to use otherwise healthy subjects (age and gender matched) and an immediate release paliperidone formulation.

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/s/

Steve Hardeman
3/3/2006 01:39:06 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,850

Janssen, L.P.
C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Heddie Martynowicz, M.S., Director Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Martynowicz:

Please refer to the teleconference meeting between representatives of your firm and FDA on February 16, 2006. The purpose of this meeting was to seek concurrence on the content and format of the planned submission for a longer-term efficacy indication.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

DSI CONSULT: Request for Clinical Inspections

Date: February 13, 2006

To: Constance Lewin, M.D., Acting Branch Chief, GCP1, HFD-45
Joanne L. Rhoads, M.D., Branch Chief, GCP2, HFD-45

From: Keith Kiedrow, Pharm.D., Regulatory Project Manager, HFD-130
Division of Psychiatry Products

Subject: **Request for Clinical Site Inspections**
NDA 21-999
Johnson and Johnson
— (paliperidone) Tablets

Protocol/Site Identification:

As we have discussed, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Dr. Gregory Kaczinski 801 Scott Street Little Rock, AR 72201	R074677- SCH-305	19 subjects	Schizophrenia
Dr. Himasiri DeSilva Clinical Innovations 801 N. Tustin Ave. Suite 600 Santa Ana, CA 92705	R074677- SCH-304	32 subjects	Schizophrenia

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by July 8, 2006. We intend to issue an action letter on this application by September 30, 2006. The PDUFA due date for this application is September 30, 2006.

NDA 21-999

Request for Clinical Inspections

 (paliperidone) Tablets

Should you require any additional information, please contact Keith Kiedrow, Pharm.D., at 301-796-1924 or via email at keith.kiedrow@fda.hhs.gov.

Concurrence: (if necessary) see:

Karen Brugge, M.D., Medical Reviewer

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/s/

Keith Kiedrow
2/14/2006 10:15:33 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-999

Janssen, L.P.
C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Heddie Martynowicz, M.S., Director Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Martynowicz:

Please refer to your November 30, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (paliperidone) Extended Release Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 29, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
2/2/2006 12:24:20 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
HFD- 420
Division of Medication Errors and Technical Support (DMETS)
Attention: Diane Smith

FROM:
HFD-130 / Division of Psychiatry Products
Keith Kiedrow, Regulatory Project Manager

DATE January 20, 2006	IND NO.	NDA NO. 21,999	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT November 30, 2005
NAME OF DRUG ██████████ (paliperidone)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Schizophrenia	DESIRED COMPLETION DATE July 22, 2006

NAME OF FIRM: Janssen LP

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the attached submission that contains Janssen's new drug application for paliperidone, which can be found at the following link - [\\CDSESUB1\EVSPROD\N021999\0000](#). The Division requests feedback regarding this submission. If you have any questions, please contact Keith Kiedrow at 301-796-1924 or keith.kiedrow@fda.gov.
Thanks!

SIGNATURE OF REQUESTER
LT Keith Kiedrow, Pharm.D.
Regulatory Project Manager
301-796-1924
keith.kiedrow@fda.gov

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Keith Kiedrow

1/20/2006 04:42:00 PM



NDA 21-999

NDA ACKNOWLEDGMENT

Janssen, L.P.
C/O Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Heddie Martynowicz, M.S., Director Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Martynowicz:

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

Name of Drug Product: ; (paliperidone) Extended Release Tablets
Review Priority Classification: Standard
Date of Application: November 30, 2005
Date of Receipt: November 30, 2005
Our Reference Number: NDA 21-999

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 29, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 30, 2006.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 21-999

Page 2

If you have any questions, call LT Keith J. Kiedrow, Pharm.D., Regulatory Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

LT Keith J. Kiedrow, Pharm.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

Keith Kiedrow
12/13/2005 10:03:46 AM

which the results are positive on both primary and secondary endpoints. It was noted that, of course, the sponsor could include in their analysis plan other methods for evaluating other secondary endpoints of interest for non-US registration. However, we noted that we would not be reviewing this aspect of the plan and that our agreement refers only to the plan as outlined in these minutes.

