CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

RISK ASSESSMENT and RISK MITIGATION 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 31, 2008**
To:	**Thomas Laughren, M.D., Director** **Division of Psychiatry Products (DPP)**
Through:	**Claudia Karwoski, Pharm.D., Director (Acting)** **Division of Risk Management (DRISK)**
From:	**OSE Paliperidone Palmitate Review Team** Scientific Lead: **Kendra Worthy, Pharm.D., Senior Risk Management Analyst (Detail) (DRISK)** Team Members: **Suzanne Berkman, Pharm.D., Senior Drug Risk Management Analyst (Acting) Team Leader (DRISK)** **Mary Dempsey, Risk Management Program Coordinator (DRISK)** **Ida-Lina Diak, Pharm.D., Safety Evaluator , Division of Pharmacovigilance (DPV I)** **Laura Pincock, R.Ph., Pharm.D., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)**
Subject:	**Review of Proposed Risk Management Plan**
Drug Name(s):	**Invega® Sustenna™ (paliperidone palmitate** (b) (4) (b) (4)
Application Type/Number:	**NDA 22-264**
Applicant/sponsor:	**Johnson & Johnson**
OSE RCM #:	**2008-803**

Contents

1 INTRODUCTION AND BACKGROUND

This review follows the May 16, 2008 request from the Division of Psychiatry products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review Johnson & Johnson's September 26, 2007 submission containing a proposed pharmacovigilance plan.

Invega® Sustenna™ (paliperidone palmitate) is an atypical antipsychotic with the proposed indication for the treatment of schizophrenia and the prevention of recurrence of symptoms of schizophrenia. Paliperidone palmitate is a major active metabolite of risperidone. It is supplied as pre-filled syringes for long-acting intramuscular injection containing paliperidone palmitate equivalent to 25 mg, 50 mg, 75 mg, and 100 mg paliperidone. It is to be administered by a healthcare professional.

1.1 REGULATORY HISTORY

Invega® (paliperidone) Extended Release Tablet (3 mg, 6 mg, 9 mg, and 12 mg) was first approved in the United States on December 19, 2006 for the treatment of schizophrenia (NDA 21-999). The extended release tablet was then approved for maintenance treatment of schizophrenia on April 27, 2007 (NDA 22-043).

2 MATERIAL REVIEWED

The following materials were reviewed:

- "Paliperidone Palmitate Pharmacovigilance Plan" dated September 26, 2007 by Johnson & Johnson and submitted October 26, 2007.
- Proposed Invega® Sustenna™ package insert submitted February 25, 2008.
- Invega® Extended-Release Tablets package insert. Titusville, NJ: Janssen, L.P.; 2007.
- Risperdal® package insert. Titusville, NJ: Janssen, L.P.; 2007.
- Risperdal® Consta® package insert. Titusville, NJ: Janssen, L.P.; 2007.
- Email correspondence from Dr. Jing Zhang, medical officer, DPP. Dated June 4, 2008.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

3.1.1 Sponsor's Safety Concerns

Johnson & Johnson did not identify any safety risks in the proposed pharmacovigilance plan. However, the proposed labeling[1] includes the following risks:

- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis.
- Neuroleptic malignant syndrome

- [1] Proposed Invega® Sustenna™ package insert submitted February 25, 2008. Warnings and Precautions.

- QT prolongation
- Tardive dyskinesia
- Hyperglycemia and diabetes mellitus
- Orthostatic hypotension and syncope
- Potential for cognitive and motor impairment
- Seizures
- Suicide
- Administration (For intramuscular injection only. Avoid inadvertent injection into a blood vessel.)

Further, atypical antipsychotics as a class have a Boxed Warning which states (in pertinent part) that "[e]lderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo."[2]

The safety risks noted above are also included in the Warnings and Precautions section of the Invega® Extended-Release Tablets label. Hyperprolactinemia is listed in the Warnings and Precautions section of the Invega® label; however, it is listed in the full prescribing information section of the Invega® Sustenna™ label. Gastrointestinal narrowing is listed in the Invega® label, (b) (4) If this adverse reaction is unrelated to the oral route of administration, it should also be included in Invega® Sustenna™ labeling. Additionally, the safety risks noted above, with the exception of QT prolongation and administration, are included in the Warnings and Precautions section of the Risperdal label.[3]

3.1.2 DMEPA Safety Concerns

The Division of Medication Error Prevention and Analysis (DMEPA) has concerns regarding the dosing and administration of this product which will be communicated in a separate forthcoming review from DMEPA.

3.2 SPONSOR'S RISK MANAGEMENT PROPOSAL

The sponsor proposes a routine pharmacovigilance strategy with the following two objectives:

1. To systematically collect adverse events (AE) from multiple sources, and
2. To conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals.

The sponsor plans to submit aggregate reports, i.e. Periodic Safety Update Reports (PSURs), as required by regulations.

4 DISCUSSION

The sponsor's proposal is consistent with a routine pharmacovigilance program. Based on the e-mail communication with the medical officer[4] and review of the proposed label, the adverse event

[2] Proposed Invega® Sustenna™ package insert submitted February 25, 2008. Boxed Warning.

[3] Risperdal® package insert. Titusville, NJ: Janssen, L.P.; 2007.

[4] Email correspondence from Dr. Jing Zhang, medical officer, DPP. Dated June 4, 2008.

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