

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

DATE: May 6, 2008

FROM: Thomas P. Laughren, M.D.
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HFD-130

SUBJECT: Recommendation for approval actions for Abilify supplements for a 15 mg/day starting dose in bipolar disorder and for Abilify supplements for adjunctive therapy at a 15 mg/day starting dose in bipolar disorder patients who are “partial non-responders” to either valproate or lithium

TO: -File NDAs 21-436/S-019 (Abilify tabs), 21-713/S-014 (oral solution), 21-729/S-006 (ODT), and 21-866/S-006 (IM)
-File NDAs 21-436/S-020 (Abilify tabs), 21-713/S-015 (oral solution), 21-729/S-007 (ODT), and 21-866/S-007 (IM)
-[Note: This overview should be filed with the 7-11-07 original submission of these supplements.]

1.0 BACKGROUND

Abilify (aripiprazole) is an atypical antipsychotic (5HT2 antagonist and D2 receptor partial agonist) that is approved for both schizophrenia and bipolar disorder in adults (mania and mixed episodes), both acute and maintenance therapy for both, for schizophrenia and bipolar disorder (mania and mixed episodes) in pediatric patients, and as adjunctive treatment in patients with MDD who have had a partial response to available antidepressant therapy. These supplements provide support for:

- The efficacy and safety of a 15 mg/day starting dose in the treatment of bipolar disorder (mania and mixed episodes). [Note: Current labeling recommends a starting dose of 30 mg/day.] The support for this new claim includes the results of 2 short-term (3-week) studies in this population where the starting dose was 15 mg/day, and where the dose could be increased to 30 mg/day as needed.
- The efficacy and safety of a 15 mg/day starting dose as adjunctive therapy in bipolar disorder patients who were “partial non-responders” to either valproate or lithium. The support for this new claim includes the results of a short-term (6-week) study in this population where the starting dose was 15 mg/day, and where the dose could be increased to 30 mg/day as needed.
- We held a preNDA meeting with the sponsor on 2-26-07.

2.0 CHEMISTRY

The only CMC issues requiring review were very minor labeling changes and environmental assessment. The minor labeling issues have been addressed, and the sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

There were no pharm/tox review issues for consideration.

4.0 BIOPHARMACEUTICS

The only relevant biopharmaceutics results requiring review came from a drug-drug interaction study involving aripiprazole and lamotrigine. These data were submitted in a separate supplement but were reviewed and will be acted on as part of the review of these supplements. This review revealed no effect of aripiprazole on lamotrigine pharmacokinetics. OCP recommended a slight modification to labeling regarding these findings, and we have reached agreement with the sponsor on these changes.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Efficacy data for a 15 mg/day starting dose in mania

Our efficacy review focused on two nearly identically designed 3-week, multicenter, double-blind, parallel group, randomized, placebo-controlled, flexible-dose monotherapy studies in adult patients with bipolar disorder (mania or mixed episodes) (CN138135 and CN138162). Each study had an active comparator group, lithium for study C-135 and haloperidol for study C-162. Thus, patients were assigned to aripiprazole, an active comparator, or placebo. Patients assigned to aripiprazole had a starting dose of 15 mg/day, and the dose could be increased to 30 mg/day as early as day 4, if needed. The primary endpoint was change from baseline to endpoint in YMRS total score, and the key secondary endpoint was change from baseline to endpoint in the CGI-S-BP (bipolar) score. There was a 9-week active controlled phase following the initial 3 weeks of treatment during which patients who had been receiving placebo were switched to aripiprazole and patients already receiving active drug were simply continued. Data from this phase have not been reviewed from the standpoint of efficacy.

5.1.1.1 Study CN-138135

N=480 patients were randomized to treatment (ITT Sample: 163 to placebo, 155 to lithium, and 162 to aripiprazole). Overall, there was about a 50% dropout rate by week 3. The mean

aripiprazole dose during the 3rd week was approximately 23 mg/day. The outcome for aripiprazole vs placebo was significant for both YMRS (P<0.001) and CGI-S-BP (P=0.002).

5.1.1.2 Study CN-138162

N=485 patients were randomized to treatment (ITT Sample: 152 to placebo, 161 to lithium, and 166 to aripiprazole). Overall, there was about a 25% dropout rate by week 3. The mean aripiprazole dose during the 3rd week was approximately 23 mg/day. The outcome for aripiprazole vs placebo was significant for both YMRS (P=0.039) and CGI-S-BP (P=0.044).

