APPLICATION NUMBER:
21-436/S-018

CROSS DISCIPLINE TEAM LEADER
REVIEW
1.0 BACKGROUND

Aripiprazole is a partial agonist at dopamine D₂ receptors that is posited to act as an agonist in states of dopaminergic hypoactivity and as an antagonist in states of dopaminergic hyperactivity. It exhibits high to moderate affinity for multiple serotonin receptor subtypes (5-HT₁A, 5-HT₂A, 5-HT₂C, 5-HT₆, and 5-HT₇). This efficacy supplement to the NDA seeks a claim for the short-term use of aripiprazole as an adjunctive treatment for patients with major depressive disorder (MDD) who have been partial responders to antidepressant treatment.

We met with the sponsors on 18 February 2004 to discuss this program, and they have conducted the development program in accordance with our advice as documented in our meeting minutes of 15 December 2006. Otsuka/BMS has completed 2 short-term add-on efficacy studies in patients with MDD who did not respond fully on available antidepressant treatments (ADTs). In these short-term trials, patients first must have had a history of failing to fully respond to treatment on 1 to 3 marketed antidepressant drugs in the current episode of MDD prior to randomization to adjunctive Abilify or placebo.
arms. At least one of the antidepressant trials had been required to be prospectively defined.

2.0 CHEMISTRY

Dr. Nallaperum Chidambaram has provided no objection to the applicant’s submission of a categorical exclusion claim pursuant to 21 CFR 25.22 (b) that states, "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated introduction concentration (EIC) of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion (1 ppb).” On page 1 of his review dated 16 October 2007, Dr. Chidambaram commented that the “applicant’s claim is found to be acceptable” as “The applicant has not provided any new CMC information other than some minor editorial changes to how supplied section of the labeling.”

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approvable action for this efficacy supplement.

4.0 BIOPHARMACEUTICS

Based on the review of the drug-drug interaction studies included in this efficacy supplement regarding adjunctive treatment, Dr. Kumi recommends a number of changes to aripiprazole labeling regarding drug-drug interactions with commonly used antidepressants evaluated in the double-blind, placebo-controlled trials. The addition of aripiprazole (flexibly dosed 2 to 15 mg daily) to fluoxetine 20 to 40 mg daily (n=28) or paroxetine CR (37.5 to 50 mg daily (n=20) increased the steady state plasma concentrations of fluoxetine and norfluoxetine by approximately 18% and 36%, respectively—and paroxetine by approximately 27%. In contrast, Dr. Kumi finds that no dosage adjustment of escitalopram, venlafaxine, or sertraline is required when aripiprazole is added as adjunctive treatment.

As a post-marketing commitment, Dr. Kumi strongly recommends that the applicant perform a traditional population pharmacokinetic analysis for confirmation of the study results because even though the statistical methods employed appear reasonable, they may not have provided an accurate reflection of the changes in plasma concentrations of the antidepressants and their active metabolites. The data collected is sufficient to perform the traditional population pharmacokinetic analysis.

I am not aware of any biopharmaceutics issues at this point that would preclude an approvable action for this sNDA.

5.0 CLINICAL DATA

5.1 Efficacy Data
5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 2 short-term (6-week), double-blind, randomized, parallel group, placebo-controlled trials of identical design (CN138139 and CN138163) in patients diagnosed with MDD who were demonstrated to be to be partial responders in an 8-week prospective treatment phase on open-label antidepressant therapy (ADT) prior to randomization. Partial response was defined as <50% decrease in the 17-item HAM-D total score from baseline and a HAM-D total score of at least 14 in addition to a CGI-improvement score of 3 or greater. There was also 1 long-term, open label safety study (CN138164). The primary endpoint analysis for the 2 short-term studies was mean change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from end of the 8-Week Phase B (baseline of Phase C) to Week 14 endpoint (end of 6-Week Phase C, LOCF) in the MADRS total score compared to adjunctive placebo. The patients were randomly assigned in a 1:1 ratio to receive double-blind placebo-plus-ADT or aripiprazole-plus-ADT. The primary efficacy analyses were statistically significant in both trials.

The dose design of adjunctive aripiprazole treatment was flexible in both studies from 2 to 20 mg/day. The potential for drug-drug interactions determined the maximum dose permitted:

- Aripiprazole 2 to 15 mg daily in subjects receiving ADT that was a potent inhibitor of CYP 2D6 (i.e., fluoxetine or paroxetine controlled-release) or,
- Aripiprazole 2 to 20 mg daily in subjects receiving other ADT (i.e., escitalopram, sertraline, or venlafaxine extended-release).

The mean dose of aripiprazole received in each trial was 10.7 and 11.4 mg daily, respectively. The majority of subjects (86.3%) received an overall mean cumulative dose between 5 mg and 10 mg up to 6 weeks during the double-blind randomized treatment phase (Phase C).

Dr. Jialu Zhang provided the primary and key secondary findings from the application reproduced below (NDA 21-436 SE1 N018 Biometrics review dated 5 October 2007).

