CENTER FOR DRUG EVALUATION AND RESEARCH

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

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

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#:	21-729
Sponsor:	Otsuka America Pharmaceutical
Due Date:	October 22, 2004

Drug Name:

Generic Name:	Aripiprazole Orally Disintegrating Tablets
Trade Name:	ABILIFY DISCMELT (proposed)

Drug Categorization:

Pharmacological Class:	D_2 Receptor Partial Agonist
Proposed Indication:	Schizophrenia
Dosage Forms:	[redacted] 10, 15, 20, and 30mg
Route:	Oral

Review Information

Clinical Reviewers:	Gregory M. Dubitsky, M.D.
Completion Date:	March 23, 2004

NDA 21-729
Aripiprazole Orally Disintegrating Tablets
TABLE OF CONTENTS

Section	Page
EXECUTIVE SUMMARY	
I. Recommendations	
A. Recommendation on Approvability	4
B. Recommendation for Phase 4 Studies	4
II. Summary of Clinical Findings	
A. Brief Overview of Clinical Program	4
B. Efficacy	4
C. Safety	4
D. Dosing	5
E. Special Populations	5
CLINICAL REVIEW	
I. Introduction	
A. Background	5
B. Major Safety Findings with Aripiprazole	6
C. Administrative History	6
D. Proposed Instructions for Use	6
E. Foreign Marketing	7
II. Clinically Relevant Findings from Consultant Reviews	
A. Biopharmaceutics	7
B. Chemistry	7
C. DSI Clinical Site Inspections	7
D. DMETS	7
III. Human Pharmacokinetics and Pharmacodynamics	
A. Pharmacodynamics	7
B. Pharmacokinetics	7
IV. NDA Data Sources	
A. Primary Development Program	9
B. Published Literature	10
V. Clinical Review Methods	
A. Items Utilized in the Review	10
B. Specific Methods Used to Evaluate Data Quality	10
C. Adherence to Accepted Ethical Standards	10
D. Evaluation of Financial Disclosure	11

VI. Review of Efficacy 11
VII. Integrated Review of Safety
A. Methodology of the Safety Review 11
B. Safety Findings
1. Deaths and Other Serious AE's 11
2. Dropouts due to Adverse Events 12
3. Oral Irritation 13
C. Adequacy of Exposure & Safety Assessments 13
D. Assessment of Data Quality & Completeness 13
E. Summary of Important Safety Findings 14
VIII. Dosing, Regimen, and Administrative Issues 14
IX. Use in Special Populations 14
X. Review of Proposed Labeling 14
XI. Conclusions and Recommendations 14

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective at this time, it is recommended that this NDA be approved. Consultant reviews (biopharmaceutics, chemistry, DSI, DMETS) are not yet complete and any significant issues raised by those reviews will need to be resolved prior to approval.

B. Recommendation for Phase 4 Studies

I have no recommendations for Phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

This application is intended to support the approval of a fast dissolving oral tablet formulation of aripiprazole for the management of patients with schizophrenia. The basis of this application is bioequivalence between aripiprazole ODT and currently marketed Abilify tablets, as demonstrated by [redacted] key bioequivalence studies, CN138067 [redacted]

B. Efficacy

The sponsor provides no new efficacy data in this application. Efficacy relies on extrapolation from investigations conducted with the standard aripiprazole tablets which were approved under NDA 21-436.

C. Safety

The small amount of safety data derived from the bioequivalence studies suggests no hazard associated with this product that would preclude its approval or warrant a major change to product labeling. The determination of safety for this product relies almost entirely on extrapolation from investigations conducted with the standard aripiprazole tablet.

D. Dosing

Dosing will be essentially identical to that for Abilify tablets. The vulnerability of this product to moisture requires that it be stored in blister packaging until immediately before use.

F. Special Populations

The development plan included no studies in special populations.

CLINICAL REVIEW

I. Introduction

A. Background

Aripiprazole, a quinolinone derivative, is a novel psychotropic agent that exhibits partial agonism at D_2 receptors and 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors. Aripiprazole tablets were approved as Abilify for the acute treatment of schizophrenia in adults on 11-15-02 and data regarding longer-term safety and efficacy were submitted in supplement S-001, which was approved on 8-28-03.

Otsuka has developed a fast disintegrating tablet formulation of aripiprazole for use in treating patients with schizophrenia (referred to as aripiprazole orally disintegrating tablets or aripiprazole ODT in this review). This product has been developed under IND 62,181 and has the currently proposed proprietary name of ABILIFY DISCMELT. The rapid disintegration characteristic is intended to provide an alternative dosage form of aripiprazole, particularly for patients who have difficulty swallowing tablets.

