CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202-971/S003

CROSS DISCIPLINE TEAM LEADER REVIEW

AM 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: Nov. 30, 2014

FROM: Jing Zhang, MD. PhD.
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HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 202971/S-03

Proprietary/ Established name: Aripiprazole for Extended Release Injectable Suspension

Dosage forms/ Strength: Powder for Suspension, 300 and 400 mg

Indication: Schizophrenia (b) (4) Treatment in Adults

Recommendation: Approval

I. Introduction and Backgroun

Aripiprazole is a dopamine presynaptic D_2 auto-receptor partial agonist and belongs to atypical antipsychotic family. Same as other atypical antipsychotics, aripiprazole also acts as an antagonist at serotonin 5-HT_{1A} receptor.

ABILIFY® (aripiprazole) is initially approved by FDA for the treatment of schizophrenia in adults in 2002. Subsequently it has been approved for indications of acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder; and treatment of irritability associated with autistic disorder. The current approved indication for the immediate-release injectable formulation of aripiprazole is treatment of acute agitation associated with schizophrenia or bipolar I disorder. The IM depot formulation of aripiprazole was first approved for the indication of maintenance treatment of schizophrenia in Feb. 2013. Currently there are four formulations available for aripiprazole: ABILIFY oral tablets, oral solution, orally disintegrating tablets,

intramuscular injection (immediate-release), and extended release injectable suspension (depot).

A Type B Pre-sNDA Meeting was scheduled for July 16, 2013 to "discuss and receive Agency feedback on the clinical development program and the proposed sNDA for ABILIFY MAINTENA for the treatment of (b) (4) schizophrenia." Of note, the sponsor was satisfied with our preliminary responses, so the meeting was cancelled.

This NDA application submitted on February 7, 2014 included the results from one short-term (12-week), randomized, double-blind, placebo-controlled trial, 31-12-291, in acutely relapsed adults with schizophrenia and an open-label safety study, 31-12-297, enrolled patients who completed Trial 31-12-291.

II. Summary of Conclusions and Recommendations from Review Teams

1. CMC

The application does not provide for any changes to the drug product, manufacturing process, or specifications and there are no CMC-related labeling changes. A claim for categorical exclusion under 21 CFR Part 25.31(b) is included in the submission. Approval of the supplement may result in expanded use of the active moiety. However, the concentration of the active moiety at the point of entry into the aquatic environment will be below 1 ppb (0.224 ppb). Therefore, our CMC review team concluded that the claim of categorical exclusion is accepted.

2. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical pharmacology/toxicology issues for this application.

3. Clinical Pharmacology/Biopharmaceutics

There are no unresolved clinical pharmacology/biopharmaceutics issues for this application.

4. Clinical/Statistical

This submission consists of only one pivotal study, 31-12-291, (b) (4) The study was conducted from October 12, 2012 to August 30, 2013 in 41 study sites (37 in the US, 2 in Croatia and 2 in Latvia).

Dr. Phillip Kronstein is the medical reviewer who performed efficacy and safety review on the submission. Yeh-Fong Chen, PhD is the statistical review who focused on the efficacy review. Please refer to their reviews for more information.

Study design

Study 31-12-291 is a 12-week, multicenter, randomized, double-blind, placebo-controlled trial to study the efficacy and safety of aripiprazole intramuscular depot in acute treatment of schizophrenia in adults. The trial included a 13-day Screening Phase, a 12-week Acute Treatment Phase, and a 14 day Safety Follow-up phase. Eligible patients, 18 to 65 years with DSM-IV-TR diagnosis of schizophrenia, had to be experiencing an acute exacerbation of psychotic symptoms. The dose of aripiprazole IM depot was 400 mg q4 weeks with allowed decrease to 300 mg for safety and return to 400 mg for efficacy if needed. If subjects had not been exposed to aripiprazole in the past, oral aripiprazole 10 mg daily was given for 3 days "to establish tolerability" prior to the 7-day washout period. Completers of the acute treatment phase were able to enter the 6-month open-label extension trial (Study 31-12- 297) at the Investigator's discretion.

