CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-866

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: September 20, 2006

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

SUBJECT: Recommendation for approval action for Abilify Injection (aripiprazole) for agitation associated with schizophrenia or bipolar disorder

TO: File NDA 21-866
[Note: This overview should be filed with the 11-30-05 original submission of this NDA.]

1.0 BACKGROUND

Abilify Injection (aripiprazole) is an atypical antipsychotic agent that is also available as tablets, orally disintegrating tablets, and oral solution for the treatment of schizophrenia and mania associated with bipolar disorder. Abilify Injection was developed under IND 60,158. The proposed doses are 5.25 to 15 mg per injection.

There are 2 other intramuscular injectable forms of atypical antipsychotic drugs available for treating agitation, i.e., Geodon Injectable for agitation in schizophrenia and Zyprexa Injectable for agitation in schizophrenia or bipolar disorder. The development program for Abilify Injection was similar to those for these other 2 products.

2.0 CHEMISTRY

To my knowledge, all CMC issues have been resolved, and there are no issues that would preclude an approval action for this NDA.

3.0 PHARMACOLOGY

To my knowledge, all pharm/tox issues have been resolved, and there are no issues that would preclude an approval action for this NDA.

4.0 BIOPHARMACEUTICS

The median time to peak plasma concentration after IM injection of Abilify Injectable is about 3 hours. Overall systemic exposure after IM injection and oral administration is about the same. However, Cmax after IM injection is about 19% higher.

To my knowledge, all biopharmaceutics issues have been resolved, and there are no issues that would preclude an approval action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application considered 3 short-term trials in patients with agitation in schizophrenia or bipolar disorder. There were 2 studies in schizophrenia and 1 in bipolar mania:

-CN138-012: schizophrenia; fixed Abilify Inj dose of 9.75 mg; haloperidol 6.5 mg; placebo;
-CN138-050: schizophrenia; fixed Abilify Inj doses of 1, 5.25, 9.75, and 15 mg; haloperidol 7.5 mg; placebo;
-CN138-013: mania; fixed Abilify Inj doses of 9.75, and 15 mg; lorazepam 2 mg; placebo;

In all 3 studies, the primary focus was on clinical status 2 hours after the initial injection (patients could receive up to 3 injections over 24 hours, but not oftener than every 2 hours). The primary efficacy assessment was the PANSS Excited Component. The sponsor also looked at CGI-I, and in fact we had discussed with them the possibility of using CGI-I or S as a key secondary outcome. They formalized the CGI-I as a key secondary endpoint in their analyses plans for 1 of the 2 schizophrenia trials (the second trial was already completed).

In all 3 studies, all Abilify Inj doses of 5.25 mg and higher were statistically significantly superior to placebo on the PANSS Excited Component and on the CGI-I in both schizophrenia trials. In study 050, the 9.75 mg dose was numerically superior to both the 5.25 mg dose and the 15 mg dose. In study 013, the 9.75 and 15 mg doses appeared to be about equally effective.

5.1.4 Conclusions Regarding Efficacy Data

Both Drs. Hearst, Khin and Chen considered all 3 studies positive in support of the claim, and I agree. I also agree with Dr. Khin that the 9.75 mg dose can be the recommended dose. Labeling will note that there did not seem to be any additional benefit with the 15 mg dose compared to — mg.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for these supplements included safety data from a total of 7 studies (3 clinical pharmacology trials, 3 RCTs, and a dose tolerance trial in agitated patients with dementia). There were a total of 749 patients who received Abilify Inj in the 4 ph 2/3 trials and 60 subjects in the ph 1 trials.

5.2.2 Adverse Event Profile for Abilify Inj in Agitation

The adverse event profile for Abilify Inj was roughly the same as that for orally administered Abilify.

5.2.3 Conclusions Regarding Safety of Effexor XR in the Treatment of Panic Disorder

I agree with Dr. Hearst that all of the safety issues for this drug 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 reached agreement with the sponsor on final labeling.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would adversely affect conclusions about the safety of Abilify Inj in the treatment of agitation.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Abilify Inj is not approved anywhere at this time for the treatment of agitation.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 sites and there were no findings that would preclude accepting the data from those sites.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling

As noted, we have reached agreement on final labeling.

10.2 Approval Letter

The approvable letter includes the mutually agreed upon final labeling. There is one ph 4 commitment, i.e., an agreement by the sponsor to ensure that the table in labeling with dosing instructions (i.e, dose and required volume of solution) will be made readily available to clinicians by attaching it to each vial, if feasible.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that Abilify Inj is effective and acceptably safe in the treatment of agitation associated with schizophrenia and bipolar mania. We have reached agreement on final labeling and I will issue an approval letter for this application. There is one ph 4 commitment that the sponsor has agreed to.

cc:
Orig NDA 21-866
HFD-130
HFD-120/TLaughren/MMathis/NKhin/EHearst/DBates

DOC: Abilify IM_Laughren_AP 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/

Thomas Laughren
9/20/2006 01:03:19 PM
MEDICAL OFFICER