- We indicated that the sponsor may include (in the NDA submission) an analysis of other secondary endpoints to be utilized for registration in countries outside the U.S., however, we will not review those data and any findings based on the results of such analyses will not be included in labeling.

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/s/

Thomas Laughren
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MEMORANDUM OF MEETING MINUTES

Meeting Date: April 25, 2003
Location: WOC II - 4th Floor Conference Room
Application: IND 65,850 (Paliperidone OROS)
Type of Meeting: Pre-Phase III
Chair: Russell Katz, M.D.
Recorder: Steve Hardeman, R.Ph.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

- See attached sponsor minutes

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

- See attached sponsor minutes

BACKGROUND: Johnson & Johnson requested a meeting to discuss their proposed nonclinical and clinical drug development plans.

Meeting:

email to Claude McGowan 7-1-04:

On page 5 of your minutes, Dr. Freed amended our response to question 3 (last sentence) to strike out "not only by mean scores but also"

The sentence now reads as follows:

"V/hen asked, FDA replied that the histopathology data should be presented by individual incidence."

She added the following sentence as the last sentence.

"Mean scores are acceptable when provided in addition to incidences, but not as the sole summary of histopathology data."

Attachment:

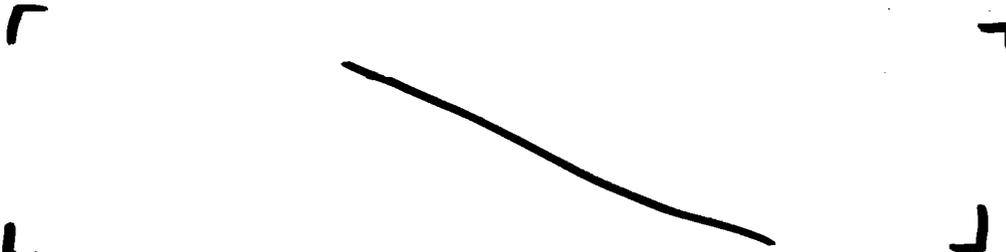
Sponsor Meeting Minutes

Extended-Release OROS® Paliperidone
IND 65,850
Minutes of the April 25, 2003 Pre-Phase 3 Meeting with FDA

Executive Summary

- In general, FDA noted that the J&JPRD briefing document did not present a clear picture of how exposures with OROS® paliperidone formulations compare with the paliperidone exposure derived from treatment with risperidone.
- Availability of human exposure data will have an impact on the preclinical program requirements. J&JPRD will need evidence of a similar enantiomeric conversion of paliperidone after paliperidone administration when compared with oral risperidone administration.
- J&JPRD's response to FDA's request for additional human data on OROS® paliperidone exposure will impact FDA's response the question of adequacy of chronic non-rodent (dog) toxicity requirements, adequacy of preclinical data for registration and whether a carcinogenicity study with paliperidone is required.
- The genotoxicity proposal is inadequate for paliperidone. The studies completed with paliperidone (Ames Test and Mouse Lymphoma Assay) will have to be repeated and an *in vivo* micronucleus test will need to be added to the battery of tests.
- The peri-natal developmental data cannot be bridged from the risperidone study for paliperidone. A peri-natal study will therefore be required.
- A food effect study, at the highest dose strength of OROS® paliperidone that will be used in the targeted population, should be done in patients even if dose-linearity of the formulation can be shown.
- FDA would not comment on the need for a study in hepatically impaired patients without having more data available from the paliperidone metabolism (AME) study.
- The approach proposed by J&JPRD regarding drug interaction studies with paliperidone and drugs metabolized by the liver could (tentatively) be possible but J&JPRD needs more data, FDA would be available for a telephone conference to discuss this after J&JPRD submits the results of the AME study.
- There are no specific drug interaction requirements. However, if there is an *in vitro* prompt (signal) or a concomitantly administered drug intended to be included in the product labeling, then an *in vivo* study will be required. FDA is willing to have a teleconference with J&JPRD once results are available from the AME study performed to confirm whether any interaction studies are needed.

