

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-264**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 10, 2009

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Laura Pincock, R.Ph, PharmD, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Diane C. Smith, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Invega Sustenna (Paliperidone Palmitate) Injection  
25 mg, 50 mg, 75 mg, 100 mg and 150 mg

Application Type/Number: NDA 22-264

Applicant/Sponsor: Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals,  
Inc.

OSE RCM #: 2009-286

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## 1 EXECUTIVE SUMMARY

Invega Sustenna (Paliperidone Palmitate) is an extended release intramuscular injection for the acute and maintenance treatment of schizophrenia in adults. Invega Sustenna is a product line extension of Invega (Paliperidone) oral tablets. Paliperidone palmitate is an ester of paliperidone and is dosed based upon the palmitate ester according to CMC. As such, DMEPA considered the vulnerability of labeling the product strength based on the ester paliperidone palmitate as compared to labeling the product strength in terms of milligram equivalents of paliperidone.

The findings of our Label and Labeling Risk Assessment indicate that improvements can be made prior to approval to the presentation of the product strength, proprietary name, established name, and the dosage form statement on the container labels and carton labeling to provide consistency and reduce the likelihood of confusion. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

## 2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed the applicant's labels and labeling for the proposed name, Invega Sustenna, in OSE Review # 2008-117, dated August 5, 2008. This review noted the expression of strength on the labels and labeling was inconsistent with the dose provided in the Dosage and Administration Section of the labeling. Specifically, we recommended the Applicant avoid the term "milligram equivalents" or the abbreviation "mg eq". Subsequently on October 21, 2008, the applicant submitted a Complete Response Briefing Book, which contained justification to present the product strengths in terms of milligram (mg) paliperidone equivalent. The applicant noted that confusion could arise if the product strengths were presented in terms of paliperidone palmitate versus mg paliperidone equivalents.

## 3 MATERIALS REVIEWED

Revised container labels and carton labeling were submitted on February 2, 2009. The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of these labels and labeling. We also reviewed the justification provided by the Applicant contained in the Complete Response Briefing Book, dated October 21, 2008. See Appendix A through E for images.

## 4 DISCUSSION

The Applicant was requested to label this product using the "mg" amount of the ester paliperidone palmitate rather than the "mg equivalent" amount of paliperidone. Labeling the product in this manner would provide for strengths of 39 mg, 78 mg, 117 mg, 156 mg and 234 mg per syringe. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

DMEPA does not agree with the

Applicant's rationale. Using the term 'mg equivalent' is confusing and can lead to incorrect dosage calculations and conversions. Postmarketing experience with other products that express doses/strengths in terms of "equivalents" (e.g., Fosphenytoin equivalents) demonstrates such confusion. Furthermore, there is no existing data (of which FDA is aware) that any particular 'even' strengths, are 'more identifiable' than other strengths. Thus, we additionally do not agree with the Applicant's rationale to [REDACTED] (b) (4)

In a meeting with the Division of Psychiatry Products, Office of New Quality Drug Chemistry, the Division of Medication Error Prevention and Analysis and the Chair of the CDER Labeling and Nomenclature Committee (LNC) on June 8, 2009, the team discussed the Applicant's proposal and the differences of opinion as to the preferred expression of strength. ONDQA wanted the strength expressed in terms of the ester and clinical liked the whole numbers. DMEPA did not have a preference as to how the strength was expressed but did request that whichever method was chosen, the container, carton and insert all needed to be consistent.

Following discussion the group agreed that the product strength should be expressed as the ester (paliperidone palmitate) on the container labels, carton and throughout the insert labeling. It was agreed that the syringe strengths should be labeled as 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg of paliperidone palmitate, and not as 25 mg, 50 mg, 75 mg, 100 mg, or 50 mg of paliperidone. Additionally, there should not be any references to milligram equivalents, or paliperidone equivalents, or any similar terms throughout the labels and labeling, other than in the Description section of the Insert Labeling. [REDACTED] (b) (4)

## 5 RECOMMENDATIONS

Our evaluation noted areas of needed improvement on the container labels, carton and insert labeling. We noted the use of the inappropriate dosage form, [REDACTED] (b) (4) and provide comments on the insert labeling in Section 5.1 *Comments on the Division*. Section 5.2, *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communications to the Applicant with regard to this review. If you have any further questions or need clarification on this review, please contact Abolade Adeolu, OSE Project Manager, at 301-796-4264.