Otsuka is seeking approval of aripiprazole ODT on the basis of bioequivalence to currently approved aripiprazole tablets. This application is supported by [redacted] key bioequivalence studies, CN138067 [redacted] The former study evaluated the highest approved strength of the tablets, 30mg [redacted] The sponsor is requesting a waiver of the requirement to demonstrate bioequivalence for the 10, 15, and 20mg tablets. A food effect study has not been

conducted since such a study has been performed with the 15mg approved tablet and a food effect study with the 30mg approved tablet is currently underway.

B. Major Safety Findings with Aripiprazole

In patients with schizophrenia, aripiprazole is not known to possess any remarkable toxicities.

C. Administrative History

[redacted]

Subsequently, protocols for [redacted] definitive bioequivalence studies using a selected [redacted] formulation were submitted: protocol CN138067, submitted on 1-13-03, to evaluate the 30mg strength [redacted]

The above studies were completed and this NDA was submitted and received on 12-22-04. A Refuse-to-File meeting was convened on 2/9/04 and the application was deemed to be fileable. A consult was sent to the Division of Scientific Investigations on 2-11-04 to request inspection of study CN138067. Also, a consult was forwarded to the Division of Medication Errors and Technical Support on 3-9-04 to evaluate the trade name extension "ABILIFY DISCMELT."

D. Proposed Instructions for Use

The instructions for use provided in the proposed labeling advise that the blister packaging should not be opened until the drug is to be taken. Directions for opening the blister are given and, using dry hands, the tablet is to be placed on the tongue. It can be taken with or without [redacted] The tablet should not be split.

E. Foreign Marketing

There is no foreign postmarketing data for aripiprazole ODT.

II. Clinically Relevant Findings from Consultant Reviews

A. Biopharmaceutics

The review of the bioequivalence studies by the Office of Clinical Pharmacology and Biopharmaceutics is pending completion at this time.

B. Chemistry

The review of chemistry, manufacturing and controls data by the Office of New Drug Chemistry has not yet been completed.

C. DSI Clinical Site Inspection

The Division of Scientific Investigations was requested to inspect study CN138067. This inspection is pending at the current time.

D. DMETS

The Division of Medication Errors and Technical Support was consulted to evaluate the acceptability of the sponsor's trade name proposal, ABILIFY DISCMELT. The report of this assessment has not yet been completed.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacodynamics

No new pharmacodynamic data are presented in this NDA.

B. Pharmacokinetics[1]

The aripiprazole ODT development program is comprised of [redacted] bioavailability/bioequivalence trials that were conducted in healthy adult subjects, [redacted]

[1] The information presented is based on the Summary of Bioequivalence/Bioavailability provided in this submission. PK data will be reviewed in detail in a separate review by staff from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

[redacted] studies which demonstrated the bioequivalence between 30mg [redacted] ODT's with corresponding reference commercial tablets (CN138067 [redacted]. These studies are summarized below.

[redacted]

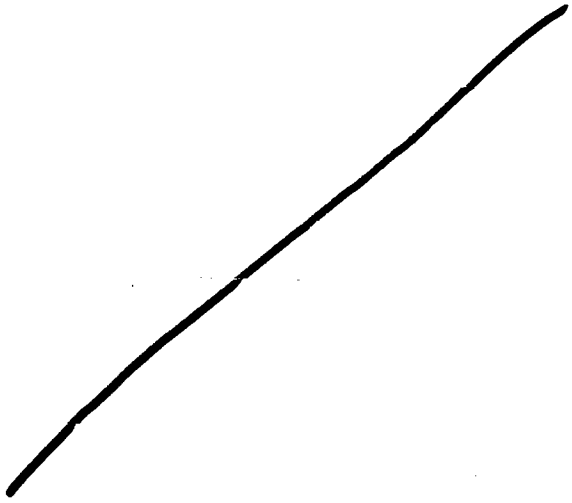
Study CN138067

This was a randomized, open-label, three-period, two-treatment crossover study in 48 healthy adult subjects. Each subject received a 30mg aripiprazole commercial tablet (Treatment A) and a 30mg ODT (Treatment B) in randomized sequence. In the third period, subjects received the same treatment as in the second period. [redacted] Serial blood samples for PK assessments were collected over a period of 384 hours (17 days) post-dose. There was a washout period of at least 28 days between treatments.

