

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-713

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#: 21-713
Sponsor: Otsuka America Pharmaceutical
Due Date: September 21, 2004

Drug Name:

Generic Name: Aripiprazole Oral Solution
Trade Name: ABILIFY Oral Solution

Drug Categorization:

Pharmacological Class: D₂ Receptor Partial Agonist
Proposed Indication: Schizophrenia
Dosage Forms: 1mg/mL Oral Solution
Route: Oral

Review Information

Clinical Reviewers: Gregory M. Dubitsky, M.D.
Completion Date: March 27, 2004

NDA 21-713
Aripiprazole Oral Solution
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	5
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	8
E. Foreign Marketing	8
II. Clinically Relevant Findings from Consultant Reviews	
A. Biopharmaceutics	8
B. Chemistry	8
C. Pharmacology/Toxicology	8
III. Human Pharmacokinetics and Pharmacodynamics	
A. Pharmacodynamics	8
B. Pharmacokinetics	8
IV. NDA Data Sources	
A. Primary Development Program	10
B. Published Literature	11
V. Clinical Review Methods	
A. Items Utilized in the Review	11
B. Specific Methods Used to Evaluate Data Quality	11
C. Adherence to Accepted Ethical Standards	12
D. Evaluation of Financial Disclosure	12
VI. Review of Efficacy	12

VII. Integrated Review of Safety	
A. Methodology of the Safety Review	12
B. Safety Findings	
1. Deaths and Other Serious AE's	12
2. Dropouts due to Adverse Events	13
3. Oral Irritation	13
C. Adequacy of Exposure & Safety Assessments	14
D. Assessment of Data Quality & Completeness	14
E. Summary of Important Safety Findings	14
VIII. Dosing, Regimen, and Administrative Issues	14
IX. Use in Special Populations	15
X. Review of Proposed Labeling	15
XI. Conclusions and Recommendations	15

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

From a clinical standpoint, it is recommended that this NDA be approved.

Consultant reviews (biopharmaceutics, chemistry, and pharmacology/toxicology) have not yet been completed. Any significant issues raised by those reviewers will need to be addressed before final 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 an oral solution of aripiprazole for the management of patients with schizophrenia.

Three studies comprise the development plan for Abilify Oral Solution. Two initial pharmacokinetic studies (CN138019 and CN138063) revealed that the oral solution was not bioequivalent to the marketed Abilify tablets due to more rapid absorption and greater maximum plasma concentrations of aripiprazole with the solution versus the tablet. To permit extrapolation of safety and efficacy experience from Abilify tablets, a third study (CN138108) was conducted to estimate the oral solution dose that produced exposures which approximated those produced by the maximum recommended dose of Abilify tablets (30mg), with the understanding that oral solution dosing would be capped at that dose.

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 three clinical pharmacology 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 the oral solution relies almost entirely on extrapolation from investigations conducted with the standard aripiprazole tablet.

D. Dosing

Dosing of the oral solution will be equal (milligram-for-milligram) to the Abilify tablet dose except at the highest recommended dose: for the 30mg Abilify tablet, 25mg (25 mL) of the oral solution should be substituted.

Abilify Oral Solution will be supplied in a child-resistant bottle with a calibrated dosing device.

E. 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 D₂ receptors and 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors. Aripiprazole was approved as Abilify tablets for the acute treatment of schizophrenia in adults on 11-15-02 under NDA 21-436. Data regarding longer-term safety and efficacy were submitted in supplement S-001 to that NDA, which was approved on 8-28-03. The tablet has been shown to be safe and effective in the dose range 10 to 30 mg/day. Doses are taken once daily without regard to meals.

Otsuka has developed an oral solution formulation of aripiprazole with the trade name ABILIFY Oral Solution under IND 62,216. This formulation will provide an alternate means of administering aripiprazole to patients

who have difficulty swallowing tablets, with the expectation of improving compliance.

Otsuka is seeking approval of aripiprazole oral solution on the basis of extrapolating safety and efficacy data from the tablet. However, the solution is not bioequivalent to the tablet and extrapolation is based on two presumptions: 1) at solution doses under 25mg, the small differences in exposure between equal milligram doses of solution and tablet are not likely to be clinically relevant and 2) at a solution dose of 25mg, exposure is less than that produced by the maximum recommended tablet dose (30mg). Solution doses above 25mg will not be recommended.

