CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-999

APPROVAL LETTER

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) dated and received November 30, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega (paliperidone) 3, 6, 9, 12 mg Extended-Release Tablets.

We acknowledge receipt of your submissions dated:

October 4, 2006	October 11, 2006	October 20, 2006	October 27, 2006
November 1, 2006	November 20, 2006	December 8, 2006	

The October 20, 2006 submission constituted a complete response to our September 29, 2006 action letter.

This new drug application provides for the use of Invega (paliperidone) Extended-Release Tablets for the treatment of schizophrenia.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling enclosed with this letter. Accordingly, this application is approved effective on the date of this letter.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate this submission "**FPL for approved NDA 21-999**." Approval of this submission by FDA is not required before the labeling is used.

We note that, at this time, you do not intend to market the 12 mg tablet strength. Therefore, we have not included this strength in the enclosed labeling.

Dissolution Methods and Specifications

We note your agreement during our December 14, 2006 teleconference to adopt the following dissolution methods and specifications for all tablet strengths:

The final regulatory dissolution method for all strengths of Paliperidone Extended Release tablets are shown in Table 1.

Table 1 Final Regulatory Dissolution Method and Specifications for Paliperidone Extended Release Tablets 3 mg, 6 mg, 9 mg, and 12 mg

Parameter	Dissolution Method and Specifications
Apparatus type:	USP Type VII Reciprocating Disk
Media:	NaCl 2 gm/L (0.2% w/w) in 0.0825 N HCl pH 1.0 ± 0.5
Volume:	50 ml
Temperature:	37 ± 0.5 °C
Frequency:	Agitation by Reciprocating Arm 30 cycles per minute (cpm)
Amplitude:	2 – 3 cm
Sampling Times:	2, 8, 14, 18, and 24 hours
Specifications (% of Label Claim)	2 hours [redacted] 8 hours [redacted] 14 hours [redacted] 18 hours [redacted] 24 hours [redacted]
Acceptance Criteria:	Conforms to USP XXVIIII <724> acceptance Table 1 for extended-release articles

Expiry

An 18 month expiry date, as requested, is granted based upon the available stability data.

Pediatric Research Equity Act (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 2 to 11 years and deferring pediatric studies for ages 12 to 17 years for this application.

Postmarketing Commitments

We remind you of your postmarketing study commitments agreed upon in your submission dated October 20, 2006. These commitments are listed below.

1. The pre- and postnatal developmental study in rats did not use high enough doses to adequately evaluate the effects of paliperidone on this phase of reproduction. You have agreed to repeat the study in postmarketing using doses that include a maximally tolerated dose for the dams.

Protocol Submission:	by January, 2007
Study Start:	by July, 2007
Final Report Submission:	by December, 2008

2. You have agreed to, within 3 months of approval, provide information that addresses the possibility that ethanol might result in dose dumping. This should include information on the solubility of the coating materials in ethanol, and information from other similar OROS formulations. If such information cannot exclude the possibility of dose dumping and/or is not available, you have agreed to conduct a dissolution experiment in ethanolic solutions and provide the results.

   Final Report Submission: by March, 2007

3. We note that in the one study that included a 3 mg dose of paliperidone ER, the dose was shown to be about as effective as higher doses. We therefore believe that you have not fully evaluated the lower end of the dose response curve. You have agreed to conduct a study to better explore for a minimal effective dose.

Protocol Submission:	by April, 2007
Study Start:	by November, 2007
Final Report Submission:	by January, 2011

4. Deferred pediatric studies under PREA

   Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

   Deferred pediatric studies under PREA for the treatment of adolescent schizophrenia ages 12 to 17 years, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

   Final Report Submission: by 12/2009

   Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

   Submit clinical protocols to your IND for paliperidone. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to The Division of Psychiatry Products and two copies of both the promotional materials and the package insert directly to:

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

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

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely yours,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple
12/19/2006 05:25:51 PM

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Janssen, L.P.
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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) dated November 30, 2005, received November 30, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for paliperidone 3, 6, 9, 12, 15 mg Extended-Release Tablets.