Twenty subjects discontinued from the study prematurely. Thirty subjects had data for both formulations and only data from these subjects were included in the statistical analysis. Based on parent drug levels, the 30mg ODT was bioequivalent to the 30mg reference tablet with respect to Cmax, AUC(0-tau), and AUC(inf). Although the ranges for

Tmax were the same for both (1.5-12.0 hours), the median Tmax for the ODT was one hour later than that for the commercial tablet.

Frequent early PK sampling was done to examine for the possibility of buccal absorption after ODT administration. Aripiprazole levels in the first 2 hours after dosing revealed no substantial difference between the two formulations.



IV. Description of Clinical Data Sources

A. Primary Development Program

The clinical development plan for aripiprazole ODT comprised the [redacted] bioequivalence/bioavailability studies described above.

In these trials, a total of 136 subjects received at least one dose of aripiprazole in a dose of [redacted] 30mg; 118 of these subjects received aripiprazole as an ODT.

Among all 136 subjects who received aripiprazole, the mean age was 30.6 years and the age range was 18-45 years. Most of the subjects (80%) were male. Also, most of the subjects were Black (21%), Hispanic (46%), or White (33%).

No Phase 2/3 clinical trials were conducted with aripiprazole ODT.

B. Published Literature

The sponsor provided no systematic search of the published literature.

On 3-22-04, I searched PubMed for relevant articles using the search string "(OPC-14597 OR aripiprazole) AND (disintegrating [redacted]." Only one article was retrieved using this search: Kelleher JP, et al. Advances in atypical antipsychotics for the treatment of schizophrenia: new formulations and new agents. CNS Drugs 2002;16(4):249-61. This article was examined and revealed no significant safety problems associated with the use of aripiprazole. It contained no specific mention of the aripiprazole ODT formulation.

V. Clinical Review Methods

A. Items Utilized in the Review

All materials examined in this review were provided electronically by the sponsor on 12-22-03 and were reviewed in the CDER Electronic Document Room (EDR).

B. Specific Methods Used to Evaluate Data Quality

The Division of Scientific Investigations has been requested to inspect study CN138067. The report of that inspection has not been completed.

C. Adherence to Accepted Ethical Standards

All three studies were conducted in accordance with Good Clinical Practice.

D. Evaluation of Financial Disclosure

Requests for financial disclosure information were sent to the 3 principal investigators and 5 sub-investigators who participated in the [redacted] trials in this NDA. All individuals responded and none had disclosable information.

VI. Review of Efficacy

The bioequivalence studies were not designed to evaluate the efficacy of aripiprazole ODT and no clinical efficacy data was reviewed in conjunction with this NDA.

VII. Integrated Review of Safety

A. Methodology of the Safety Review

This safety review will be abbreviated compared to that conducted for most NDA's and will focus on: 1) any serious adverse experiences (i.e., deaths, non-fatal serious adverse events, and adverse events that led to premature discontinuation) that might suggest a particular hazard related to aripiprazole ODT treatment and 2) the potential for oral irritation with aripiprazole ODT.

B. Safety Findings

1. Deaths and Other Serious Adverse Events

In these studies, serious adverse events were defined as any occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability or incapacity, is a cancer, is a congenital anomaly or birth defect, an overdose, results in the development of drug dependency or drug abuse, or is otherwise considered medically important (such as a convulsion that does not result in hospitalization).

There were no deaths or other serious adverse events reported among the 136 subjects exposed to aripiprazole in these three trials.

A listing of all treatment-emergent adverse events reported in these trials was examined to detect any other medically significant event. One such event was identified: syncope was reported in 3 subjects in study CN138067. In two of

these subjects (#15 and #29), syncope occurred 4 hours and 1.5 hours, respectively, after dosing with aripiprazole 30mg ODT. In the other subject (#40), syncope occurred 12 hours after dosing with the aripiprazole 30mg commercial tablet. Thus, the reporting rate for syncope was 1.7% (2/118) with ODT and 0.8% (1/121) with the commercial tablet. A causal relationship to aripiprazole cannot be ruled out and it is possible that the risk may be higher with ODT exposure although the difference in reporting rates is not statistically significant (p=0.6, 2-tailed Fishers exact test). These rates are not very different from those observed in the original short-term trials of aripiprazole in schizophrenia, although the overall placebo rate exceeded the drug rate in that pool of studies (0.6% for aripiprazole and 1.0% for placebo).

2. Dropouts due to Adverse Events

In these [redacted] trials, a total of eight patients dropped out due to adverse events.

Four of these patients discontinued study participation due to vomiting which started within a few hours of receiving aripiprazole [redacted] two had received the reference tablet and two had received ODT.