B. Major Safety Findings with Aripiprazole

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

C. Administrative History

A pilot study (CN138019) was conducted in late 2000 under the aripiprazole tablet IND (IND 42,776) to assess the oral bioavailability of aripiprazole 3mg when administered as an oral solution relative to the 15mg commercial tablet in healthy volunteers. In this study, the dose-normalized Cmax and AUC after solution administration were appreciably greater than those with the tablet. Thus, the rate and extent of absorption of aripiprazole were greater with the solution versus the tablet in this trial.

An IND application (IND 62,216) for aripiprazole oral solution was submitted on 3-20-01 and received on 3-21-01. This application included a protocol for study CN138026, a study to compare the pharmacokinetics of an 11mg dose of aripiprazole oral solution to a 15mg tablet as well as to examine the effect of food on aripiprazole pharmacokinetics after solution administration. The study was allowed to proceed. However, the sponsor subsequently decided not to initiate this study and, instead, conducted study CN138063, which examined the dose proportionality of the solution (at 5, 10, and 15mg) and compared the solution versus tablet pharmacokinetic characteristics at these doses. The protocol for this trial was submitted on 8-3-01.

Preliminary data from the latter trial further supported the findings of the pilot study and the sponsor concluded that the solution and tablet were not bioequivalent.

Therefore, at their request, we met with the sponsor on 10-30-02 to address the possible need for a clinical study of the oral solution. The sponsor had proposed a 6 week, multicenter, randomized, double-blind, placebo-controlled inpatient trial in patients with schizophrenia (CN138091). We informed them that if the blood levels of aripiprazole following the solution in PK studies were bracketed by levels achieved with tablet doses which were likely to be approved (and subsequently were approved), then a clinical study was not necessary. We recognized, however, that such bracketing was unlikely to hold true for a 30mg dose in solution and, for safety purposes, suggested that capping the recommended solution dose at a level between 20mg and 30mg could address this issue. Accordingly, we recommended that they explore the pharmacokinetics of the solution at doses of 20, 25, and 30mg to gauge the maximum dose for labeling. In that meeting, we also informed them that a food effect study would not be needed.

On 1-13-03, the sponsor submitted a protocol for study CN138108, a relative bioavailability study which compared 20mg and 30mg solution doses to the 30mg commercial tablet.

That study was completed and this NDA was submitted and received on 11-20-03. A Refuse-to-File (RTF) meeting was convened on 1-12-04 and it was revealed by chemistry staff that the solution contained 2 previously undetected degradants that exceeded the qualification threshold. It was decided that input from the pharmacology/toxicology staff was needed and a second RTF meeting was convened on 1-20-04. It was concluded that these moieties would need to be studied in at least one animal species if that had not already been done. If further study is required, that could delay final approval of the application. The application was filed, with a PDUFA Due Date of 9-21-04.

Finally, on 2-6-04, a protocol for another clinical pharmacology study (CN138137) was submitted. The objective of this investigation is to compare the bioavailability of aripiprazole 25mg in solution versus the 30mg marketed tablet. Clinically, this study was deemed safe to proceed.

D. Proposed Instructions for Use

A table (Table 4) is provided in proposed labeling to guide clinicians in dosing patients with the oral solution. In summary, the oral solution can be given on a milligram-per-milligram basis in place of the 5, 10, 15, and 20mg tablets. For the highest tablet strength (30mg), a 25mg dose (25 mL) of the oral solution should be substituted.

E. Foreign Marketing

There are no foreign postmarketing data for Abilify Oral Solution.

II. Clinically Relevant Findings from Consultant Reviews

A. Biopharmaceutics

The review of the clinical pharmacology studies by the Office of Clinical Pharmacology and Biopharmaceutics is currently pending.

B. Chemistry

The review of chemistry, manufacturing and controls data by the Office of New Drug Chemistry is not yet finished.

C. Pharmacology/Toxicology

The pharmacology/toxicology review is pending at this time. This review will need to address the need for further study of the previously undetected impurities.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacodynamics

No new pharmacodynamic data are presented in this NDA.

B. Pharmacokinetics¹

The Abilify Oral Solution development program is comprised of three clinical pharmacology studies that were conducted

¹ The information presented is based on the Summary of Clinical Pharmacology provided in this submission. These data will be discussed in detail in a separate review by staff from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

in healthy adult subjects. These studies are summarized below.

