CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202971Orig1s000

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: 28 February 2013

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

TO: File NDA 202971 [26 Sep 2011 submission]

SUBJECT: Approval recommendation for aripiprazole for extended release injectable suspension (Abilify Maintena) for the treatment of schizophrenia

Background and Regulatory History
Abilify Maintena (aripiprazole for IM injection) is a depot formulation of the atypical antipsychotic aripiprazole approved as an oral formulation for the treatment of schizophrenia, bipolar disorder, adjunctive treatment of MDD, and irritability of autism.

This NDA (developed under IND 67,380) was designed to support a claim for the treatment of schizophrenia at doses of 300 mg or 400 mg delivered intramuscularly (IM) (b) (4). The clinical claim is based upon the findings of a single maintenance trial in patients with schizophrenia.

Chemistry Manufacturing and Controls
The sponsor intends to market this drug in a kit with sterile water for injection. Dr. Claffey reviewed this application from the CMC group. Drs. Ryan and Nguyen from CDRH, and Dr. Cole from Microbiology also conducted reviews. All CMC, device-related issues, and product labeling/medication errors questions were resolved in the last review cycle, but there was a problem with the sterile water in the kit.

The problem stemmed from an inspection at the manufacturing facility where the sterile water to be included in the kit was to be manufactured. While there was no problem identified with the water, there were other site problems that compelled the Office of Compliance to issue a "withhold" recommendation for the entire facility and so the Division issued a CR Letter on 26 July 2012.

The sponsor arranged for a new manufacturer for the sterile water after receiving the CR Letter and that manufacturer has been found to be acceptable by OC.

Nonclinical Pharmacology/Toxicology
There are no unresolved pharmacology/toxicology issues for this application.

Office of Clinical Pharmacology
Three clinical pharmacology trials were included in this NDA: a single dose *in vivo* release characteristics study (CN138-020), a single dose PK study (31-007-02), and a multiple dose PK study (31-07-244). The sponsor conducted population PK analyses and simulations to evaluate

drug-drug interactions, missed doses, and dose dumping. Drs. Zhang and Brar reviewed the data and agreed that they support the proposed use for maintenance treatment. They also agreed with the Sponsor's proposed two week oral supplementation strategy at the beginning of treatment as well as dose adjustments required for 2D6 poor metabolizers and for patients taking strong 2D6 and 3A4 inhibitors.

Clinical

Efficacy

Because aripiprazole has been approved to treat schizophrenia, the division required a single additional efficacy and safety trial (31-07-246) for this injectable formulation. This maintenance trial demonstrates that this formulation will delay time to relapse in patients with schizophrenia.

Patients on oral formulations of approved drugs, including aripiprazole, were stabilized on oral aripiprazole at labeled doses for 4 weeks. Stable patients were then switched to study drug injected at 400 mg each month (could be reduced to 300 mg if adverse reactions) while continuing oral medication for the first 2 weeks after the first injection (to allow the depot to reach therapeutic blood concentration). Patients stable on the depot for 12 weeks were then randomized to continue the depot or to switch to IM placebo and observed for relapse. Time to relapse was the primary endpoint and percentage relapsed was the key secondary. Four hundred and three patients were randomized and the results were statistically significant (HR was 0.2 [$P < 0.0001$] for the primary) and relapse percentages of 10% on drug and 40% placebo.

Drs. Dubitsky, Zhang, and Laughren from the clinical team and Dr. Parfionoval from Biostatistics all agreed that this study supports the sponsor's claim.

Safety

Safety data for this formulation were derived from 3 PK studies and 7 large phase 3 trials (study for US efficacy presented above and multiple EU trials). Safety data were available from 1287 patients receiving one or more doses in the recommended dose range of 300 mg - 400 mg. This group included 832 patients who received monthly injections for at least 6 months and 630 with monthly injections for at least 12 months.

The safety profile of the depot formulation mirrored what is known about the oral formulation except for injection site adverse events we expect to see with depot formulations. There were 12 deaths in patients on depot, but they were from widely variable causes and most were related to underlying disease (cancer, heart disease, schizophrenia (suicide)). Therefore, the safety profile of the depot formulation has been adequately characterized in labeling.

Revised Labeling

Labeling has been negotiated and agreement reached.

Conclusions and Recommendations

The sponsor has provided adequate evidence that Abilify Maintena is efficacious to reduce the risk of relapse in patients with schizophrenia. There were no new or unexpected clinical safety findings. The review team has recommended approval of this supplement and I agree with the team. There are no outstanding review or inspection issues. Labeling has been negotiated and finalized.

The sponsor has agreed to labeling and this application should be approved by the PDUFA date.

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/s/

MITCHELL V Mathis
02/28/2013