Primary and Key Secondary Results in Study 138139
Primary and Key Secondary Results in Study 138163

<table>
<thead>
<tr>
<th>Variable</th>
<th>Double-Blind Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N = 172</td>
</tr>
<tr>
<td>PRIMARY EFFICACY ENDPOINT</td>
<td>N = 172</td>
</tr>
<tr>
<td>MADRS Total Score</td>
<td>25.63 (0.51)</td>
</tr>
<tr>
<td>Mean end of Phase B (SE)</td>
<td>-5.62 (0.64)</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>-2.84 (-4.53, -1.15)</td>
</tr>
<tr>
<td>p-VALUE</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

| Variable                        | Placebo                      | Aripiprazole                 |
|                                | N = 164                      | N = 167                      |
| KEY SECONDARY EFFICACY ENDPOINT| N = 164                      | N = 167                      |
| Sheehan Disability Scale Mean Score | 5.35 (0.20)                 | 5.06 (0.19)                 |
| Mean Change at Week 14 (SE)    | -0.46 (0.14)                 | -1.11 (0.19)                |
| Treatment Difference (95% CI)  | -0.46 (-0.99, 0.01)          | 0.055                        |
| p-VALUE                        |                              | 0.012                        |

[Source: Sponsor's Clinical Study Report Table 7.1, verified by the reviewer]

5.1.2 Comment on Other Important Clinical Issues Regarding the Aripiprazole Efficacy Data

Secondary Efficacy Variables

The key secondary endpoint analysis, the change in the Sheehan Disability Scale (SDS) Mean Score from the end of Week-8 (Phase B open-label ADT) to end of Phase C (week 14, LOCF), was on the borderline in Study 138139 and statistically significant in Study 138163. The sensitivity analyses by observed case analysis (OC analysis) on the total MADRS score showed consistent significant results, as recorded in Dr. Zhang's review.

Clinical Predictors of Response
There had been an observation of a potential interaction between treatment and gender in Study 138139. The treatment\*gender interaction was not found, however, in Study 138163. Given the lack of consistency across studies and the relatively small sample size of males compared to females in Study 138139, Dr. Zhang found that the inconclusive evidence supporting the existence of a treatment\*gender interaction is unconvincing at this stage (page 21 of Dr. Zhang’s Biometrics review dated 5 October 2007). I concur based on the lack of consistency in the data coupled with small patient population sizes coupled with the absence of a persuasive biological explanation for such an interaction with gender.

**Duration of Treatment**

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of aripiprazole as adjunctive treatment of partial response to treatment with antidepressant drugs.

**5.1.3 Conclusions Regarding Efficacy Data**

The sponsor has in my view, as well as in the views of Dr. Brugge and Dr. Zhang as detailed in their reviews, provided sufficient evidence to support the claim of short-term efficacy of aripiprazole as adjunctive treatment of antidepressant therapy in patients diagnosed with MDD who are partial responders.

**5.2 Safety Data**

**5.2.1 Clinical Data Sources for Safety Review**

The safety data for this efficacy supplement were derived from a total of n=1055 subjects/patients exposed to aripiprazole across 2 MDD clinical trials and one long-term study comprising the Abilify Adjunctive Treatment of MDD program. The aripiprazole-exposed patient breakdown included n=371 patients in the randomization phase (Phase C) of the 2 short-term trials and 930 patients/subjects in the 52-week open label study of MDD patients found to be partial responders to antidepressant therapy who provided safety data. This represents approximately an additional 39.9 patients-years of exposure (page 158 of 11,068 of the application) to the aripiprazole safety database. The All Aripiprazole Dataset comprises 12,925 patients who have been exposed to aripiprazole in the Phase 2/3/4 clinical studies.

**5.2.2 Common Adverse Drug Reaction Profile for Aripiprazole As Adjunctive Treatment of Major Depressive Disorder**

The profile of aripiprazole continues to include akathisia, restlessness, and constipation as in monotherapy trials of schizophrenia and bipolar disorder. Akathisia occurrence was greater in the placebo-controlled trials in the aripiprazole group (49.6%) versus placebo (26.8%). Restlessness was greater also in the placebo-controlled trials in the aripiprazole exposed group (26.7%) versus the placebo (13.4%) exposed group. In the trials of
Aripiprazole as adjunctive to ADTs, insomnia, fatigue/somnolence, and blurred vision were also common adverse drug reactions observed that are commonly associated with exposure to antidepressant drugs. The elevated incidence of these ADRs (≥5% incidence and twice that of adjunctive ADT-placebo group) may be due to an interaction between aripiprazole and ADT effects.

There were some differences in AE profiles associated with aripiprazole adjunctive treatment correlated with characteristics of the individual antidepressants used.

