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: September 25, 2007

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

SUBJECT: Recommendation for approvable actions for Abilify Pediatric Supplements for schizophrenia

TO: File NDAs 21-436/S-017 (Abilify tabs), 21-713/S-012 (oral solution), 21-729/S-004 (ODT), and 21-866/S-004 (IM)
[Note: This overview should be filed with the 3-23-07 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. We issued a written request (WR) for both schizophrenia and mania (2-11-03), and these supplements are a partial response to that WR. The 3-23-07 response includes the results from a single acute study in schizophrenia (Study 31-03-239), longer-term safety data from open-label Study 31-03-241, and also pediatric tolerability and PK data from Study 31-03-238.

--

. We held a preNDA meeting with the sponsor on 1-18-07. The labeling included with this supplement is in PLR format, and so this re-formatted labeling was also included within the scope of our review.

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

The only pharm/tox issue for consideration was the re-formatted labeling, and this has been addressed.

4.0 BIOPHARMACEUTICS

OCP has considered the pk data derived from this program sufficient to support these supplements, including the proposed labeling. They determined that AUC and Cmax appear to be linear in pediatric patients. However, they have made some slight modifications to labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on a single short-term, multicenter, double-blind, parallel group, randomized, efficacy and safety study in adolescent patients (ages 13-17) with schizophrenia (Study 31-03-239).

5.1.1 Study 31-03-239 (Acute Schizophrenia)

This was a 6-week placebo-controlled study in adolescent patients (ages 13-17) with schizophrenia. It was conducted at multiple international sites and also the US (n=141 total centers). Patients could be inpatients or outpatients. N=294 patients (in the ITT dataset) were randomized 1:1:1 to 3 treatment groups: aripiprazole 10 mg/day (n=99); aripiprazole 30 mg/day (n=97); placebo (n=98). Roughly 85% of patients completed the study (with roughly comparable rates for all 3 groups). Patients were roughly half male, about 60% Caucasian, and the mean age was 15.5 years. The primary endpoint was change from baseline to endpoint on the PANSS total score, and the primary analysis was ANCOVA (LOCF). The Hochberg procedure was used to correct for multiple comparisons. Both dose groups were superior to placebo (p=0.006 for 30 mg and p=0.041 for 10 mg), with only a slight numerical superiority for the 30 mg dose over the 10 mg dose at endpoint: change from baseline of -28.6 for 30 mg vs -26.7 for 10 mg vs -21.2 for placebo). However, weekly data did suggest an earlier onset of effect in the 30 mg group vs the 10 mg group. The placebo effect was surprisingly large for this study. No endpoints were designated as key secondary endpoints and no multiple comparison procedure was planned for secondary endpoints. Therefore, I will not comment further on secondary endpoints. Subgroup analyses based on gender and race for this study generally suggested that the positive results were seen across subgroups. Drs. Zhang, Chen, and Mathis all considered this a positive study, and I agree.

5.1.2 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for this study. As noted, there was no clear indication of greater efficacy for the higher dose compared to the lower dose. The sponsor has proposed language suggesting that

" however, we disagree. We will propose labeling ----------

5.2 Safety Data

Safety data for these supplements were derived from the 3 trials noted above, i.e., a single acute study in schizophrenia (31-03-239), a longer-term open-label study (31-03-241), and a pediatric tolerability and PK study (31-03-238). There were roughly 200 pediatric patients exposed to aripiprazole in study 239, with roughly 1/3 extending beyond 42 days into the open label study. There was one clearly accidental death in an aripiprazole-exposed patient in study 241. There were several serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for aripiprazole in adults, i.e., EPS, somnolence, and GI symptoms, with slightly higher rates for some of these in pediatric patients compared to adults. Of note, there were no clear metabolic or growth effects, no laboratory effects, and if anything, a decrease in QTc. I agree with Drs. Mathis and Zhang that these adverse events can be adequately addressed in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided an extensive literature review and this did not reveal any important new safety information regarding the pediatric population.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, aripiprazole is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in pediatric patients.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

9.1 Labeling

We have included a modified version of labeling with the approvable letter.

9.2 Foreign Labeling

Aripiprazole is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in pediatric patients.

9.3 Approvable Letter

The approvable letter includes our proposed labeling.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of adolescent patients with schizophrenia. However, before we can take an approval action, we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
9/25/2007 04:33:34 PM
MEDICAL OFFICER