CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207946Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	
From	Lucas Kempf, MD
Subject	Cross-Discipline Team Leader Review
NDA	207946
Applicant	Janssen Pharmaceuticals, Inc.
Date of Submission	November 18, 2014
PDUFA Goal Date	May 18, 2015
Proprietary Name / Established (USAN) names	INVEGA TRINVA/Paliperidone Palmitate
Dosage forms / Strength	Extended-Release Injectable Suspension for Intramuscular Use (3-month formulation) 273mg, 410 mg, 546 mg, or 819 mg IM every 3 months
Proposed Indication(s)	1. Treatment of schizophrenia in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months
Recommended:	**Approval**

1. Introduction

Schizophrenia is serious, chronic disabling psychiatric syndrome that impairs cognition and perception. It requires daily medication to minimize symptoms and improve functioning. Unfortunately, due to the cognitive deficits many patients find it difficult to remember to take their medication daily, when they miss doses their cognition worsens and they forget more doses. This cycle leads to frequent relapse. Several medications have one month injectable formulations to avoid the need for daily medication supervision. Many long term stable patients are typically seen by their physician in outpatient practice every three months for monitoring. Currently, there are no other long-acting (3 month) formulations of depot antipsychotic medications. Due to the novel formulation, issues involving the PK and safety are the primary focus of the review.

2. Background

PP3M is the 3-month formulation of paliperidone palmitate. Paliperidone palmitate is the palmitate ester prodrug of paliperidone (9-hydroxy-risperidone). It is a selective, monoaminergic antagonist that exhibits the dopamine Type 2 (D2) and serotonin type 2A (5HT2A) antagonism of the second-generation, antipsychotic drugs. Paliperidone is an active metabolite of risperidone. The main

differences between the 3-month formulation of paliperidone palmitate (PP3M) and the 1-month formulation of paliperidone palmitate (PP1M) are (b) (4) and the larger injection volume.

There is extensive efficacy and safety knowledge of risperidone (approved on December 29, 1993) and its active metabolite paliperidone in pre and post marketing. The oral formulation of paliperidone was approved December 19, 2006 and the PP1M formulation was approved in July 31, 2009. Dose titration for the one month IM formulation can take 4 months. Therefore, PP3M is planned for patients that have already established efficacy and tolerability of the PP1M at that planned dose.

In addition to injection site reactions, antipsychotic drugs have many important safety issues including:
• Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
• Neuroleptic Malignant Syndrome
• QT Prolongation
• Tardive Dyskinesia
• Metabolic changes that may increase cardiovascular/cerebrovascular risk (e.g., hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain)
• Orthostatic Hypotension and Syncope
• Leukopenia, Neutropenia, and Agranulocytosis
• Hyperprolactinemia
• Potential for Cognitive and Motor Impairment
• Seizures
The main regulatory issues are with the manufacturing of the new formulation, no new safety findings and the PK profile.

3. CMC/Device

CMC team under David Claffey also advised approval and I concur with their assessments. Their assessment of the risk of this formulation is eloquently described below from their review page 4.

> The most obvious risk associated with the proposed product is faster than expected in vivo release or dose-dumping of the three-month supply of drug. This potential risk is raised for this dosage form as it does not have a physical dissolution-rate controlling barrier like other extended release products (e.g. membrane, coating). Rather, it depends entirely on the intrinsic aqueous insolubility of the drug substance. The dissolution rate directly correlates with the (b) (4) The in vivo performance of the product is assured through the drug substance and drug product manufacturing control strategy, (b) (4)

Issues involving manufacturing and sterility were adequately addressed and CMC had no issues with their processes.

CDRH review was conducted by Kathleen Fitzgerald and she found no outstanding deficiencies in the application. The injection device in similar to the device used in the PP1M except for the gauge of the needle and the volume of the syringe.

4. Nonclinical Pharmacology/Toxicology

Dr. Elzbieta Chalecka-Franaszek's (Pharm/Tox) was primary non-clinical reviewer. I agree with her assessments about the safety of the formulation but there is a disagreement between the primary and secondary reviews of the calculations of the acceptable levels of the excipients and whether to update the DMF. I agree with Dr. Aisar Atrakchi, Ph.D. in her secondary review of the calculations. Basically, the disagreement was around the calculation of amount of exposure to two mutagenic excipients.

Briefly, the nonclinical toxicology support for the 3-month injectable formulation (F015) is largely derived from the nonclinical experience with the 1-month long acting injectable formulation (F013). The 3-month formulation (F015) has the same active ingredient and excipients as the 1-month formulation (F013) but at different concentrations.