Eligible subjects were randomized in a 1:1 ratio to either aripiprazole IM depot or placebo, received gluteal muscle injection every 4 weeks during the 12-week Acute Treatment Phase for a total of three injections. For the first 14 days, subjects randomized to aripiprazole IM depot also received concomitant oral aripiprazole, 10 to 20 mg/d.
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The primary efficacy endpoint was the change from baseline to Week 10 in the PANSS total score. The key secondary efficacy endpoint was the change from baseline to Week 10 in the Clinical Global Impression - Severity (CGI-S) scale.

The primary analysis was performed using the Mixed Model Repeated Measure (MMRM) approach. Analyses included the categorically fixed effects of treatment, region (pooled sites), trial week, and treatment-by-week interaction, as well as the continuously fixed covariates of baseline score-by-week interaction. An unstructured covariance structure was used to model the within-subject errors and Kenward-Rodger degree of freedom was used to test the fixed effects.

Efficacy Review

Three hundred forty patients were randomized from 41 trial sites, where 168 were assigned to aripiprazole IM depot 400 mg/300 mg and 172 were assigned to placebo. However, only 162 patients on aripiprazole IM depot 400 mg/300 mg and 167 patients on placebo group were included in the modified Intent to Treat (mITT) population—the primary efficacy sample.

The demographic characteristics and disease characteristics were similar between two treatment groups. Most subjects randomized were male (79.1%), Black/African American (65.6%) and non-Hispanic/Latino (90.3%). The mean age was 42.4 years and mean BMI was 28.5 kg/m^2. Most subjects (96.2%) were enrolled in the US. Patients enrolled were markedly ill with mean PANSS total score 103 (range 82 -144).

The overall completion rate was low in this trial, 64.3% in the aripiprazole IM depot and 49.4% of placebo groups, respectively, at Week 10. Similar low completion rates were also

seen in the acute treatment trials with other atypical antipsychotics depots. Therefore, we feel the data from this trial are still adequate to support the proposed claim. The most frequent reasons of discontinuation were "lack of efficacy" in placebo group (29.1% in placebo vs. 7.1% in aripiprazole) and "subjects withdraw consent" in aripiprazole group (19.0% in aripiprazole versus 8.7% in placebo).

For the primary efficacy analysis, the treatment difference between the aripiprazole IM depot 400 mg/300 mg group (mean change -26.8) and the placebo group (mean change -11.7) at Week 10 was –15.1, which is statistically significant with $p<0.0001$. The treatment difference at Week 12 was -14.6, which was also statistically significant with $p<0.0001$.

The sponsor also performed sensitivity analyses by ANCOVA for the last observed carried forward data (ANCOVA-LOCF) and observed cases (ANCOVA-OC). The results from both analyses were consistent with those by MMRM— the p-values were less than 0.05 for all weeks.

For secondary efficacy analysis, the differences of CGI-S score between the aripiprazole IM depot and placebo groups at every week were all statistically significant, with a p-value ≤ 0.0001.

The sponsor also performed exploratory subgroup analyses for gender, race, age, ethnicity, and BMI for the change from baseline to endpoint (Week 10) in PANSS total score and CGI-S score and did not find any significant differences.

Our statistical reviewer, Yeh-Fong Chen, PhD, confirmed the sponsor's analyses and agreed that the data from Study 31-12-291 support the efficacy of aripiprazole IM depot 400 mg/300 mg in treating patients with schizophrenia, based on the prospectively specified efficacy endpoints.

Yeh-Fong Chen, PhD, also found that the sponsor included the following statement in the proposed product labeling (section 14) (b) (4)

(b) (4)

(b) (4)

I agree with her review and her recommendation to remove these languages from the product label.

It is also noted that more than half of patients who were randomized were aripiprazole naïve (58% in aripiprazole IM depot and 56% in placebo). Additional analyses indicated that aripiprazole IM depot had a larger treatment effect in aripiprazole naïve patients than in those who had been previously treated with aripiprazole. However, aripiprazole IM depot appeared to be effective in both subgroups.

Surprisingly, more patients in placebo group (7.6% vs. 4.2%) discontinued study due to adverse events. There was a higher than normal percentage of dropouts due to withdrawal of consent in the aripiprazole IM depot group (19%; twice the rate of placebo), and of amount these patients, 63% were aripiprazole naïve, which may indirectly indicate these subgroup patients did not tolerate aripiprazole IM depot group as well as the placebo group.