5.1.2 Efficacy data for adjunctive therapy in bipolar disorder patients who were “partial non-responders” to either valproate or lithium t a 15 mg/day starting dose

Our efficacy review focused on a 6-week, multicenter, double-blind, parallel group, randomized, placebo-controlled, flexible-dose, adjunctive therapy study in adult patients with bipolar disorder (mania or mixed episodes, with or without psychotic features) (CN138134) who were partially non-responsive to either lithium or valproate. Thus, patients were assigned to either adjunctive aripiprazole or adjunctive placebo, on a 2:1 ratio. Patients assigned to adjunctive aripiprazole had a starting dose of 15 mg/day, and the dose could be increased to 30 mg/day as early as day 7, if needed. The primary endpoint was change from baseline to endpoint in YMRS total score, and the key secondary endpoint was change from baseline to endpoint in the CGI-S-BP (bipolar) score. N=384 patients were randomized to treatment (ITT Sample: 130 to placebo and 247 to aripiprazole). Overall, about 81% of patients completed the study. The outcome for aripiprazole vs placebo was significant for both YMRS (P=0.002) and CGI-S-BP (P=0.014).

5.1.3 Summary of Efficacy

There was unanimous agreement within the review team on the positive outcomes for the primary and key secondary endpoints in these studies. I agree.

5.2 Safety Data

The safety data for the monotherapy supplements were derived from a total of n=917 bipolar patients exposed to treatment with aripiprazole monotherapy. This was a database that combined aripiprazole exposures from this program and the previous monotherapy studies of aripiprazole in bipolar disorder. Overall, the adverse event profile for aripiprazole when used as monotherapy in bipolar disorder was similar to that seen when it has been used in other disorders.

The safety data for the adjunctive therapy supplements were derived primarily from study 134. Overall, the adverse event profile for aripiprazole when used as adjunctive treatment in bipolar disorder was similar to that seen when it has been used in other disorders. There was a suggestion that the combination of aripiprazole and lithium was associated with a somewhat higher incidence of akathisia than was seen with aripiprazole alone or with the aripiprazole/valproate combination.

5.3 Clinical Sections of Labeling

We made several modifications to the sponsor's proposed labeling, and have now reached agreement on final labeling.

6.0 WORLD LITERATURE

The sponsor warranted that they conducted an extensive literature review and found no relevant papers that would adversely affect conclusions about the safety of aripiprazole for the proposed use.

7.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, i.e., 1 for study 162 from the 15 mg/day starting dose program and 1 for study 134 from the adjunctive therapy program. Data from the study 162 site were deemed to be acceptable. However, data from 6 patients from the study 134 site were deemed to be unreliable. A re-analysis of the data for study 134 was still positive, even without the data from this unreliable site.

8.0 PREA REQUIREMENTS

We decided to waive the requirement for pediatric studies with a starting dose of 15 mg/day, because the recommended pediatric starting dose is 2 mg/day, and the target dose is 10 mg/day. Regarding pediatric studies for adjunctive therapy, it is our judgment that it is reasonable to extrapolate from the adult adjunctive studies to pediatric patients. Thus, we have not requested pediatric adjunctive studies. Given our current views on extrapolation from adult studies, we have also extrapolated from the adult schizophrenia and bipolar studies (i.e., positive acute studies in adults and pediatric patients, and positive maintenance studies in adults) to maintenance therapy in pediatric patients with these conditions, resulting in our judgment that this product is entitled to maintenance claims for both conditions in the pediatric population.

9.0 LABELING AND APPROVAL LETTER

We have included the mutually agreed upon final label with the approval letter.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe as monotherapy with a starting dose of 15 mg/day in the treatment of patients with bipolar disorder (manic or mixed episodes) and as adjunctive therapy (i.e., added on to either lithium or valproate) with a starting dose of 15 mg/day in the treatment of patients

with bipolar disorder (manic or mixed episodes). We have now reached agreement with the sponsor on final labeling, and we will issue the attached approval letter along with agreed upon final labeling.

cc:

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HFD-130/TLaughren/MMathis/GZornberg/KBrugge/DBates

DOC: Aripiprazole_15 mg Start Dose_ Adjunctive Therapy_Bipolar_Laughren_AP_Memo.doc

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/s/

Thomas Laughren
5/6/2008 09:00:03 AM
MEDICAL OFFICER