The area of agreement is over the interpretation of the nonclinical studies. Due to the concerns that the concentration and volume may have specific issues with local toxicity that differs from the reference drug, local tolerability studies with the 3-month injectable formulation (F015) in the minipig were conducted. Minipigs were dosed up to the highest clinical dose of F015 and F013; a single injection of F015 at 525 mg was compared with 3 injections of F013 at 150 mg. According to the Applicant, "at necropsy, i.m. injection of the paliperidone palmitate formulations in the skeletal muscle resulted in dose-related local reactions, with no relevant differences between the 2 formulations. These local reactions were confirmed at the histological level. There were no clear-cut differences in quantitative (multi)focal chronic inflammation between the two formulations."

Aisar Atrakchi, Ph.D.'s memo addresses the difference in the calculation and recommendation for the limit of the 2 genotoxic impurities, (b) (4) and (b) (4) in drug substance. Her assessment is summarized below. Her calculations are based on the recommendations in ICH M7 (June, 2014) using the Less than Lifetime (LTL) approach for paliperidone palmitate administered once every 3 months over the lifetime of patient (70 years) with the same cancer risk of 1 in 100,000 cases. She also noted that these 2 impurities have not been detected in the drug substance (combined impurities (b) (4) ppm), in a total of 180 lots tested to date. These 2 impurities have also been qualified previously in toxicology studies including the 2 yr carcinogenicity conducted with the 1-month paliperidone injectable suspension.
She determined that the limits for the 2 genotoxic impurities (b) (4) and (b) (4) in paliperidone palmitate drug substance are to be set at not more than (b) (4) ppm for each impurity based on LTL approach in ICH M7 guideline (2014). Also, the DMF holder has set a limit of (b) (4) ppm for these impurities. The DMF holder has the option of maintaining this limit especially since the sponsor has been able to keep the combined impurity limit to (b) (4) ppm and this limit of (b) (4) ppm was recommended by the Division previously for the paliperidone palmitate 1-month injectable suspension based on the draft guidance of 2008 on genotoxic impurities. Alternatively, the DMF holder set the limit to the (b) (4) ppm which is calculated based

on the LTL approach in ICH M7 (2014).
She states that she disagrees with Dr. Chalecka-Franaszek's calculation that used the (b) (4) ug limit for genotoxic impurities in pharmaceuticals administered daily over a lifetime. The correct approach based on M7 is to use the LTL approach for pharmaceuticals administered intermittently over lifetime. M7 assessment is very conservative since it considers the worst case scenario of dose dumping and tumor incidence in the most sensitive sex and species while maintaining the cancer risk of 1 in 100,000 cases.

5. Clinical Pharmacology/Biopharmaceutics

Study PSY-1005, a Phase 1 PK study, provides exposure and safety data. I concur with the finds of the detailed OCP review by Dr. Kofi Kumi. The submitted studies provide adequate data to support administration.

The 3-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug begins at day 1 and continues to be measurable at 18 months. Following a single intramuscular dose of PP3M, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tmax of 30-33 days. Following intramuscular injection in the deltoid muscle was on average, an 11-12% higher Cmax compared to the gluteal muscle. The release profile and dosing regimen of PP3M results in sustained therapeutic concentrations. The total exposure of paliperidone following PP3M administration was dose-proportional over a 273-819 mg dose range and approximately dose-proportional for Cmax. The mean steady-state peak:trough ratio for a PP3M dose was 1.6 following gluteal administration and 1.7 following deltoid administration. Following administration of PP3M, the apparent volume of distribution of paliperidone is 1960 L. Based on a population pharmacokinetic analysis, the median apparent half-life of paliperidone following PP3M administration over the dose range of 273-819 mg ranged from 84-95 days following deltoid injections and 118-139 days following gluteal injections.

The sponsor's proposal (b) (4) was not recommended based on the OCP analysis of the data. I concur and labeling negotiations are ongoing with the sponsor.

The proposed dosing scheme appears to correlate based on PK.

If the last INVEGA® SUSTENNA® (PP1M)dose is:	Initiate INVEGA® TRINZA® (PP3M) at the following dose:
78 mg	253 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

For missed doses. Patients that have missed a regular dose for up to 4 months should be reinitiated on the regular dosing regimen as soon as possible. Patients that have missed a regular dose for up to 9 months need to be reinitiated based on a predefined scheme where two doses (1 week apart) of PP1M are used to bring the patient to therapeutic concentrations before

PP3M administration is resumed. Patients that have missed a regular dose for more than 9 months need to be reinitiated based on a predefined schedule where two doses (1 week apart) of PP1M are administered, followed by 3 additional PP1M injections (1 month apart).

The switching strategy from PP3M to oral was found to be appropriate.

