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APPLICATION NUMBER:

22-264

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	22-264 (N000)
Drug Name:	Invega SustennaTM (paliperidone palmitate) (b) (4)
Indication:	Schizophrenia
Applicant:	Johnson & Johnson
Dates:	Date of Document: 2/03/2009
	PDUFA Due Date: 8/03/2009
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring	Peiling Yang, Ph.D.
Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products, HFD-130
Clinical Team:	Clinical Reviewer: Jing Zhang, M.D.
	Clinical Team Leader: Gwen Zornberg, M.D.
Project Manager:	Kimberly Updegraff

Table of Contents

1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The statistical reviewer agreed that Study 3007 was a positive study, where all three doses (25, 100 and 150 mg eq.) showed statistically significant effects in comparison with placebo on the primary endpoint, PANSS total scores. However, the efficacy findings on the PSP scores have not been replicated; thus this reviewer suggests that these findings not be included in the label. In addition, although 150 mg eq. performed numerically better than 100 mg eq., the numerical advantage was small and statistically indistinguishable (p=0.59); thus, it remains unclear whether 150 mg eq. would have an additional beneficial effect.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In response to the complete response letter for the original NDA application for paliperidone palmitate as a treatment of schizophrenia in adult patients, the sponsor included an additional efficacy study (Study 3007), which was designed to confirm the efficacy and safety of the paliperidone palmitate 25 and 100 mg eq. doses previously observed in the Phase 3 studies R092670-PSY-3003 (100 mg eq. dose) and R092670-PSY-3004 (25 and 100 mg eq. doses), to explore the efficacy and safety of a higher dose (paliperidone palmitate 150 mg eq.) and to examine a new dosing regimen used to increase the initial exposure to paliperidone (initial dose of 150 mg eq. in the deltoid muscle followed by either deltoid or gluteal injections at the target dose).

Study 3007 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study designed to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate (25, 100 and 150 mg eq.) compared with placebo. Study medication was administered as 4 doses: an intial i.m. injection of placebo or paliperidone palmitate 150 mg eq. followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36 and 64. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The primary endpoint is the change in the PANSS total score (sum of the scores of all 30 PANSS items) from the start of the double-blind treatment period (baseline) to the end of the double-blind treatment period (Day 92 or last post baseline assessment). Secondary endpoints included the changes from baseline to the end of the double-blind treatment period (Day 92 or last post baseline assessment) in the PSP and the CGI-S scores, where PSP was designated as a key secondary endpoint.

Based on statistically significant results shown on all three doses in comparison with placebo for the primary endpoint and on two higher doses for the key secondary endpoint, PSP scores, the sponsor concluded that paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m. injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36 and 64, was statistically significantly

more effective than placebo in improving the PANSS total score at end point in the 13-week double-blind study in subjects with schizophrenia. The sponsor even claimed that there was a dose response with respect to efficacy for the primary endpoint, with mean change in the PANSS total score at end point showing incrementally greater improvement across the 3 doses of paliperidone palmitate.

1.3 STATISTICAL ISSUES AND FINDINGS

The statistical reviewer basically confirmed the sponsor's analysis results for Study 3007. It was agreed that data supported the efficacy of paliperidone palmitate as a treatment for adult patients with schizophrenia. (b) (4)

Regarding the sponsor's dose response claim, although paliperidone palmitate 150 mg eq. seemed to perform numerically better than 100 mg eq. the observed difference between them appeared very small. With a p-value 0.59 for the comparison between these two treatment arms, it is not clear whether paliperidone palmitate 150 mg eq. would contribute any additional benefit.

2. INTRODUCTION

2.1 OVERVIEW

Paliperidone palmitate is the palmitate ester of paliperidone. The original new drug application for paliperidone palmitate (b) (4) was submitted by the sponsor on October 25 of 2007 for the treatment of schizophrenia in adults. In that submission, 4 phase 2/3 studies for subjects with acute psychosis were evaluated. It was determined that the efficacy of paliperidone palmitate (25 and 100 mg eq.) in treating patients with schizophrenia was demonstrated. However, due to some issues regarding the product quality, the NDA application was not approved.

To promote the use of higher initiation doses of paliperidone palmitate in a new dosing regimen and also explore the efficacy and safety of a higher dose (paloperidone palmitate 150 mg eq.), the sponsor conducted and included an additional efficacy study (Study 3007) along with this NDA re-submission. The sponsor also included their exploration for the effects of BMI on pharmacokinetics, clinical efficacy and clinical safety in this submission. They concluded that no consistent clinically remarkable difference was observed among the 3 BMI categories (normal, overweight, and obese) with regard to the overall pattern and incidences of treatment-emergent adverse events. They further concluded that at the highest recommended dose of 150 mg eq. paliperidone palmitate was generally safe and well tolerated across all BMI categories, supporting the safety and tolerability of the recommended dosing regimen.

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