### 5.1 COMMENTS TO THE DIVISION

1. The Applicant used the term [REDACTED] (b) (4) throughout the labels and labeling to describe the dosage form of the proposed product throughout the labels and labeling. We note this is not an official U.S. Pharmacopeia (USP) dosage form. The chemistry review also noted this inappropriate dosage form statement. ONDQA recommended that the Applicant to replace the term "[REDACTED] (b) (4)" with the term "Extended-release Injectable Suspension" to appropriately reflect the proposed dosage form. We concur with this recommendation.
2. The syringe strengths should be referred to as 39 mg, 78 mg, 117 mg, 156 mg, and

234 mg of paliperidone palmitate, and not as 25 mg, 50 mg, 75 mg, 100 mg, or 50 mg of paliperidone throughout the insert labeling. Additionally, there should not be any references to milligram equivalents, or paliperidone equivalents, or any similar terms throughout the labels and labeling, other than in the Description section of the Insert Labeling. (b) (4)

## 5.2 COMMENTS TO THE APPLICANT

### A. All Labels and Labeling

1. Express the product strength of the prefilled syringes as the ester (paliperidone palmitate) throughout the labels and labeling (e.g., 39 mg, 78 mg, 117 mg, 156 mg and 234 mg). Delete all references to “milligram equivalents”, or “paliperidone equivalents”, or any similar terms throughout the labels and labeling, with the exception of the Description section of the Insert Labeling. (b) (4)
2. Revise the statement (b) (4) to read “For Single Use Only - Use Entire Content of Syringe”. These statements should be prominently displayed together to prevent multiple use/reuse of the syringe and to remind practitioners that one syringe is a complete dose.
3. Revise the established name to read “Paliperidone Palmitate Extended-release Injectable Suspension”.

### B. Carton Labeling

1. See Comments A 1 through A 3.
2. Revise the presentation of the proprietary name so that it appears entirely on the same line in the same size and font. As currently presented, the "Sustenna" portion of the proprietary name appears in a larger font size than the "Invega" portion of the name and the two words appear on separate lines. The current presentation may lead health care practitioners to believe the name is just "Sustenna", when in fact the full proprietary name is Invega Sustenna.
3. Revise the product strength so that it is proportionate to the font size of the proprietary and established names. Although the product strength appears immediately after the established name, the font size is small and makes the strength less prominent. Thus it may be difficult for practitioners to readily recognize the product strength.

### C. Container Label

See Comments A 1 through A 3.

### D. Professional Sample Carton Labeling

1. See Comments A 1 through A 3.
2. Increase the prominence of the statement "Sample. Not for sale or reimbursement." This statement is small and may be overlooked by practitioners. Increasing the size will allow healthcare practitioners to clearly identify that this is a professional sample.

E. Professional Sample Container Label

1. See Comments A 1 through A 3.
2. Increase the prominence of the statement “Sample. Not for sale or reimbursement” by bolding or increasing the font size. Increasing the size will allow healthcare practitioners to clearly identify that this is a professional sample.

F. Insert Labeling

We have no comments on the prescribing information labeling.

G. Information Sheet for Providers

Revise the statement “Do not administer intravenously or subcutaneously” to read “For Intramuscular Injection Only”. Negative statements such as ‘Not for Intravenous Injection’ or ‘Not for Subcutaneous Injection’ may actually have the opposite intended effect and have inadvertently encouraged wrong routes of administration due to the reader's focus on the route of administration and the potential for overlooking the negative words ‘not’ or ‘do not’.

7 pp withheld in full immed. after this page as (b)(4) draft labeling.

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/s/

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Diane Smith  
7/10/2009 01:22:32 PM  
DRUG SAFETY OFFICE REVIEWER

Laura Pincock  
7/10/2009 02:21:15 PM  
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Carol Holquist  
7/10/2009 03:03:55 PM  
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: August 5, 2008

TO: Kimberly Updegraff, Regulatory Project Manager  
Jing Zhang, Medical Officer  
Division of Psychiatry Products

FROM: John Lee, Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD  
Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-264

APPLICANT: Johnson and Johnson PR&D

DRUG: Paliperidone palmitate (b) (4)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of schizophrenia and prevention of recurrence of symptoms

CONSULTATION REQUEST DATE: January 4, 2008

DIVISION ACTION GOAL DATE: August 2, 2008

PDUFA DATE: August 26, 2008

## I. BACKGROUND

Johnson and Johnson submitted NDA 22-264 to support the use of paliperidone in the treatment of schizophrenia and prevention of recurrence of symptoms.

### Schizophrenia

Schizophrenia is a chronic debilitating mental illness which affects 0.5 to 1% of the United States (US) population. The risk for schizophrenia has been found to be generally consistent across diverse geographic, ethnic, cultural, and socioeconomic groups. Schizophrenia affects men and women with equal frequency but appears about 10 years earlier in men than in women, typically in late teens or early twenties.