	Weeks since last PP3M dose		
Last PP3M Dose	≥ 3 months to ≤ 18 weeks	> 18 weeks to ≤ 24 weeks	> 24 weeks
	Doses of oral paliperidone extended-release tablets		
273 mg [175 mg eq.]	3 mg	3 mg	3 mg
410 mg [263 mg eq.]	3 mg	3 mg	6 mg
546 mg [350 mg eq.]	3 mg	6 mg	9 mg
819 mg [525 mg eq.]	6 mg	9 mg	12 mg

The PK of paliperidone from the PP3M formulation was dose-proportional over a dose range of 75 to 525 mg eq. after single dose administration.

There was no evidence of change of dosing based on site of injection, sex, age, race, or BMI.

Labeling based on the OCP analysis is still pending at the time of this review.

6. Clinical Microbiology

The clinical microbiology review was when in the CMC review and found to be satisfactory.

7. Clinical/Statistical- Efficacy

I agree with the efficacy review and analysis of Dr. Christina Burkhart in her clinical review and statistical review by Yang Wang, Ph.D., Office of Biostatistics. Please see their reviews for detailed discussion. Efficacy was based on the phase 3 relapse prevention trial PSY-3201 and randomized, double,-blind placebo controlled, multicenter, relapse prevention study of variable duration proceeded by a 17-week, open-label transition phase with PP1M and a 12-week open-label maintenance phase with PP3M. PSY-3011 was a randomized double-blind, parallel group, multicenter non-inferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase with PP1M.

In the Double-blind Phase, PP3M was superior to placebo in delaying relapse of symptoms of schizophrenia in subjects who had been stabilized during a 29-week Open-label treatment. A preplanned interim analysis was conducted after the 42nd relapse event. Statistically significant difference between the 2 treatment groups for the time to relapse of symptoms of schizophrenia was demonstrated favor of PP3M. In the final analysis there was a statistically significant difference between the 2 treatment groups in the time to relapse with a longer time

to relapse in subjects assigned to PP3M ($p<0.0001$). Strikingly, three times as many subjects in the Placebo group (29.0%) as in the PP3M group (8.8%) experienced a relapse event. The most common reasons for relapse were increase in PANSS total score and psychiatric hospitalization. Analyses of the efficacy of PP3M compared with placebo with regards to time to relapse of symptoms of schizophrenia was consistent after adjusting for age, sex, race, BMI or region. Analyses of secondary efficacy variables provided further support.

8. Safety

I agree with the safety review and analysis of Dr. Christina Burkhart in her clinical review. Please see her review for detailed discussion. The safety database was adequate given the extensive knowledge of this compound. Within this application safety was based on the phase 3 relapse prevention trial PSY-3201 and randomized, double,-blind placebo controlled, multicenter, relapse prevention study of variable duration proceeded by a 17-week, open-label transition phase with PP1M and a 12-week open-label maintenance phase with PP3M. PSY-3011 was a randomized double-blind, parallel group, multicenter non-inferiority study of 48 weeks duration preceded by a 17-week, open-label stabilization phase with PP1M. The completed PSY-1005 phase one trial of PK and safety was also included in her analysis.

No unique safety findings were noted. There is a slight increase in rated pain on injection presumably from the increased volume but no patients discontinued from the increased discomfort.

9. Advisory Committee Meeting

There is no need for an AC meeting for this change in formulation.

10. Pediatrics

PP1M is not approved for use in the pediatric population. The Applicant has requested and been granted a waiver for the study of PP3M in the pediatric population. There is very little use of injectable antipsychotics in the child population but the use data in adolescence has been increasing. It will be possible in the future that the numbers will increase to the level that it may be necessary to study these products in children.

1) DPMH suggests that the “Indications” and “Dosage and Administrations” sections of the labeling clearly reflect that the proposed product is to be used in “adults only” because of the increased risks of serious adverse events associated with paliperidone use and the availability of shorter-acting antipsychotics, including oral paliperidone.

2) Additional language should be added to “8.4 Pediatric Use” to convey that use of this particular long-acting formulation is not recommended because of the potential longer duration of any serious adverse event compared to shorter-acting products.

11. Other Relevant Regulatory Issues

There are no other outstanding issues.

12. Labeling

DMEPA review Deborah Myers, RPh, MBA provided the labeling review. I agree with her assessment that the revised label (syringe) and labeling (PI, IFU and carton labeling) is acceptable from a medication error perspective. I also agree with her assessment that the human factor studies were acceptable.

Labeling negotiations are ongoing at this time and will be appended if available.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approve.

- Risk Benefit Assessment

The team is agreed that the risk benefit ratio is in favor of approval. There is no evidence of a unique safety signal for this new formulation. Stable patients will benefit from a reduction in shot frequency.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

None.

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/s/

LUCAS P KEMPF
05/13/2015

MITCHELL V Mathis
05/15/2015