We acknowledge receipt of your submission as follows:

January 12, 2006	March 29, 2006	May 4, 2006	May 26, 2006
June 15, 2006 (2)	June 27, 2006	July 27, 2006	July 31, 2006
August 2, 2006	August 29, 2006	September 12, 2006	

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

Clinical Pharmacology and Biopharmaceutics

1. The proposed dissolution specifications are not acceptable. We are proposing the following specifications:

   2 hours
   8 hours
   14 hours [redacted]
   18 hours
   24 hours

We request that you adopt the following regulatory dissolution method and specifications for Paliperidone Modified Release Tablets, (see Table 1).

Table 1 Proposed Regulatory Dissolution Method and Specifications for Paliperidone Extended Release Tablets 3 mg, 6 mg, 9 mg, and 12 mg

Parameter	Proposed Dissolution Method and Specifications
Apparatus type:	USP Type VII Reciprocating Disk
Media:	NaCl 2 gm/L (0.2% w/w) in 0.0825 N HCl pH 1.0 ± 0.5
Volume:	50 ml
Temperature:	37 ± 0.5 °C
Frequency:	Agitation by Reciprocating Arm 30 cycles per minute (cpm)
Amplitude:	2 – 3 cm
Sampling Times:	2, 8, 14, and 18 hours
Specifications (% of Label Claim)	2 hours [redacted] 8 hours [redacted] 14 hours [redacted] 18 hours [redacted] 24 hours [redacted]
Acceptance Criteria:	Conforms to USP XXVIIII <724> acceptance Table 1 for extended-release articles

2. [redacted]

3. Our review suggests that there might be some advantage in terms of side effects for the (+) enantiomer compared to the racemate when both are administered as OROS formulations and this may be of interest to you. If pursued this review finding would need to be confirmed as well as possibly whether there is similar or differential efficacy.

4. Our review of the available information and your dose response analysis lead us to believe that it may be possible to predict who may be better or worse candidates for increasing or decreasing the dose from 6 mg in the case of an inadequate therapeutic response or unacceptable side effects. This may also be useful in obtaining an adequate therapeutic response more quickly as well as assuring who is likely to obtain a fair therapeutic trial before switching to another product. Additional analysis of samples for genotype as well as pharmacodynamic modeling would be needed to investigate this. We would be amenable to discussing this in the future.

Chemistry Manufacturing and Controls

1. As noted in comment 1 above, please update the release and stability specifications for the paliperidone drug product to include the recommendation made by Clinical Pharmacology and Biopharmaceutics.

2. Please also provide a revised post-approval stability protocol that includes 0-18 hr test data points for dissolution and all stability data at the 0-18 hr time points for the drug product.

Clinical

Please submit the ECG data for study SCH-1009 to FDA's ECG warehouse so the QT measurements on these ECGs can be verified.

Foreign Regulatory Update/Labeling

We require a review of the status of all paliperidone actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If paliperidone has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for paliperidone along with English translations when needed.

World Literature Update

Prior to the approval of paliperidone, we require an updated report on the world archival literature pertaining to the safety of paliperidone. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of paliperidone. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The

report should emphasize clinical data, but new findings in pre-clinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Labeling
Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

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

Safety Update

Our assessment of the safety of paliperidone is based on our review of all safety information provided in your original and subsequent submissions, including your safety update of December 31, 2005. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

Post Approval (Postmarketing) Commitments
We ask that you commit to examining the following four issues and submitting study reports for them post approval. For these postmarketing commitments for which we have not included a submission report date, please propose time frames for the submission of the reports following approval of the NDA.

1. The pre- and postnatal developmental study in rats did not use high enough doses to adequately evaluate the effects of paliperidone on this phase of reproduction. This study should be repeated in phase IV using doses which include a maximally tolerated dose for the dams.

2. Within 3 months of approval, you should provide information that addresses the possibility that ethanol might result in dose dumping. This should include information on the solubility of the coating materials in ethanol, and information from other similar OROS formulations. If such information cannot exclude the possibility of dose dumping and/or is not available, a dissolution experiment in ethanolic solutions should be performed and the results provided.

3 

4. We note that in the one study that included a 3 mg dose of paliperidone ER, that dose was shown to be effective. Thus, you have not fully evaluated the lower end of the dose response curve. Therefore, you should conduct a study to better explore for a minimal effective dose in phase IV.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We

will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment – labeling

27 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Approvable Letter- 1

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

/s/

Robert Temple
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