

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-436/S-018

SUMMARY REVIEW

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

DATE: November 16, 2007

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

SUBJECT: Recommendation for approval actions for Abilify Adjunctive Therapy for Major Depressive Disorder (MDD) Supplements

TO: File NDAs 21-436/S-018 (Abilify tabs), 21-713/S-013 (oral solution), 21-729/S-005 (ODT), and 21-866/S-005 (IM)
[Note: This overview should be filed with the 5-16-07 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, and also for schizophrenia in adolescents.

This supplement provides support for a claim of adjunctive treatment in patients with MDD who have had a partial response to available antidepressant therapy. This support includes the results of 2 short-term adjunctive treatment studies in this population. We discussed this program with the sponsor in a 2-18-04 meeting, and then held a preNDA meeting with the sponsor on 12-15-06.

2.0 CHEMISTRY

The only CMC issues requiring review were the labeling 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

Results from several drug-drug interaction studies were submitted as part of these supplements, and these were reviewed by Kofi Kumi, Ph.D. from OCP. Co-administered aripiprazole resulted in increased exposures to fluoxetine and decreased exposures to paroxetine, but had no effect on escitalopram, venlafaxine, or sertraline. OCP recommended several modifications to labeling regarding these findings, and we have reached agreement with the sponsor on these changes.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on two identically designed 6-week, multicenter, double-blind, parallel group, randomized, placebo-controlled, flexible-dose adjunctive therapy studies in adult patients with MDD who were partial responders to antidepressant treatment (ADT) (CN138139 and CN138163). Partial response was defined as having an “inadequate” response to at least 1 course of ADT by history in the current episode and to 1 prospective course in the same episode. For the prospective course, inadequate meant less than 50% improvement in HAM-D-17, HAM-D-17 total score ≥ 14 , and CGI-I ≥ 3 , on 1 of 5 antidepressants (escitalopram, sertraline, venlafaxine XR, fluoxetine, or paroxetine CR). For prior treatment, inadequate meant less than 50% improvement as perceived by the patient. Patients meeting these criteria continued on their antidepressant and were randomized (1:1) to receive adjunctive aripiprazole or placebo. The aripiprazole dose range was 2-15 mg/day in patients receiving a potent 2D6 inhibitor, and 2-20 mg/day in others. The primary endpoint was change from baseline to endpoint in MADRS total score, and the key secondary endpoint was change from baseline to endpoint in SDS total score.

5.1.1 Study CN-138139

N=362 patients were randomized to adjunctive therapy (178 to placebo and 184 to aripiprazole). Completion rates were high, with 90% of placebo and 88% of drug patients completing the 6-week double-blind phase. The mean aripiprazole adjunctive dose was 10.7 mg/day. The outcome was highly significant for MADRS ($P < 0.001$), but only marginally significant for SDS ($p = 0.055$).

5.1.2 Study CN-138163

N=381 patients were randomized to adjunctive therapy (190 to placebo and 191 to aripiprazole). Completion rates were high, with 85% of placebo and 85% of drug patients completing the 6-week double-blind phase. The mean aripiprazole adjunctive dose was 11.4 mg/day. The outcome was highly significant for MADRS ($P = 0.001$) and for SDS ($p = 0.012$).

5.1.3 Other Efficacy Issues

Analyses based on gender suggested that most of the effect for study 139 was coming from the female participants, however, this gender discrepancy was not as clear for study 163. These differences are also difficult to interpret given the generally smaller male sample in these studies. There were no data in this program to address dose response or to address maintenance efficacy for this adjunctive therapy.

5.1.4 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for the primary endpoint in these studies. I agree. Although the finding is marginal for SDS in study 139, it is strong in study 163, and I am inclined to think that, overall, there is enough here to support the inclusion of this key secondary endpoint into labeling.

5.2 Safety Data

The safety data for these supplements were derived from a total of n=1055 patients exposed to adjunctive treatment with aripiprazole. There were 371 patients exposed in the 2 short-term trials and 930 in open label extensions (obviously there was overlap here). Overall, the adverse event profile for aripiprazole when used as adjunctive therapy was similar to that seen when it has been used alone.

5.3 Clinical Sections of Labeling

We made a number of 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 FOREIGN REGULATORY ACTIONS

To my knowledge, aripiprazole is not approved anywhere at this time as adjunctive treatment for MDD.

8.0 DSI INSPECTIONS

Inspections were conducted at 3 sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVAL LETTER

9.1 Labeling

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

9.2 Foreign Labeling

Aripiprazole is not approved anywhere at this time as adjunctive treatment for MDD.

10.0 RECOMMENDATIONS BY DR. BRUGGE FOR ADDITIONAL STUDIES

The clinical reviewer for this NDA, Dr. Karen Brugge, has not recommended phase 4 commitments, however, has recommended several phase 4 studies, presumably as voluntary efforts on the part of the sponsor.

-One such study would be a monotherapy study that would exclude any patients with histories of GAD or substance abuse, and would not require partial responsiveness to antidepressant therapy, presumably out of concern that the responsiveness observed in the conducted trials was not really an antidepressant effect.

Comment: Such a study would answer a different question than was being addressed in this program, and I don't see the need for the sponsor to address it as part of this program. In fact, I think the sponsor's question of whether or not aripiprazole adds benefit to antidepressant treatment in the heterogeneous mix of MDD patients who are seen in typical practice settings is the more relevant question.

-A second study would be a full factorial study including both and antidepressant and aripiprazole alone, the combination, and a placebo-placebo group, presumably to try to better understand the role of each individual component, both for efficacy and safety.

Comment: Although such a study would answer some additional questions, it is not practical, and does not address the questions of greatest interest, i.e., does aripiprazole add any value in depressed patients who are partial responders to antidepressants. Thus, I disagree with adding this recommendation.

-A third study would be one that explored the safety, and presumably the efficacy, of initiating treatment with the combination of aripiprazole simultaneously.

Comment: This study would also address a different set of questions, and not the ones of most interest. Thus, again, I don't intend to recommend this study to the sponsor.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe as an adjunctive treatment of patients with MDD who have partially responded to antidepressant treatment. 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.

Appears This Way on Original

cc:

Orig NDAs 21-436/S-018 (Abilify tabs), 21-713/S-013 (oral solution), 21-729/S-005 (ODT), and 21-866/S-005 (IM)

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

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/s/

Thomas Laughren
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MEDICAL OFFICER