CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-264 Resubmission** **Sponsor's responses to FDA's Complete Response letter of August 25, 2008**
SERIAL NUMBER:	**0000**
DATE RECEIVED BY CENTER:	**February 3, 2009**
PRODUCT:	**Paliperidone palmitate (Invega® Sustenna™)**
INTENDED CLINICAL POPULATION:	**adults with schizophrenia (acute and maintenance treatment)**
SPONSOR:	**Ortho-McNeil-Janssen Pharmaceuticals, Inc.**
AGENT:	**Johnson & Johnson Pharmaceutical R & D, L.L.C., 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560**
DOCUMENTS REVIEWED:	**electronic submission**
REVIEW DIVISION:	**Division of Psychiatry Products (HFD-130)**
PHARM/TOX REVIEWER:	**Elzbieta Chalecka-Franaszek, Ph.D.**
PHARM/TOX TEAM LEADER:	**Aisar Atrakchi, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barry Rosloff, Ph.D.**
DIVISION DIRECTOR:	**Thomas Laughren, M.D.**
PROJECT MANAGER:	**Kimberly Updegraff, R.Ph.**

Date of review submission to Division File System (DFS): June 17, 2009

Content of submission:

This is a resubmission to the NDA 22-264 addressing comments raised by the Division in the Complete Response letter dated August 25, 2008 including items agreed to during the Sponsor's meeting with the Division on November 21, 2008.

In this resubmission reference is made to the original NDA 22-264 for paliperidone palmitate (b) (4) that was submitted by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. on October 25, 2007 for the treatment of schizophrenia in adults on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Reference is also made to the Division's Complete Response letter dated August 25, 2008 and to Sponsor's meeting with the Division on November 21, 2008 to discuss the content of this resubmission.

During the November 21, 2008 meeting, the Sponsor indicated that the paliperidone palmitate development program included the use of a clinical 150 mg eq. dose of paliperidone palmitate. According to the Sponsor, the nonclinical development program provided in the submitted NDA 22-264 was conducted to support the 150 mg eq. dose in addition to the 25 to 100 mg eq. dose range. No additional nonclinical studies were conducted to further support the 150 mg eq. dose, and no further information or analyses were planned to be included in the resubmission; (b) (4) The Division confirmed acceptability of this plan for the Sponsor's resubmission.

Therefore, no new pharmacology/toxicology data were submitted and/or reviewed at present.

Executive Summary

I. Recommendations

A. Recommendation on approvability:

The nonclinical studies submitted in support of the original NDA 22-264 for paliperidone palmitate were sufficient to recommend approval of the application from a pharmacology/toxicology perspective provided the Sponsor revise the drug substance specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) µg per injection (b) (4) ppm). This recommendation was communicated to the Sponsor in the CMC information request letter dated April 24, 2009.

B. Recommendation for nonclinical studies:

No additional nonclinical studies are recommended.

C. Recommendations on labeling:

The Sponsor has accepted the labeling changes proposed by the Division based on the recommendations of the pharmacology/toxicology reviewer in sections 8.1 (Pregnancy), 12.1 (Mechanism of action), 12.2 (Pharmacodynamics), and 13.1 (Carcionogenesis, Mutagenesis, Impairment of Fertility). (b) (4)

The following labeling text is a version that includes changes proposed by the Division and Sponsor and should be considered as final with the exception of paliperidone palmitate units (mg eq.) which are still under consideration by the Division.

8.1 Pregnancy

(b) (4)

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see Risperdal package insert).

There are no adequate and well controlled studies of INVEGA® SUSTENNA™ in pregnant women. INVEGA® SUSTENNA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) receptor antagonist and a serotonin Type 2 ($5HT_{2A}$) receptor antagonist.

12.2 Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D_2) receptor antagonist and a serotonin Type 2 ($5HT_{2A}$) receptor antagonist. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro.*

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

(b) (4)

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.