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APPLICATION NUMBER:

207946Orig1s000

SUMMARY REVIEW

M E M O R A N D U M

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

DATE: 18 May 2015

FROM: Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products, HFD-130

TO: File NDA 207946

SUBJECT: Summary memo and approval decision for paliperidone palmitate extended-release injectable suspension (3-month injection interval formulation, PP3M) for the treatment of schizophrenia

Background and Summary

Paliperidone palmitate extended-release injectable formulation (3-month injection interval), or PP3M, is a 3-month formulation of paliperidone palmitate, a selective D2 and 5-HT2A antagonist (atypical antipsychotic) already approved in a 1-month formulation for injection. The PP3M formulation allows for every three month dosing which has potential clinical utility for patients who are, by the nature of their disease, often noncompliant with treatment.

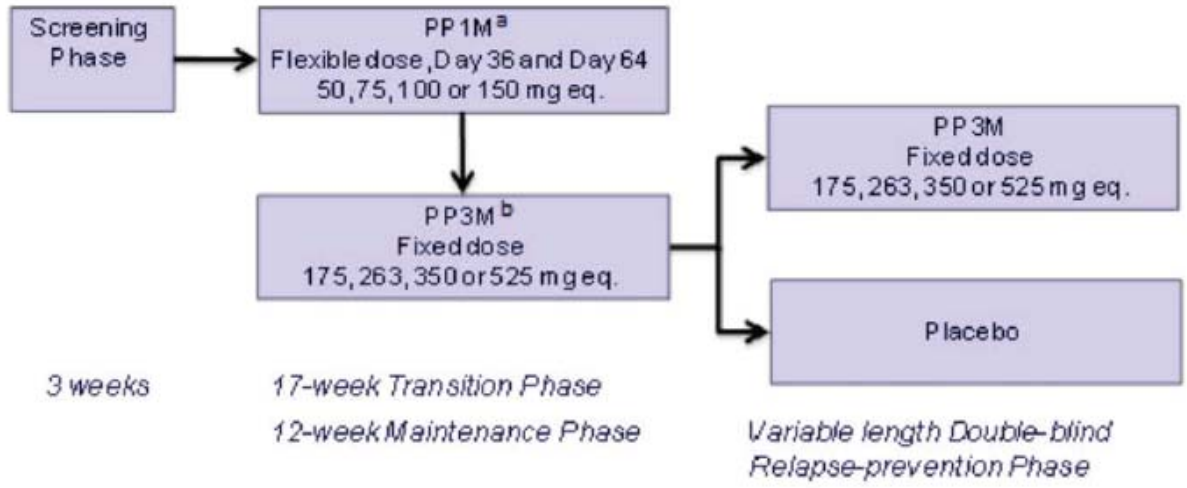
Paliperidone is the metabolite of risperidone, an atypical antipsychotic approved since 1993. Oral paliperidone was approved in 2006 and the one month injectable formulation (PP1M) was approved in 2009. PP3M was designed to be given only to patients who have tolerated the PP1M formulation. Titration of PP1M can take up to 4 months and so PP3M is to be labeled for use in patients who have already had efficacy from and demonstrated tolerability to PP1M.

Clinical Summary and Statistics

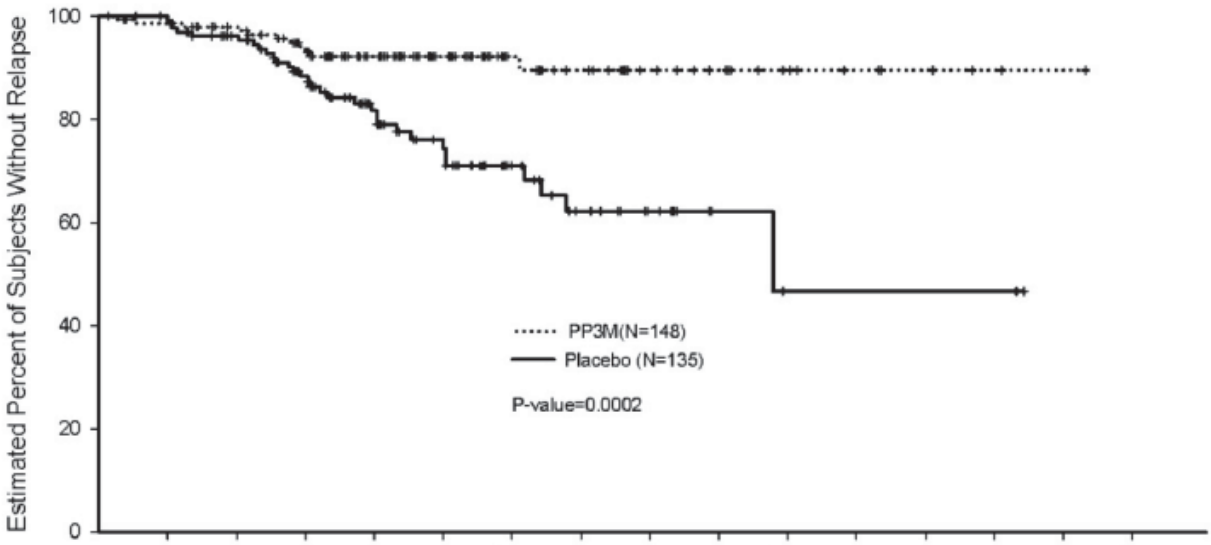
Efficacy

Dr. Christina Burkhart conducted the clinical review and Dr. Wang conducted the statistical review. Efficacy was based on a randomized, double-blind, placebo-controlled relapse-prevention study wherein patients were stabilized for 12 weeks on PP3M after a transition from PP1M. The primary efficacy endpoint was Time to Relapse after randomization to continue PP3M or switch to placebo (see below).