Study CN138019

This was a randomized, open label, two-period, two-treatment crossover study in 16 healthy adults. On two occasions, separated by at least 21 days, each subject received the 15mg aripiprazole reference tablet or aripiprazole 3mg as an oral solution after an overnight fast of at least 10 hours; fasting was to continue until 4 hours post-dose. Serial blood samples for PK assessments were collected over a period of 384 hours (17 days) post-dose.

Pharmacokinetic data were available for 14 subjects. Dose-normalized PK parameters are displayed in Table 1 below. The rate and extent of aripiprazole absorption was greater for the solution compared to the tablet. Also, the mean Tmax was considerably greater for the tablet versus solution (5.00 vs. 1.50 hours).

	15mg Tab	3mg Solution
Cmax (ng/mL/mg)	3.1 (33)	4.4 (33)
AUC(inf) (ng-hr/mL/mg)	186 (60)	257 (76)
AUC(0-T) (ng-hr/mL/mg)	173 (57)	205 (72)

The 90% confidence intervals for the ratio of solution to reference tablet were (1.231, 1.663) for Cmax and (1.259, 1.552) for AUC(inf).

Study CN138063

This was a randomized, open-label, three-period, six-treatment incomplete crossover study in 60 healthy adults. Each subject received three of six possible treatments in random sequence (5, 10, and 15mg in oral solution and 5, 10, and 15mg tablets). All treatments were given after a fast of at least 10 hours; subjects continued to fast for 4 hours post-dose. Blood samples for pharmacokinetic assessments were collected over a period of 384 hours (17 days) post-dose. There was a washout period of at least 21 days between treatments.

The PK dataset consisted of 24, 24, and 23 subjects who received the 5, 10, and 15mg solution, respectively, and 19, 21, and 23 subjects in the 5, 10, and 15mg tablet

groups, respectively. The oral solution produced aripiprazole levels which were dose-proportional for both Cmax and AUC(inf). The doses of oral solution needed to produce exposures equivalent to the three aripiprazole tablet doses were computed and are displayed in Table 2 below. In each case, the solution dose was lower than the tablet dose, particularly for the 10mg and 15mg tablet strengths.

TABLE 2 ESTIMATED ORAL SOLUTION DOSES TO PRODUCE EXPOSURE EQUIVALENT TO TABLETS		
Tablet Dose	AUC(inf)	Cmax
5mg	4.76mg	4.35mg
10mg	9.30mg	8.01mg
15mg	13.8mg	11.5mg

Study CN138108

This was a randomized, open-label, three-period, three-treatment crossover study in 46 healthy volunteers. The study objective was to estimate the aripiprazole oral solution dose that would produce a drug exposure (AUC(inf)) comparable to the exposure produced by administration of the 30mg commercial tablet. On each of three occasions, subjects received one of three treatments (solution 20mg, solution 30mg, or tablet 30mg). There was a washout period of at least 28 days between treatments. Dosing was performed after an overnight fast of at least 10 hours, with four hours of fasting post-dose. Blood samples for PK assessment were obtained over a period of 384 hours (17 days).

Data from 29 subjects were used to estimate the dose of oral solution. The estimated solution dose based on AUC(inf) was 25.02mg (95% CI 22.74, 27.53). A post-hoc analysis was done to determine the oral solution dose based on Cmax. This dose was roughly comparable to that found by the analysis based on AUC: 24.05mg (95% CI 20.81, 27.81).

IV. Description of Clinical Data Sources

A. Primary Development Program

The clinical development plan for Abilify Oral Solution comprised the three clinical pharmacology studies described above at the time of this NDA submission.

In these three studies, a total of 122 healthy adult subjects received at least one dose of aripiprazole. Aripiprazole was administered as an oral solution in 109 subjects and as a tablet in 101 subjects. Among the subjects who received a solution, 58 received one single dose and 51 received two single doses.

Among all 122 subjects who received aripiprazole, the mean age was 33.4 years and the age range was 18-45 years. Most of the subjects (66%) were male. Also, most of the subjects were Black (34%), Hispanic (15%), or White (50%).

In addition to the three completed studies, a protocol for study CN138137 was submitted after this NDA was received. This study will compare the bioavailability of aripiprazole 25mg as oral solution to the 30mg tablet in 36 healthy subjects, age 18-45.