- J&JPRD will need to demonstrate that a single high-dose OROS[®] paliperidone tablet strength performs pharmacokinetically the same as multiples of lower OROS[®] paliperidone tablet strengths.
- Convincing evidence that steady-state exposures to paliperidone after administration of the highest approved oral RISPERDAL[®] dose are greater than the steady-state exposures obtained with the highest proposed OROS[®] paliperidone doses to be used in phase 3 studies is needed prior to initiating phase 3.
- FDA would like to see a description in the Investigator's Brochure of the results of study R076477-INT-1 in which QTc prolongation (> 60 msec), supine heart rate changes, and higher incidence of orthostatic intolerance were recorded. FDA and requested that J&JPRD provide additional data from the ongoing R076477-SCH-101 study to support cardiovascular safety.
- The ICH numbers for total patient exposure and safety data appear to be okay. However, the number of patients treated long-term should be at therapeutic doses.
- Assuming that the pivotal studies are positive, FDA agreed that data from placebo-controlled trials together with safety data from open-label and geriatric trial would likely be acceptable to support product registration.
- The inclusion of the results of secondary endpoint analysis in the product labeling may be possible if it based on a reasonable analysis plan. J&JPRD and FDA should agree on analysis plan beforehand and these secondary endpoints should be of a different domain than the primary endpoints.

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- The proposed trial in geriatric patients is acceptable but no efficacy information would be allowed in the product label. FDA suggested J&JPRD consider including elderly patients in the controlled trials (n=100, 25/arm) or make the proposed geriatric trial a controlled trial.
 - The proposal for pediatric trials (request waiver for schizophrenic patients aged 12 years and younger and request a deferral from conducting schizophrenic trials in patients aged 13-17 until completion of the Phase 3 program) was acceptable.

Detailed Summary

On April 25, 2003, Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) participated in a Type B meeting with the Division of Neuropharmacological Drug Products (DNDP) and representatives from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The purpose of the meeting was to discuss and reach consensus on the proposed nonclinical and clinical drug development plan for extended-release OROS[®] paliperidone. The FDA representatives were provided a briefing document prior to the meeting that contained questions and supporting rationale for Pre-Clinical, Clinical PK/PD and Efficacy and Safety issues pertinent to the development program. FDA and J&JPRD participants in the meeting are listed below.

J&JPRD Participants:

Srdjan Stankovic, MD	Global Clinical Leader
Nancy Van Osselaer, PhD	Global Clinical Pharmacokinetics
Patrick Sterkens, IR	Global Preclinical Development
Krishna Talluri, MD	Project Physician
Megan Zoschg, PharmD	US Regulatory Affairs Liaison
Peter Briscoe, MD	Compound Development Team Leader
Toni-Marie Nearing	FDA Liaison
Pilar Lim, PhD	Global Biostatistics
Kathleen Basmadjian, PhD	Global Regulatory Affairs
Claude McGowan, PhD	US Regulatory Affairs Liaison

FDA Participants:

Russell Katz, MD	Division Director
Lois Freed, PhD	Pharmacology/Toxicology Team Leader
Paul Andreason, MD	Psychopharmacology Team Leader
Ray Baweja, PhD	Biopharmaceutics Team Leader
Karen Brugge, MD	Medical Reviewer
Steve Hardeman, RPh	Sr. Regulatory Project Manager

