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APPLICATION NUMBER:

21-729

MEDICAL 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: October 12, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable Action for Aripipazole Orally Disintegrating Tablet (ODT) [redacted] strengths ([redacted] 10, 15, 20, and 30 mg)

TO: File for NDA 21-729
[Note: Should be filed with 12-22-03 original submission.]

Background

Abilify (aripiprazole) is currently available in oral tablet strengths (5, 10, 15, 20, and 30 mg) for the treatment of schizophrenia (approved 11-15-02, under NDA 21-436). This application provides data in support of an orally disintegrating aripiprazole tablet, [redacted] for the same indication. The clinical program for this new formulation consisted of [redacted] bioequivalence studies (CN138067 [redacted] that demonstrated equivalence between this new ODT formulation and currently approved tablets. These studies were conducted under IND 62,181.

The pharmacokinetic data in this application have been reviewed by Kofi Kumi, Ph.D., from OCPB, and the clinical data have been reviewed by Greg Dubitsky, M.D., from the clinical group. No new pharm/tox data were submitted as part of this application, however, brief comments on pharm/tox issues have been submitted to the file by Sonia Tabacova, Ph.D., from the pharmacology group. The CMC data for this application have been reviewed by Gurpreet Gill-Sangha, Ph.D., from the chemistry group.

The sponsor's proposed dosing for this new formulation is identical to that for the currently approved oral tablets.

Pharmacokinetic Findings

The clinical program for this new formulation consisted of [redacted] bioequivalence studies [redacted] CN138067 [redacted] CN138067 [redacted] were the definitive BE studies, and they compared the highest [redacted] strengths of the ODT formulation and the currently approved

tablets (i.e., 30 [redacted], and bioequivalence was demonstrated [redacted] OCPB also recommends that we accept the requested waiver for the 10, 15, and 20 mg strengths. In these BE studies, the ODT tablets were administered without water, i.e., there was no treatment arm "with water" to test that method of administration. No food effect study was requested, since such studies have been conducted with the conventional tablets at 15 and 30 mg strengths. OCPB has also proposed dissolution specifications, and we are awaiting confirmation from the sponsor regarding acceptance of these revised specifications.

Pharmacology/Toxicology Findings and Issues

No new pharm/tox data were submitted with this application. The only possible pharm/tox concern would be the question of whether or not toxic adducts might form by interaction of either of the two major excipients for this formulation with other ingredients in the formulation. The two major excipients are aspartame and crospovidone. Crospovidone is an inert polymer that is not absorbed. Apparently, compatability data for crospovidone with other ingredients of the formulation have been provided and reveal no concerns. In addition, crospovidone has been used as an inactive ingredient in many approved products at much higher doses than would be used in this product. Aspartame is a food additive, and compatability data for this excipient with other ingredients of the formulation have not been provided. Thus, compatability data would need to be provided for aspartame before final approval.

CMC Issues

The only CMC issue I am aware of is the fact that aspartame is a major excipient, and therefore, needs to be mentioned in labeling. In fact, they have included this fact in Precautions, Information for Patients, as required by regulations. Thus, in my view, this issue has been addressed.

The proposed name Abilify Discmelt has been deemed acceptable by DMETS.

Clinical Review

There were no safety findings from the 3 clinical studies that would suggest any added risk from this new formulation. There was no need for efficacy data since efficacy was extrapolated from existing data.

DSI Review

One of the 2 pivotal BE studies was inspected (CN138067), and was acceptable except for concentration data for 3 subjects. OCPB has analyzed the data with and without the data for these 3 patients, with similar results.

Labeling

OCPB has recommended a very modest change to labeling regarding dosing with [redacted] The sponsor has proposed that the ODTs can be taken with or without [redacted] Since the BE studies did not include "with [redacted] " arms, OCPB recommends taking without [redacted], but nevertheless, adds that they can be taken with [redacted] if needed. I don't object to this modest change.

PREA Requirements

We are recommending waiving these requirements since a pediatric program is already underway for the tablets.

Conclusions/Recommendations

I agree that this application is approvable, and I recommend that we issue the attached approvable letter with draft labeling, in anticipation of final approval.

cc:
Orig NDA 21-729/Aripiprazole ODT
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PAndreason/GDubitsky/SHardeman

DOC: Memo Aripiprazole ODT AE1.doc

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/s/

Thomas Laughren
10/12/04 03:48:34 PM
MEDICAL OFFICER

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