Non-compliance is a major problem in using antipsychotic agents to treat schizophrenia. Medication gaps as short as 1 to 10 days have been shown to be associated with an increased risk of hospitalization and suicide attempts. The cumulative relapse rate in schizophrenia has been estimated to be about 80% by 5 years. Discontinuing drug therapy has been shown to increase the relapse risk five-fold. The use of long-acting injectable agents has been shown to reduce the relapse rate by about one-third at one year (from 40 to 25%).

### Paliperidone palmitate

Paliperidone is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 antagonism combined with predominant serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation antipsychotic drugs. The oral paliperidone extended release formulation was approved by the Food and Drug Administration on 19 December 2006 for the treatment of schizophrenia and on 27 April 2007 for maintenance treatment of schizophrenia. Paliperidone ER tablets are also approved and marketed in the European Union for the treatment of schizophrenia.

Paliperidone palmitate is a long-acting injectable with a long duration of action and acceptable systemic and local tolerance. Relatively constant plasma concentrations are achieved using monthly dosing. Given that paliperidone has been extensively investigated in the oral tablet program, it is expected that its documented safety and efficacy will extend to the injectable formulation, paliperidone palmitate.

### Study Protocol

R092670-PSY-3003 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose response study in adults with a diagnosis of schizophrenia for at least one year and severely symptomatic at screening. The study consisted of a screening period (up to 7 days) followed by a 13-week double-blinded treatment period (four treatment groups, paliperidone palmitate 50, 100, or 150 mg equivalent or placebo). Each subject received an intramuscular injection on Days 1, 8, 36, and 64, and end-of-study assessments were performed on Day 92.

349 randomized subjects received the study medication, had baseline and post baseline efficacy assessments, and received the same study treatment for the duration of the study. The primary efficacy endpoint was the change from baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score. Major safety assessment consisted of noting the incidence, severity, and relationship of treatment-emergent adverse events and changes from baseline in clinical laboratory tests, vital signs, physical examination, body weight, body mass index, electrocardiograms (ECGs), and extrapyramidal symptom scale scores. The inspected

site, which contributed approximately 9% of the subjects in this study, was selected for inspection based on enrollment of large numbers of study subjects.

Four sites were originally targeted for inspection by the Division of Psychiatry Products, which were selected due to high enrollment. However, this audit only covered one of the four originally requested sites, as the Division of Psychiatry Products withdrew their request for inspection of three of the four sites (Litman, Lowy, and Chaganti). The request for the inspection of Drs. Litman and Lowy's sites was withdrawn based on recent inspectional history, since these sites were inspected within 4 months of consult request date and no major deficiencies were observed. The request for the inspection of Dr. Chaganti's site was withdrawn since he was recently inspected, received a recent Warning Letter, and the data from the site did not significantly affect the overall efficacy and safety analysis outcome.

## II. INSPECTION RESULTS

Clinical Site	Protocol Subjects	Inspection Dates	Classification	
			Interim	Final
Steven Glass, MD CNS Research Institute, PC Clementon, New Jersey	R092670-PSY-3003 (31 subjects)	7/7 - 7/21 2008	VAI	VAI

NAI = no action indicated (no deviations from regulations); VAI = voluntary action indicated (no significant deviations from regulations); OAI = official action indicated (significant deviations from regulations); NA = not applicable

### Steven Glass, MD

CNS Research Institute, PC  
130 White Horse Pike  
Clementon, NJ 08021

#### a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.
- Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
- Subjects: 35 subjects were screened, 31 enrolled, and 14 completed the study. Consent forms, randomization information, termination dates and reasons, and source PANSS scores were reviewed for all subjects. Concomitant medications, adverse events, ECGs (limited visits), laboratory tests, and subject selection criteria were reviewed for all subjects who received the study drug. Drug accountability was evaluated for 9 randomly selected subjects.

#### b. General observations and commentary:

- Cited deficiencies (Form FDA 483): Delayed signing of Addendum I to the consent

form (3 subjects), which described updated safety information not contained in the original consent form

- Other significant findings:
  - Patient evaluation visits out of protocol-specified time window (most approved by the sponsor)
  - Minor discrepancies between source data (which matched electronic case report forms) and data listings
- c. Assessment of data integrity: Although minor regulatory violations were noted, it is unlikely that these would affect data integrity. Data from this site are considered reliable.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Serious deficiencies were not observed at inspection of this clinical site. Minor deficiencies consisted of suboptimal informed consent procedures for signatures on addendum to the informed consent documents and a limited number of protocol violations that are not expected to importantly impact data integrity. The data generated from this site are considered acceptable in support of the proposed indication.

{See appended electronic signature page}

John Lee, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
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Division of Scientific Investigations  
Office of Compliance

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/s/

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John Lee  
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