Meeting Highlights

Provided below is a summary of the outcome of the meeting. For ease of review, the questions submitted in the briefing document are first stated followed by the major points made during the discussion for each question. In general, FDA noted that the J&JPRD briefing document did not present a clear picture of how exposures with OROS[®] paliperidone formulations compare with the paliperidone exposure derived from treatment with risperidone. If the paliperidone PK profile with the OROS formulation at the highest dose to be used in Phase 3 results in lower exposures (including both AUC and shape of curve over time) to paliperidone than those observed with risperidone treatment at the highest registered dose of 16mg, FDA is willing to consider some of our bridging proposals and safety assumptions. If the PK profile of paliperidone demonstrates higher exposures with OROS[®] paliperidone than with the highest approved Risperdal dosage regimen it will impact on the FDA's position on safety requirements.

Pre-clinical Questions

General Issues: In general, availability of human exposure data will have an impact on the preclinical program requirements. FDA wants a clearer description of the relationship between paliperidone exposures achieved with OROS® paliperidone administration compared to paliperidone exposure achieved with risperidone administration, at the highest phase 3 and approved doses, respectively. J&JPRD will also need evidence of a similar enantiomeric conversion of paliperidone after paliperidone when compared with administration of oral risperidone. Lastly, there should be no new metabolites following administration of paliperidone when compared to risperidone.

In toxicokinetic studies, FDA asked that J&JPRD not use active moiety concentrations but to provide data on risperidone and paliperidone concentrations separately.

Question 1: Based on the preclinical bridging strategy to risperidone, J&JPRD considers the 12-month, repeated-dose toxicity study with risperidone in dog, together with the planned 6-month toxicity study with paliperidone in rat, sufficient to meet ICH guidelines and to support the Phase 3 development program with extended-release OROS® paliperidone (up to 58 weeks of exposure).

Does the Division agree?

FDA Response:

J&JPRD's response to the request for additional human data on OROS® paliperidone exposure will impact FDA's response to this issue.

FDA noted that we would need to submit additional toxicokinetic data as the 12-month dog study with risperidone was conducted by administering a gelatin-capsule while the comparative paliperidone versus risperidone study was performed with oral solution.

Question 2: Does the Division agree that the completed and planned preclinical toxicity studies with paliperidone, supplemented by the extensive preclinical toxicity evaluation of risperidone, are adequate for registration?

FDA Response:

J&JPRD's response to the request for additional human data on OROS® paliperidone exposure will impact FDA's response to this issue.

FDA provided comments on the proposed preclinical program for paliperidone based on the list of studies in Table 1 of the briefing book. For details, see questions as indicated:

- Chronic dog study (see question 1)
- Carcinogenicity studies (see question 3)

- Genotoxicity studies (see question 4)
- Reproduction toxicity studies (see question 5)

The single dose data are sufficient. The repeated dose 6-month rat and 3-month mouse studies will fill the gap in rodent toxicity studies. Dietary administration in rodent studies would give a profile closer to that anticipated with an extend-release oral formulation, provided that the exposure remained adequate.

FDA noted that J&JPRD will need to submit the results of the OROS[®] single-dose dog study before advice can be given, and that the additional bridging study, if required, will be a 3-month OROS[®] study not a 1-month OROS[®] study as J&JPRD proposed.

Question 3: Does the Division agree that results of the rat and mouse carcinogenicity studies with risperidone are sufficient for the registration of paliperidone, pending results demonstrating a similar profile of pre-neoplastic lesions for paliperidone and risperidone in the 6-month rat study, and a similar toxicological profile for paliperidone and risperidone in the 3-month mouse study?

FDA Response:

J&JPRD's response to the request for additional human data on OROS[®] paliperidone exposure will impact FDA's response to this issue. It is too early to address the carcinogenicity requirements due to lack of data. FDA is open to discussing these requirements after the results of the 3-month mouse and 6-month rat studies and additional human data (noted above) are provided.

When asked, FDA replied that the histopathology data should be presented not only by mean scores but also by individual incidence.