Study Design



Results—Time to Relapse During DB Phase, Interim Analysis



Number of Subjects Left

Time	0	28	56	84	112	140	168	196	224	252	280	308	336	364	392	420
PP3M	148	143	133	104	81	59	35	28	19	15	9	6	4	2	1	0
Placebo	135	131	116	91	61	44	27	18	12	4	2	2	2	0	0	0

The study was halted in accordance with the protocol when statistical significance in favor of PP3M was demonstrated at the pre-planned interim analysis of Time to Relapse. The results were highly statistically significant at the interim analysis p=0.0002. Approximately three times as many patients in the placebo group (29%) as in the PP3M group (9%) experienced a relapse event with the most common relapse events being worsening of psychotic symptoms or psychiatric hospitalization. These results were the same in subgroup analyses based upon age, sex, race BMI, and region. Secondary efficacy variable analysis provided further support of efficacy.

Safety
There is a large safety database for evaluating this drug given the multiple oral formulations and injections of risperidone/paliperidone products. No unique safety findings were noted for this formulation other than a small increase in subjectively rated pain on injection, presumably related to the increased injection volume.

Conclusion
Sufficient evidence has been presented to support the safety and efficacy of PP3M for the treatment of schizophrenia.

Chemistry Manufacturing and Controls (CMC)
Dr. David Claffey and the CMC team have recommended approval. Manufacturing and sterility were adequately addressed by the Sponsor.

Nonclinical Pharmacology/Toxicology
Dr. Chalecka-Franaszek completed the review and recommended approval. There were limited data required of this submission secondary to similarities between PPM3 and the approved PP1M formulation, but the Sponsor did conduct two local tolerability studies in the mini pig. The team identified similar granulomatous lesions at the injection site for both PP1M and PP3M, but noted that the injection sites of the PP3M had more advanced histologic appearance than in the PP1M injection sites. While not an approval issue, the team recommended that this difference be included in labeling and we have incorporated that language.

Dr. Chalecka-Franaszek also recommended that the DMF be updated to limit the dose of each of two Ames mutation assay positive impurities ((b) (4) and (b) (4)) to (b) (4) per injection. Dr. Atrakchi, the nonclinical team supervisor, cites ICH M7 (June 2014) in disagreeing with Dr. Chalecka-Franaszek's recommendation. Dr. Atrakchi argues that Section 7.3 of M7 (Acceptable intakes in relation to LTL [Less than Lifetime] Exposure), discusses the approach to LTL exposure to mutagenic impurities in pharmaceuticals in which the cumulative lifetime dose is uniformly distributed over the total number of exposure days during LTL. This would allow for a higher "daily" intake of impurity with drug than would be the case for lifetime exposure, and still maintain a comparable carcinogenic risk for daily and non-daily dosing (1 in 100,000). When calculated in this way, PP3M administered every 90 days will have 280 dosing days over 70 years (a "lifetime"), which for these impurities, would result in less than the 20 micrograms/day limit as presented in ICH M7. Therefore, the nonclinical supervisor recommends the limits for the 2 genotoxic impurities in the drug substance be set at NMT (b) (4) ppm for each impurity based on the LTL approach outlined in the 2014 ICH M7 Guideline. I interpret ICH M7 in the same way as Dr. Atrakchi and therefore I agree with her. The DMF holder had set a limit of (b) (4) ppm for these impurities as was done for PP1M, and they have recently reduced this limit to (b) (4) PPM.

Office of Clinical Pharmacology (OCP)
Dr. Kumi reviewed Study PSY-1005, a single-dose Phase 1 PK study, as well as data from the Phase 3 study, and he has recommended approval. He concluded that PP3M dissolves slowly after injection and becomes hydrolyzed to paliperidone and absorbed. Drug release begins at Day 1 and minimal concentrations are still measurable at 18 months after the last dose. Time to maximum concentration is 30-33 days and total exposure is proportional over the dosing range of 273 mg to 819 mg. Dr. Kumi determined that PP3M administered at doses 3.5-times higher than PP1M result in paliperidone exposures similar to those obtained with three monthly dose of PP1M. Differences

in gluteal versus deltoid injection sites were minimal, and dosing is therefore the same for both sites of administration. Multiple models were constructed to provide information on switching between formulations of paliperidone, as well as calculated best corrections for missed dose scenarios and this information has been included in labeling to assist the prescriber.

Labeling
The team constructed labeling based upon PP1M labeling, and updated it to include information specific to the PP3M formulation. Comments/suggestions/edits from the team were considered and sent to the Sponsor multiple times for concurrence. The Office of Prescription Drug Promotion also reviewed the label and their changes were incorporated. The sponsor has accepted the labeling changes and a final version will be attached to the letter.

Postmarketing Requirements/Commitments
No post-marketing requirements or commitments have been identified.

Conclusions
Sufficient information has been submitted to conclude that PP3M is safe and effective in treating schizophrenia

The labeling has been negotiated to current Division standards.

The sponsor has agreed to the negotiated label; this application should be approved by the PDUFA date.

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