Safety Review

The studies used to evaluate the safety of aripiprazole IM depot are a pivotal efficacy and safety study, 31-12-291, and an open-label safety study, 31-12-297, which is an open label extension of that study 31-12-291. The safety review mainly focuses on the safety data obtained from study 31-12-291. Due to the open label nature of study 31-12-297, the safety data from this study was mainly used to review deaths and serious or unexpected adverse events. Dr. Phillip Kronstein is the primary reviewer for safety. Please refer to his review for details.

In this clinical program, as of cutoff date of June 30, 2013, ABILIFY MAINTENA has been evaluated for safety in 2,188 adult patients in schizophrenia clinical trials with approximately 2,646 patient-years of exposure. A total of 1,230 patients were treated for at least 180 days and 935 patients had at least 1 year of exposure.

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Study 31-12-291

No deaths were reported in the study.

Fourteen (4.1%) of 339 subjects reported serious adverse events (SAEs), including 8/167 (4.8%) of aripiprazole IM depot subjects and 6/172 (3.5%) of placebo subjects. SAEs reported for ≥1% of aripiprazole IM depot subjects were “schizophrenia” (n=3) and “psychotic disorder” (n=2), which were related to patient’s underline psychiatric condition. No new clinically significant SAEs were believed to be associated to aripiprazole treatment in this study.

Twenty patients (5.9%) discontinued the study due to treatment-emergent adverse events (TEAEs), which included 7/167 (4.2%) subjects in the aripiprazole IM depot group and 13/172 (7.6%) for placebo. The reasons reported for ≥1% of subjects in any treatment group were “schizophrenia” and “psychotic disorder”, which indicated lack of treatment efficacy.

TEAEs reported at a rate of ≥5% in the aripiprazole IM depot group and at least twice the rate of placebo were increased weight (16.8% vs.7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs. 0.6%), and sedation (5.4% vs 1.2%).

The common adverse event profile of the aripiprazole IM depot was similar to the oral aripiprazole except the injection site related adverse events.

No clinically significant laboratory findings in this study. The only clinically relevant hematology value reported for ≥5% of aripiprazole IM depot subjects and at an incidence greater than placebo was low absolute neutrophil count (5.7% vs 2.1%), defined as absolute neutrophils of ≤1.5 thous/μL. Neutropenia is a labeled AE in the Warning and Precaution section of the product label. Dr. Kronstein reviewed all 8 cases who had absolute neutrophils of ≤1.5 thous/μL and were in aripiprazole treatment, and felt 4 of the 8 cases were probably drug related. None of the cases were fatal, serious, or led to discontinuation of study. However, he identified that 3 of 4 cases had a low absolute neutrophil count (ANC) at the screening. He proposed to add low ANC as a possible risk factor for neutropenia in the label. I agree with his recommendation.

No subject in either treatment group had a TEAE related to lipid parameters.
There was a higher incidence of clinically relevant increases, from baseline for the aripiprazole IM depot group vs. placebo to week 12, in fasting total cholesterol (≥40 mg/dL, 12.3% vs. 5.5%), fasting calculated LDL cholesterol (≥30 mg/dL, 14.2% vs. 8.7%) and fasting triglycerides (≥50 mg/dL, 19.7% vs. 18.2%). A lower incidence of clinically relevant decreases from baseline in fasting HDL (≥20 mg/dL) occurred in the aripiprazole IM depot group (5.7%) compared to placebo (10.9%).

No subject in either treatment group had a TEAE related to glucose metabolism. At Week 12, there was a mean increase from baseline in fasting glucose values in the aripiprazole IM depot group (9.82 mg/dL) and in the placebo group (0.69 mg/dL).

No clinically relevant mean changes from baseline were observed in vital sign parameters (excluding weight) during the Acute Treatment Phase. The mean changes in weight from baseline for the aripiprazole IM depot group were 3.5 kg at Week 12 and 2.8 kg at the last visit, compared to 0.8 kg at both Week 12 and at the last visit for the placebo group. The incidence of weight gain ≥7% was higher in aripiprazole IM depot group (21.5% vs. 8.5%).

Metabolic changes are well known adverse events for aripiprozole treatment. The findings of lipid, glucose parameters and weight gain in this study are consistent with the safety profile of oral aripiprazole and these adverse events had been labeled in the Warning and Precaution section of the label.