- Akathisia was found by Dr. Brugge to be highest in subgroups with concomitant use of ADTs with relatively high CY2D6 inhibitor activity (i.e., paroxetine CR and fluoxetine) compared to the other ADT groups.
- Disturbance of attention was found by Dr. Brugge to be most elevated in the venlafaxine XR subgroup of aripiprazole compared to placebo adjunctive treatment groups (6% and 1%, respectively) vs. 0% and 3% for adjunctive aripiprazole compared to placebo and other antidepressants.

The potential for clinically relevant drug-drug interactions provides further support for Dr. Kumi’s recommendation that the applicant perform a traditional population pharmacokinetic analysis for confirmation of the study results.

5.2.3 Adverse Reactions of Particular Interest

There were no deaths in the adjunctive MDD database. According to Dr. Brugge in her review (page 82), “no additional less common AEs were found that were considered as serious AEs based on the following review… of the integrated placebo-controlled dataset.” Moreover, no new laboratory abnormalities were revealed in this application. Finally, Dr. Brugge noted that “it is difficult to interpret or explain the above observations of AEs with potential gender subgroup differences.”

5.2.4 Use in Elderly Patients

As aripiprazole and the antidepressant drugs evaluated are approved drugs, the sponsor did not conduct any special population studies. Patients aged greater than 65 years were excluded from the short-term registration trials of adjunctive treatment of MDD (-139 and -163).

5.2.5 Risk: Benefit Evaluation

In view of the known morbidity and mortality of such a serious disorder as Major Depressive Disorder, treatment of patients with only a partial response to antidepressant treatment with an antidepressant alone is considered inappropriate in the literature and is no longer the accepted standard of care. To the best of my knowledge, no other antipsychotic drug is approved for the indication of adjunctive treatment of unipolar depression partially responsive to antidepressant therapy. Consequently, these pivotal trials demonstrate significant efficacy in an area of unmet clinical need without clinically
material difference in the adverse drug reaction profile compared to monotherapy of schizophrenia or bipolar disorder in short-term trials.

5.2.6 Conclusions Regarding the Safety of Aripiprazole As Adjunctive Treatment of Major Depressive Disorder Partially Responsive To Antidepressant Therapy

The adverse drug reaction profile for aripiprazole in the adjunctive treatment of MDD is similar to that observed with aripiprazole in the treatment of schizophrenia and bipolar for corresponding dosage levels. I am in agreement with Dr. Brugge’s conclusion on pages 8 (reiterated on pages 33 and 47) of her review that: “Safety results failed to reveal any new and clinical[ly] remarkable safety profile or signal that is not already in approved labeling, except that some of the results were suggestive of an exaggerated effect of combining aripiprazole with ongoing ADT treatment.”

5.3 Clinical Sections of Labeling

We have made modifications to the sponsors’ proposed Abilify labeling that has been converted to PLR format for the first time in the context of the approval of the pediatric schizophrenia and bipolar disorder indications.

6.0 WORLD LITERATURE

The sponsor provided certification that they reviewed the literature and found no relevant articles that would adversely affect conclusions about the safety of aripiprazole in the adjunctive treatment of partial response to antidepressants in patients diagnosed with MDD.

7.0 FOREIGN REGULATORY ACTIONS

The applicant provided a listing of approved applications for foreign marketing of Abilify and discusses their foreign marketing experience in Section 6 of Module 2.7.4 of the submission. Abilify had not been submitted previously for approval for an (b) (4) indication. Abilify is approved for the indications of schizophrenia and/or bipolar mania in approximately 40 countries (provided by the sponsors Table 6.1.A in section 6 of Module 2.7.4 of the submission). The sponsor stated that Abilify has not been withdrawn from the market in any country.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC)

It was decided that there was no need to take this application to the PDAC.

9.0 DSI INSPECTIONS
Inspections were conducted at three sites, and data from these sites were deemed by the Consumer Safety Officer, Diane Tesch, to be acceptable as documented in her review dated 10 September 2007 (page 2).

10.0 PHASE 4 COMMITMENTS

A traditional population pharmacokinetic analysis for confirmation of the study results Phase 4 commitment is recommended.

11.0 LABELING AND APPROVABLE LETTER

We will include a modified version of the new PLR version of labeling with the approvable letter.

12.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that BMS/Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of the adjunctive treatment of major depressive disorder. Based on the data provided in the reviews Drs. Brugge, Kumi, Zhang, and Chidambararam, I recommend that an approvable action be taken. I concur with Dr. Kumi’s recommendation as a Phase 4 commitment that the applicant perform a traditional population pharmacokinetic analysis for confirmation of the study results. Before we can take an approval action, we need to reach an agreement on labeling. Thus, I recommend that we issue the approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:
Orig NDA 21-436
Orig NDA 21-713
Orig NDA 21-729
Orig NDA 21-866
ODE-I/R Temple
HFD-130
HFD-130/GZornberg/KBrugge/MMathis/TLaughren/NKhin/WBender/SHardeman

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

/s/
Gwen Zornberg
10/29/2007 03:55:07 PM
MEDICAL OFFICER