Overall, vomiting was experienced by 9.3% of subjects after ODT and 9.1% of subjects after standard tablet. It was dose-related, occurring in 27% of subjects after 30mg of aripiprazole and 9% [redacted] this pattern was consistent when examined by formulation. Thus, it is likely that vomiting was causally related to aripiprazole administration in these trials but the risk of vomiting appeared to be independent of the formulation administered.

Other dropouts due to adverse events are summarized below:

- Patient #39 in study [redacted] dropped out due to dysphagia, fever, and lymphangitis on study day 3 after receiving aripiprazole [redacted]. These events were accompanied by a tachycardia (130 bpm) and leukocytosis (WBC=16,700). All events had resolved on follow-up.
- Patient #21 in study CN138067 discontinued due to pharyngitis beginning on day 27 after receiving aripiprazole 30mg standard tablet and lasting 16 days.

• Patient #21 [redacted] dropped out due to fever which lasted 3 days with onset on study day 4 after receiving aripiprazole [redacted] standard tablet.
• Patient #48 [redacted] discontinued from the trial due to chills, headache, chest congestion, fever, laryngitis, pharyngitis, and voice alteration which began on day 1 and lasted for 8 days after receiving aripiprazole [redacted] standard tablet. This subject was also noted to have slightly elevated bilirubin levels of 2.1 mg/dl and 2.2 mg/dl on days 28 and 56, respectively (normal value less than or equal to 2 mg/dl).

3. Oral Irritation

No specific assessments for oral irritation were performed in these studies. The listing of all treatment-emergent adverse events for these studies was examined for any events that might suggest oral irritation. The following pertinent events were reported: dental disorder (toothache), mouth disorder (white film in mouth), dry mouth, pharyngitis, dysphagia, and gingivitis. Each of these was reported in one subject after ODT dosing except for toothache, which was reported in one subject after each formulation, and pharyngitis, which was reported in 3 subjects after ODT and 5 subjects after the commercial tablet.

C. Adequacy of Patient Exposure and Safety Assessments

The safety assessment of aripiprazole ODT relies primarily on the safety experience with aripiprazole, which was approved based on safety data from over 4,700 patients in Phase 2/3 clinical trials and has been marketed for over a year in the U.S.

Specific assessment of mouth irritation in the submitted trials under this NDA would have been useful. Nonetheless, adverse event findings, while not highly sensitive for detecting such an event, suggest that mouth irritation after aripiprazole ODT administration is neither common nor severe.

D. Assessment of Data Quality and Completeness

Based on my review of this submission, the clinical data appear to be reasonably complete.

A DSI inspection of the site which conducted study CN138067 is pending.

E. Summary of Important Safety Findings

This review revealed no safety concerns which would preclude the approval of aripiprazole ODT or new safety issues that would require a change to the labeling of Abilify.

VIII. Dosing, Regimen, and Administration Issues

In view of the tendency of aripiprazole ODT's to rapidly disintegrate, it is important to protect the tablets from moisture during storage and during placement on the tongue. Proposed labeling does appropriately advise that the ODT's should be maintained in blister packaging until immediately before use and that the tablets should be handled with dry hands. Also, labeling cautions against damaging the tablets during removal from blister packaging and splitting the tablets.

IX. Use in Special Populations

This NDA provides no information about the use of aripiprazole ODT in special populations.

X. Review of Proposed Labeling

The labeling proposed by the sponsor very closely parallels the approved labeling for Abilify. Additional information regarding the ODT has been added to the following sections: DESCRIPTION, CLINICAL PHARMACOLOGY/Pharmacokinetics, PRECAUTIONS (new section entitled "Phenylketonurics" is added), DOSAGE AND ADMINISTRATION, and HOW SUPPLIED.

The directions for taking aripiprazole ODT under DOSAGE AND ADMINISTRATION appear to be acceptable from a clinical viewpoint. Other sections will be reviewed by the biopharmaceutics and chemistry reviewers.

XI. Conclusions and Recommendations

On face, aripiprazole ODT appears to be bioequivalent to the Abilify tablets and is expected to be reasonably safe and effective. At this time, consultant reviews (biopharmaceutics, chemistry, DSI, DMETS) have not yet been

completed and, thus, any significant issues raised by those reviews will need to be resolved prior to approval.

From a clinical perspective at this time, I have no objection to the approval of this marketing application.

Gregory M. Dubitsky, M.D.
March 23, 2004

cc: NDA 21-729
HFD-120/Division File
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/TLaughren
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/s/

Greg Dubitsky
3/23/04 02:55:30 PM
MEDICAL OFFICER

Thomas Laughren
10/12/04 03:53:19 PM
MEDICAL OFFICER
I agree that this NDA is approvable--TPL