Question 4: Does the Division agree that no additional *in vitro* or *in vivo* genotoxicity studies with paliperidone are required for registration?

FDA Response:

The genotoxicity proposal is inadequate for paliperidone. The studies completed with paliperidone (Ames Test and Mouse Lymphoma Assay) are not acceptable according to the ICH guidelines. The Ames Test needs to carry into the range of precipitation; Mouse Lymphoma Assay needs to be repeated with a higher concentration in order to achieve sufficient levels of cytotoxicity. In addition, an *in vivo* micronucleus test will need to be added to the battery of tests.

Question 5: Does the Division agree that no rat pre- and postnatal developmental toxicity study with paliperidone is required for registration?

FDA Response: The peri-natal developmental data cannot be bridged from the risperidone study. Data with paliperidone itself need to be generated. A peri-natal study will therefore be required.

FDA questioned whether J&JPRD had followed-up on the literature report (see meeting minutes from the R09670 pre-IND meeting of August 1, 2000) describing neurotoxicity findings in monkeys treated with antipsychotic drugs. J&JPRD agreed to follow-up.

Clinical Pharmacokinetics/Pharmacodynamics Questions:

General Issues: Data investigating the highest dose strength of the formulation that will be used in the Phase III program must be provided. It is not sufficient to investigate the multiples of the lower dose strength. Although immediate release paliperidone has linear kinetics, this does not imply linear kinetics with the paliperidone OROS formulation at all dose strengths. Data have to be provided to demonstrate that at higher dose strengths the bioavailability is the same.

Question 6: Does the Division agree that the effect of food on the bioavailability of extended-release OROS[®] paliperidone is sufficiently demonstrated in study C-2002-034, in which 4 mg extended-release OROS[®] paliperidone was administered as 2 tablets of 2 mg to healthy subjects in a fasting state and after a high-fat breakfast, and that no additional studies are required for registration?

FDA Response:

FDA requested a food effect study at the highest dose strength of OROS[®] paliperidone that will be used in the targeted patient population, even if dose-linearity of the formulation can be shown. This study should be done in patients because of tolerability issues in healthy volunteers. J&JPRD must also demonstrate dose-proportionality for all OROS[®] tablet strengths (not just the dose) and the bioavailability should be compared to a reference immediate release (IR) paliperidone, even if an IR paliperidone formulation will never be marketed. FDA agreed to discuss study design of the dose-proportionality and food effect investigation at a future meeting/teleconference, possibly the planned meeting with the DNDP Chemistry and OCBP Biopharmaceutics Reviewers.

Question 7: Does the Division agree that no studies with paliperidone in hepatically-impaired patients are required for registration?

FDA Response:

FDA would not comment on this query without having more data available from the paliperidone metabolism (AME) study.

Question 8: Does the Division agree, pending results demonstrating that metabolism accounts for less than 30% of paliperidone elimination, that no metabolic drug-interaction studies with paliperidone and drugs metabolized by the liver are required for registration?

FDA Response:

J&JPRD needs more data, but the proposed approach could (tentatively) be possible. FDA would be available for a telephone conference to discuss this after J&JPRD submits the results of the AME study.

Question 9: Does the Division agree that no drug interaction studies with paliperidone and digoxin or warfarin are required for registration?

FDA Response:

There are no specific drug interaction requirements. However if there is an *in vitro* prompt (signal) or a concomitantly administered drug intended in the product labeling, then an *in vivo* study will be required. FDA is willing to have a teleconference with J&JPRD once results are available from the AME study performed to confirm whether any interactions studies are needed.

Efficacy and Safety Questions:

General Issues: FDA raised concern that J&JPRD had no experience with the high doses proposed for the Phase 3 trials (up to 18 mg). The 2 critical issues were:
1) What data do J&JPRD have to demonstrate that an OROS[®] paliperidone tablet strength will perform pharmacokinetically the same as multiples of lower OROS[®] paliperidone tablet strengths? FDA noted that the presumed linearity (dose vs. dosage formulation) "seems to be a leap of faith". 2) Concern was expressed about both the AUC and the shape of the curve and attempts to go from 6 days at 12 mg (given as 6 tablets of 2 mg OROS[®] paliperidone in R076477-SCH-101) to 18 mg for 58 weeks was considered very ambitious.

