CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

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: July 31, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Invega Sustenna (paliperidone palmitate (b) (4)) for schizophrenia (both acute and maintenance efficacy)

TO: File NDA 22-264
[Note: This overview should be filed with the 2-3-09 response to the 8-25-08 CR letter.]

1.0 BACKGROUND

Paliperidone palmitate (b) (4) is a depot formulation of paliperidone, an atypical antipsychotic (5HT2 and D2 receptor antagonist). Paliperidone is the major active metabolite of risperidone and has essentially the same pharmacological profile as risperidone which is approved for the treatment of schizophrenia and bipolar mania. Paliperidone is available in an extended release oral formulation for both the acute and maintenance treatment of schizophrenia. This NDA seeks a claim for this depot formulation for both the acute and maintenance treatment of schizophrenia, in a dose range of 25 to 150 mg eq intramuscular injections (either deltoid or gluteal) every month. As noted, a CR letter was issued for this NDA on 8-25-08. This letter identified a number of product quality issues and labeling issues, provided a proposed dissolution method and specifications, and requested a safety update. We met with the sponsor on 11-21-08 to discuss various issues pertinent to a resubmission of this application. These issues and their resolution will be summarized in the sections below. The application was resubmitted on 2-3-09.

2.0 CHEMISTRY

Issues that needed resolution:

Drug master file for the (b) (4)
Issue: The DMF was noted to be inadequate in the CR letter.

Resolution: The sponsor has submitted information that has been determined to address the deficiencies.

Expression of dose strengths of drug substance vs active portion of molecule in the package insert, syringe labeling, and carton labeling

Issue: In their originally proposed package insert, syringe labeling, and carton labeling, the sponsor wanted to emphasize the active portion of the molecule (paliperidone mg equivalents), rather than actual drug substance strength (paliperidone palmitate). In the CR letter, we emphasized to the sponsor the problem this would pose for us in terms of FDA policy regarding what information is required in the established name. We discussed this issue at length at our 11-21-08 meeting with the sponsor, essentially indicating that it would be a review issue when they resubmitted the application. We have discussed this issue extensively within FDA subsequent to the resubmission of this application, and the FDA groups that would be most impacted by deviation from FDA policy on this matter (ONDQA, DMEPA, and OGD) argued strongly against permitting the sponsor to focus on paliperidone equivalents. The concerns are that this would be confusing, would be a potential source of medication errors, and would be very problematic at the point that a generic paliperidone depot formulation becomes available. Therefore, we have taken a position that the package insert, syringe labeling, and carton labeling should note only the drug substance strengths (i.e., 39, 78, 117, 156, and 234 mg of paliperidone palmitate), with no mention of the equivalents (i.e., 25, 50, 75, 100, and 150 mg eq). We did subsequently agree to include mention of the equivalents in the Description section.

Resolution: [redacted] (b) (4) We have now provided advice in the Dosage and Administration section of labeling on switching from oral paliperidone to the depot (in the form of a conversion table).

Desirability for transparent label and for calibrated markings and fill line on syringe barrel

Issue: In the CR letter, we indicated that the syringe barrel should contain calibrated markings to indicate the appropriate volume of drug product in the syringe and allow for partial doses to be given from the syringe. The letter also noted that a transparent label that would allow for viewing of the syringe calibration marks and drug product should be used for labeling of the syringes [redacted] (b) (4) In our 11-21-08 meeting, we agreed that calibrations would not be needed. We indicated that we still felt that a fill line was needed to allow determination by the user that the syringe had been filled properly, and a fill window. [redacted] (b) (4)

-We have had numerous subsequent internal discussions and interchanges regarding this issue. Some have continued to argue for the need for a fill line

Resolution: The sponsor has agreed to make this change as a phase 4 commitment.

Use of "(b) (4)" in drug product established name

Issue: In the CR letter and attached labeling, we referred to this product as "Invega Sustenna (b) (4) In subsequent discussions with ONDQA, DMEPA, and other groups within FDA that have an interest in this question, the overwhelming consensus is that we cannot continue with the (b) (4) terminology. This is not official USP terminology and not recognized, and will cause multiple problems. ONDQA has recommended the following alternative terminology: "Invega Sustenna Extended Release Injectable Suspension."

Resolution: We have decided to adopt the alternative language recommended by ONDQA. The sponsor has reluctantly accepted this alternative language.

Establishing acceptable acceptance criteria for the two genotoxic impurities, (b) (4) and (b) (4)

Issue: In the CR letter, we asked the sponsor to establish acceptance criteria equal to or less than (b) (4) ppm for the two genotroxic inpurities, (b) (4) and (b) (4)

Resolution: We now have agreement on a specification of (b) (4) ppm.

Establishing a test and acceptance limit for (b) (4)

Issue: In the CR letter, we asked the sponsor to include a test and acceptance limit for (b) (4) in the drug product specification.

Resolution: We have now agreed with the sponsor that this test would not be needed.

Other CMC syringe labeling and carton labeling issues

Issues: In the CR letter we conveyed a number of comments on syringe and carton labeling.

Resolution: Most of these issues have been resolved. We will include some final recommendations in approval letter, and also advise that they include mention of the frequency of dosing on the carton label to help clinicians distinguish this from other formulations, (b) (4)

Dissolution method and specifications

Issue: We still needed agreement on this issue.

Resolution: We now have agreement on the dissolution method and specifications.

3.0 PHARMACOLOGY

There are no pharmacology/toxicology issues at this point that would preclude an approval action for this NDA.

4.0 BIOPHARMACEUTICS

All biopharmaceutical issues have been resolved.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Original Application

Short-Term Trials

Our review of the original application focused on 3 short-term (9 to 13-week), double-blind, randomized, parallel group, placebo-controlled, fixed-dose trials in patients with acutely exacerbated schizophrenia and 1 maintenance study in schizophrenic patients stabilized on paliperidone depot. In all of these studies, the depot injections were administered in the gluteal muscle.

Studies 3003 and 3004 were 13-week studies in which patients received 3 fixed doses of paliperidone depot or placebo (50, 100, and 150 for 3003; 25, 50, and 100 for 3004). Doses were given on days 1, 8, 36, and 64. The end-of-study visit was day 92. The primary endpoint in these studies was change from baseline to endpoint on the PANSS total score. No key secondary endpoints were clearly specified and no claims were sought by the sponsor based on secondary endpoints. There was a problem in treatment distribution in study 3003 such that only 30 patients received the 150 mg eq dose. Thus, the data for this dose group are not meaningful. Study 201 was similar in design to studies 3003 and 3004 except that it was 9 weeks in duration and utilized only 2 fixed doses (50 and 100 mg eq). The 100 mg eq dose was statistically significantly superior to placebo each time it was tested (studies 3003, 3004, and 201). The 50 mg eq dose was statistically significantly superior to placebo on 2 occasions it was tested (studies 3004 and 201), but not in study 3003. The 25 mg eq dose was statistically significantly superior to placebo on the one occasion it was tested (study 3004). There was a suggestion of numerical superiority of the 100 mg eq dose over the lower doses. (b) (4)

Maintenance Study

Study 3001 was a maintenance study involving a 33-week open label phase (9 weeks of transition and 24 weeks of stabilization) before randomization. During the double-blind randomized phase, patients who were stable responders were randomized to either paliperidone depot (monthly injections of 25, 50, or 100 mg eq) or placebo. The primary endpoint was time to recurrence. The protocol called for an interim analysis after 68 recurrence events had occurred. This analysis was done and was highly significant in favor of paliperidone depot ($p<0.0001$). Thus, the study was stopped (stopping threshold was $p=0.0106$).

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