No TEAEs related to QT intervals were reported in either treatment group during the Acute Treatment Phase. No subjects in either treatment group had a new onset QTc interval >500 msec or had a change from baseline QTc value that was ≥60 msec.

During the Acute Treatment Phase, aripiprazole IM depot treated patients had higher incidence of EPS-related TEAEs (19.2% vs. 8.1%). Except for akathisia and tremor, the incidence of EPS-related TEAEs was comparable between the treatment groups. Akathisia accounted for approximately half of the EPS-related TEAEs in the aripiprazole IM depot group during this trial. The incidence rate of EPS-related TEAEs in this study was comparable with the findings in other previously conducted controlled aripiprazole clinical trials.

At Week 12, there were mean decreases from baseline in prolactin for the aripiprazole IM depot group (−6.4±13.5 ng/mL) and the placebo group (−1.1±14.5 ng/mL). These decreases may be result of subjects being switched from an antipsychotic more likely to cause prolactin elevation (taken before the trial) to aripiprazole.

Nine (5.4%) of 167 aripiprazole IM depot and 2/172 (1.2%) placebo subjects experienced TEAEs related to the injection site, which were mainly injection site pain. Investigators rated pain, swelling, redness, and induration at the injection site as absent for most subjects in both treatment groups.

Study 31-12-297

No deaths reported in study 31-12-297.

A total of 5/74 (6.8%) subjects had 6 serious adverse events during this open-label extension trial. One subject had a spontaneous abortion (patient had history of spontaneous abortion at age 18 due to unspecified uterus problem), 2 subjects had depression, one subject had worsening of schizophrenia, and one subject had an exacerbation of schizophrenia and suicidal ideation. None of the SAEs appeared to be related to aripiprazole IM depot therapy.

A total of 6/74 (8.1%) subjects were discontinued from aripiprazole IM depot due to TEAEs. One subject had a moderate TEAE of "hepatic enzyme increased" (ALT 156 U/L, AST 72 U/L, and GGT 111 U/L at the first day of received aripiprazole IM depot injection) and one subject had a moderate TEAE of "weight increased." The other TEAEs leading to discontinuation are already discussed as SAEs.

The safety profile of aripiprazole IM depot in study 31-12-297 remained no change compared to other aripiprazole IM depot clinical trials. No any new or unexpected safety signal had been identified from study 31-12-297.

5 Labeling Recommendations

Several revisions of physician labeling had been recommended by the review division, OCP team, OPDP. These recommendations had been incorporated in our labeling recommendations. We are still in the process negotiating the labeling with the sponsor. The final agreed upon labeling will be attached to the action letter when this NDA is taken action.

6 OSI Audits

Study 31-12-291 was conducted at 41 clinical investigator sites, of which two were inspected by OSI in support of this NDA review. The sites of Tram K. Tran-Johnson, Pharm. D. (Site 907) and David P. Walling, Ph.D. (Site 926) were selected for inspection based on high subject enrollment and large contribution to the overall treatment effect for the primary efficacy endpoint.

John Lee, MD., is the medical reviewer for this NDA in OSI. The inspection included an audit of case records for 46 subjects (14% of total study enrollment). He concluded in his review that no significant deficiencies were observed and all audited data were verifiable. The data from the two sites appear reliable as reported in the NDA.

7 Pediatric Plan

A full pediatric waiver had been granted by Pediatric Review Committee prior to the NDA submission. No any pediatric study is required.

8 Post Marketing Commitments or Requirements

No post marketing commitments or requirements are deemed necessary.

9 Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

10 Conclusions and Recommendations

I agree with both Doctors Kronstein and Chen that the data from Study 31-12-291 support the efficacy claim of aripiprazole IM depot 400 mg/300 mg in the treatment (b) (4) of schizophrenia in adults based on the prospectively specified efficacy endpoints. I agree with Dr. Kronstein's safety review that aripiprazole IM depot is relatively safe and well-tolerated at dose of 400 mg/300 mg in acute treatment of schizophrenia in adults. The safety profile of aripiprazole IM depot in study 31-12-291 and 31-12-297 is consistent with our previous findings. There is no any new or expected safety signals identified in this submission. I recommend that the Division take approval action on this submission once we reach agreement with the sponsor on the product labeling.

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/s/

JING ZHANG
11/30/2014