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
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