CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDAs	22264
Submission Dates	03 February 2009
Brand Name	INVEGA SUSTENNA ™
Generic Name	(25mg, 50, 75, 100, 150 mg paliperidone) Paliperidone Palmitate (b) (4)
Reviewer	Hao Zhu, Ph.D.
	Kofi Kumi, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Raman Baweja, Ph.D.
OCP Division	DCP1 (HFD-860)
OND Division	DPP (HFD-130)
Sponsor	Johnson & Johnson R&D, L.L.C.
Submission Type	

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Paliperdione has been marked as an extended release (ER) formulation with a once-daily administration schedule for the treatment of schizophrenia. Paliperidone palmitate (b) (4) was originally submitted by Johnson & Johnson Pharmacetucial Research and Development (J&JPRD) on 25 October 2007. On 25 August 2008, the division issued a complete response letter. Following the complete response letter, the discussion meetings between the sponsor and the FDA were held on 9 September 2008 and 21 November 2008. J&JPRD filed the resubmission on 03 February 2009 to address the comments and questions raised by the division in the complete response letter.

In the resubmission package, the sponsor included a recently completed clinical study report (R092670-PSY-3007) to support the initial and maintenance dose of 150 mg eq. An interim analysis of safety data from Study R092670-PSY-1008, a long-term (up to 53 weeks), open-label, safety study, was also provided to support the use of a higher initiation and maintenance dose.

The sponsor proposed dosing regimen was summarized in Table 1. The sponsor's proposal was based on the findings from the recently finished clinical trials and the population PK simulation studies.

Table 1 Summary of the Sponsor Proposed Dosing Regimen

Patient Population	Initial Dosing	Dosing Window	Maintenance Dosing	Dosing Window
(b) (4)				

Our findings, based on the independent simulation studies, were summarized below.

- The sponsor proposed target maintenance dose is 75 mg eq. q 4 weeks and can be adjusted between 25 to 150 mg eq q 4 weeks. The recommended maintenance dosing regimen is acceptable.
    - Paliperidone once daily ER formulation has been approved for the treatment of schizophrenia. The recommended dosing is 6 mg q 24 hour and can be adjusted between 3 mg to 12 mg q 24 hour.

    - The simulation showed that 75 mg eq q 4 week using long acting injection yields similar exposure as 6 mg q 24 hour for the ER formulation.
    - The simulation also indicated that 25 and 150 mg eq q 4 weeks using long acting injection yields similar exposure as 2 mg q 24 hour and 12 mg q 24 hour for the ER formulation. In the current submission, 25 mg eq q 4 weeks has shown to be effective in treating patients with schizophrenia.

- The sponsor also proposed an initial dose of 150 mg eq on the first day, followed by 100 mg eq by the end of the first week. The proposed initial dosing regimen is acceptable.
    - The desirable exposure is defined as median exposure between the steady state peak and trough concentration following 6 mg q.d. oral ER formulation.
    - Starting the treatment with 150 mg eq dose provides the benefit that the desirable exposure can be achieved within 1 week. Following the proposed initial dosing regimen, the peak exposure is below the highest clinical tested exposure that appears to be safe and well tolerated.

- The sponsor proposed that the second initial dose can be administered within 2 days prior to or after the scheduled time. In addition, the maintenance dose can be given within 1 week prior to or after the scheduled time. The simulation results demonstrated that paliperidone exposure is within the desirable exposure. Therefore the proposed dosing window is acceptable.

- The sponsor proposed an initial dose of 100 mg eq and 75 mg eq on day1 and one week later in combination with a maintenance dose of 50 mg eq for patients with mild renal impairment. The simulation results indicated that paliperidone exposure is mainly within the desirable exposure range. The peak exposure is below the highest clinical tested exposure that appears to be safe and well tolerated. Therefore, the proposed dosing regimen in patients with mild renal impairment is acceptable. It is to note that paliperidone palimtate is not recommended in patients with moderate or severe renal impairment.

- (b) (4)

- (b) (4)

(b) (4)

- We have the following proposals for patients who intend to switch from other long acting injection to paliperidone palimtate long acting injection.

    - One proposal is to use paliperidone ER formulation between the two long acting injections. This would allow the physician to titrate paliperidone dose to compensate the elimination of the previous antipsychotic drug based on the clinical response and also provide a flexible regimen to adjust the dose timely for adverse events. After the patient is stabilized on paliperidone ER formulation and most of the previous antipsychotic drug is eliminated, the paliperidone palmitate injection can be started with the standard initiation dosing.

    - For patients that cannot follow the proposed switching strategy, the alternative proposal is to switch the patients to the maintenance dosing of paliperidone palmitate long acting injection without the loading dose. However, the appropriate maintenance dose will be determined by the physician's clinical judgment and cannot be established by using pharmacokinetic simulation alone.

- The sponsor proposed a re-initiation dosing regimen (Table 1). We found that the re-initiation dosing regimens for patients who miss doses for 4 - 6 weeks and > 6 months are acceptable with the assumption that paliperidone tolerability and the underlying disease progression are not affected due to the missing doses. (b) (4)

- We recommend the re-initiation dose (doses on day 1 and day 8) for a patient who discontinues paliperidone palmitate treatment for 6 weeks – 6 months be the same dose as the previous maintenance dose with a maximum of 100 mg eq.

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.