J&JPRD should provide convincing evidence that steady-state exposures to paliperidone after administration of the highest approved oral RISPERDAL[®] dose are greater than the steady-state exposures obtained with the highest proposed OROS[®] paliperidone doses to be used in phase 3 studies. J&JPRD pointed out that paliperidone doses planned in the phase 3 program are substantively lower than the highest approved risperidone doses (based on bioavailability and pharmacological equivalency). In addition, patients on strengths higher than 12 mg would be titrated up to the higher strength and that information on this dose (i.e. 12 mg) will be available from the R076477-SCH-101 study. It was also clarified that the 12 mg strength studied in R076477-SCH-101 was not with 12 mg OROS[®] paliperidone, but rather with 6 tablets of 2 mg OROS[®] paliperidone. FDA noted that the above arguments were based on inferential logic but insufficient empirical data were presented to support the arguments. FDA also noted that information from the R076477-SCH-101 study will be helpful but this will not resolve concerns that 12 mg dose in this study is with 6 tablets of 2 mg OROS[®] paliperidone and it will not provide information on the higher dosage strengths.

FDA also referenced the R076477-INT-1 study results in which QTc prolongation (> 60 msec), supine heart rate changes, and higher incidence of orthostatic intolerance were recorded in an appendix but not mentioned either in the clinical study report or the Investigator's Brochure (IB). Therefore FDA would like to see these results in the IB and requested that J&JPRD provide additional data from the ongoing R076477-SCH-101 study to support cardiovascular safety. J&JPRD noted that data are being collected in the ongoing R076477-SCH-101 orthostatic tolerability study. FDA agreed to a teleconference once we had results from R076477-SCH-101.

Question 10: J&JPRD considers tolerability data with paliperidone from Phase 1/2 studies, together with substantial evidence of the safety of risperidone in patients with schizophrenia, sufficient to support the Phase 3 development program with extended-release OROS[®] paliperidone.

Does the Division agree with this assessment?

FDA Response:

Additional data are needed to assess whether sufficient steady-state OROS[®] paliperidone data exists at the highest dose strength to support initiating the proposed Phase 3 program. FDA expressed concern that prior to entry into Phase 3, J&JPRD would not have data on either the highest tablet strength (i.e., 9 mg state OROS[®] paliperidone) or the highest dose (18 mg) proposed for use in phase 3. FDA requested that J&JPRD submit data comparing the steady-state exposure of paliperidone after administration of the highest dose to be used in phase 3 to that of the paliperidone after administration of the highest approved dose of RISPERDAL[®]. The FDA prefers that these comparisons be done in a head-to-head study (highest OROS[®] paliperidone strength versus 16 mg oral RISPERDAL[®]).

Question 11: Does the Division consider the total patient exposure and safety data sufficient for filing the NDA?

FDA Response:

The ICH numbers appear to be achieved so this is probably okay. However, the number of patients treated long-term should be at therapeutic doses.

Question 12: Does the Division agree that positive data from the placebo-controlled trials, together with safety data from the open-label extension trials and the geriatric trial, would be sufficient to support the registration of dosage strengths of 3, 6, 9, 12, ~~18~~ extended-release OROS[®] paliperidone?

FDA Response:

Assuming studies are positive, this is likely to be acceptable.

Question 13: In the proposed controlled clinical trials, J&JPRD is planning to measure and analyze a limited number of secondary endpoints. The proposed analyses will be conducted within predefined statistical principles.

Does the Division agree that the results of these analyses could be included in the product label?

