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APPLICATION NUMBER:

22-264

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-264

COMPLETE RESPONSE

Ortho-McNeil-Jansen Pharmaceuticals, Inc.
Attention: Rodney Malchow
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, N.J. 80560

Dear Mr. Malchow:

Please refer to your new drug application (NDA) dated October 25, 2007, received October 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega Sustenna (paliperidone palmitate) (b) (4)

We acknowledge receipt of your submissions dated:

| | | | |
|-------------------|----------------------|-----------------|-------------------|
| December 12, 2007 | December 21, 2007 | January 9, 2008 | February 21, 2008 |
| February 25, 2008 | February 27, 2008(2) | May 2, 2008 | May 12, 2008 |
| May 21, 2008 | May 28, 2008 | May 29, 2008 | June 2, 2008 |
| June 3, 2008 | June 13, 2008 | June 26, 2008 | July 2, 2008 |
| July 11, 2008 | July 15, 2008(2) | August 20, 2008 | |

We also acknowledge receipt of your amendment dated August 12, 2008, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. The Drug Master File (b) (4) for (b) (4) has been found to be inadequate to support the NDA.

2. It is FDA policy that the strength of the drug substance has to be provided as part of the established name. The proposal to just remove the reference to strength (mg) from the product name is not sufficient. The historical evidence provided to justify your proposal is not sufficient because most products listed were approved quite awhile ago and do not reflect current practices. According to information you provided in the original NDA submission “paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation”, which indicates that paliperidone palmitate is a prodrug and that the palmitate ester exerts a biopharmaceutic effect.
3. Establish an acceptance criteria equal to or less than ^(b)₍₄₎ ppm for the two genotoxic impurities, ^(b)₍₄₎ and ^(b)₍₄₎.
4. ^(b)₍₄₎
5. The syringe barrel should contain calibrated markings to indicate the appropriate volume of drug product in the syringe and allow for partial doses to be given from the syringe.
6. A transparent label that allows for the viewing of the syringe calibration marks and drug product should be used for labeling of the syringes.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Please submit draft carton and container labeling revised as follows:

Syringe Labeling

1. The product strength should be relocated so that it no longer appears to be part of the proprietary name (e.g., TRADENAME 25 mg). Instead, the product strength should follow or be immediately adjacent to the established name.
2. Express the strengths of the prefilled syringes in terms of milligrams per total volume (e.g., 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, and 100 mg/mL) to decrease the potential for dose calculation errors. This information should be displayed on the syringe label and immediately following or adjacent to the established name.
3. If space permits, ^(b)₍₄₎

[Redacted] (b) (4)

Carton Labeling

1. Revise the fonts of the proprietary and established names so that the established name is at least one half the size of the proprietary name per 21 CFR 201.10(g)(2).
2. The product strength should be relocated so that it no longer appears to be part of the proprietary name (e.g., TRADENAME 25 mg). Instead, the product strength should follow or be immediately adjacent to the established name.
3. Express the strengths of the prefilled syringes in terms of milligrams per total volume (e.g., 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, and 100 mg/mL) to decrease the potential for dose calculation errors. This information should be prominently displayed on the principal display panel immediately following or adjacent to the established name so that it is not overlooked by the reader.

4. [Redacted] (b) (4)

Dissolution Method and Specification

The following dissolution method and specification are acceptable for Invega Sustenna (paliperidone palmitate) [Redacted] (b) (4)

| Parameter | Dissolution Method and Specification | |
|---------------------|---|------------------------|
| Apparatus Type | USP Type II (paddle) | |
| Media | 0.001 M HCL containing 0.489% Polysorbate 20 (Tween®20) | |
| Volume | 900 ml | |
| Temperature | 25 ± 0.5 °C | |
| Frequency | 50 rpm | |
| Sampling Times | 8,20 and 45 minutes | |
| Acceptance Criteria | 8 minutes | (b) (4) of Label Claim |
| | 20 minutes | (b) (4) of Label Claim |
| | 45 minutes | (b) (4) of Label Claim |
| Analysis | HPLC UV detection | |

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Invega Sustenna, for

this product. However, if the product approval is delayed beyond 90 days of the review date, the proposed name must be resubmitted for evaluation.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

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

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301) 796-2201.

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

**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
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