FDA Response:

This is possible if it based on a reasonable analysis plan. J&JPRD and FDA should agree on analysis plan beforehand. The secondary endpoints should be of a different domain than the primary endpoints.

FDA Response:

The FDA expressed no concerns with respect to J&JPRD's proposal.

B) Does the Division agree with the time to first recurrence of psychotic symptoms as the primary efficacy endpoint in the relapse prevention trial?

FDA Response:

The FDA expressed no concerns with respect to J&JPRD's proposal.

C) Does the Division agree that the design of the relapse prevention trial is adequate to establish dosing recommendations for extended-release OROS® paliperidone in the maintenance treatment of schizophrenia?

FDA Response:

The stabilization period is of concern. The proposed 14 weeks (8wks + 6 weeks) is acceptable although it was suggested that 6 months duration of the stabilization period is scientifically more desirable.

Question 15: Does the Division agree that the proposed trial in geriatric patients will provide supportive safety and pharmacokinetic information for use of extended-release OROS[®] paliperidone in this population?

DNDP Response:

The proposed plan is acceptable, however, no efficacy information will be included in the product label. FDA suggested that J&JPRD consider including elderly patients in the controlled pivotal trials (e.g. n=100, 25 per arm) or to make the proposed elderly trial a controlled trial. Otherwise it will be difficult to interpret the results from the proposed open-label trial. In terms of duration, FDA agreed that 6 months would be sufficient but preferred a longer period (e.g., 1 year).

Question 16: In accordance with the Pediatric Rule (21 CFR 314.55), J&JPRD requests a waiver for conducting trials in schizophrenia patients aged 12 years and younger, and requests a deferral from conducting trials in schizophrenia patients aged 13-17 years until completion of the Phase 3 program in adult schizophrenic patients.

FDA Response:

The waiver request was granted. The proposal to defer studying the adolescent patients was accepted. FDA noted that adolescent PK results would not be described in the labeling until controlled study information is reviewed.

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/s/

Steve Hardeman
5/26/04 02:22:23 PM

From: Hardeman, Steven D
Sent: Wednesday, February 11, 2004 8:18 AM
To: Oliver, Thomas F
Subject: FW: IND 65,850 Agreement on Choice of Starting Materials

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

From: McGowan, Claude [PRDUS] [mailto:CMcgowa@PRDUS.JNJ.COM]
Sent: Tuesday, February 10, 2004 3:16 PM
To: 'hardemans@cder.fda.gov'
Subject: IND 65,850 Agreement on Choice of Starting Materials

Dear Steve,

Please forward this e-mail to Dr. Thomas Oliver because my secure e-mail will not allow me to send it to him directly. Thanks, Claude.

Dear Dr. Oliver,

Reference is made to a telephone conversation today, February 10, 2004 between Dr. Thomas Oliver, DNDP Chemistry Team Leader, and Ms. Dawn Kracht of J&JPRD. Below please find a summary of the discussions and agreements made during our telephone conference.

Dr. Oliver phoned as a follow-up to J&JPRD's correspondence dated January 19, 2004 (serial no. 032) concerning the proposed starting materials in the synthesis of paliperidone.

Dr. Oliver informed Ms. Kracht that, based on the scientific package submitted, together with the proposal for starting material specifications, the Division agrees with J&JPRD's choice of [REDACTED] as starting materials in the synthesis of paliperidone.

As part of these discussions, Dr. Oliver suggested that J&JPRD include the IND correspondence of January 19, 2004 (serial no. 032), together with documentation of this telephone contact whereby FDA has agreed to J&JPRD's choice of starting materials, as part of the NDA submission.

If you have any questions, please feel free to contact Dawn Kracht at (609) 730-3082.

Sincerely,

Claude McGowan, Ph.D.
Associate Director, Regulatory Affairs
J&J Pharmaceutical Research & Development
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/s/

Thomas Oliver
2/17/04 11:12:45 AM
CHEMIST