No Phase 2/3 clinical trials were conducted with Abilify Oral Solution.

B. Published Literature

The sponsor provided no systematic search of the published literature.

On 3-27-04, I searched PubMed for relevant articles using the search string "(OPC-14597 OR aripiprazole) AND oral AND solution." No articles were identified.

V. Clinical Review Methods

A. Items Utilized in the Review

All materials examined in this review were provided electronically by the sponsor on 11-20-03 and were reviewed in the CDER Electronic Document Room (EDR).

B. Specific Methods Used to Evaluate Data Quality

A consultation request to the Division of Scientific Investigations was not issued for this NDA since no pivotal bioequivalence or clinical studies were conducted in conjunction with this application.

C. Adherence to Accepted Ethical Standards

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

D. Evaluation of Financial Disclosure

Financial disclosure information was obtained from the 3 principal investigators involved in studies CN138019, CN138063, and CN138108. None had disclosable information.

Likewise, financial information was obtained from the 6 subinvestigators from study CN138063 and the 2 subinvestigators from study CN138108. These individuals had no disclosable information.

However, financial information could not be obtained from the 14 subinvestigators from study CN138019. Since this study is not considered pivotal for the approval of this NDA, the lack of this information should not preclude approval of this application.

VI. Review of Efficacy

The clinical pharmacology studies comprising this NDA were not designed to evaluate the efficacy of Abilify Oral Solution. 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 associated with Abilify Oral Solution and 2) the potential for oral irritation with the oral solution.

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.

There were no deaths or other serious adverse events reported among the 122 subjects exposed to aripiprazole in these three trials.

A listing of all treatment-emergent adverse events reported in these three trials was examined to detect any other medically significant events. One such event was identified: increased SGOT/SGPT in subject #37 from study CN138063. However, elevated liver transaminases were present pre-treatment (SGPT=490 U/L and SGOT=160 U/L), decreased following dosing with the aripiprazole 30mg tablet, and SGPT was normal 16 days post-dose. Jaundice was not reported. This laboratory abnormality is unlikely to be causally related to aripiprazole.

2. Dropouts due to Adverse Events

In these three trials, a total of six patients dropped out due to adverse events.

Five subjects, all from study CN138108, discontinued due to vomiting. Three of these subjects vomited after 30mg as oral solution, one after 20mg as oral solution, and one after the 30mg tablet. All vomited within 4 hours of dosing. None of the episodes were deemed to be severe but all five subjects were dropped from the study since vomiting soon after dosing can confound pharmacokinetic assessments.

Overall, vomiting occurred in 6.4% (7/109) of subjects after oral solution and 6.9% (7/101) of subjects after tablets.

One subject was discontinued due to elevated liver enzymes. This case is discussed above (subject #37 in CN138063).

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.

Only two pertinent events were identified: dry mouth (reported in 3 subjects after oral solution and none after tablet) and pharyngitis (reported in 2 subjects after oral solution and 5 subjects after tablet). All cases of dry mouth were rated as mild in severity.

C. Adequacy of Patient Exposure and Safety Assessments

The safety assessment of Abilify Oral Solution rests primarily on the safety experience with aripiprazole tablets, which were approved based on safety data from over 4,700 patients in Phase 2/3 clinical trials and have been marketed for over a year in the U.S.

Specific assessment of mouth irritation in the submitted studies under this NDA would have been useful. Nonetheless, adverse event findings, while not highly sensitive for detecting such occurrences, suggest that mouth irritation after Abilify Oral Solution 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.

E. Summary of Important Safety Findings

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

VIII. Dosing, Regimen, and Administration Issues

Based on the results of study CN138108, a 25mg dose of Abilify Oral Solution is not expected to produce aripiprazole exposure (AUC or C_{max}) which exceeds that of the 30mg Abilify tablet. Thus, a 25mg solution dose may be substituted for a 30mg tablet dose. The more recent study CN138137 will provide a more definitive comparison of the bioavailabilities of the 25mg solution dose and the 30mg tablet dose.

It is presumed that at doses below 25mg, doses of the Oral Solution are clinically equivalent to equal doses of the tablet formulation. Given the lack of a clear dose-response relationship for aripiprazole tablets and the results of study CN138063, this presumption seems reasonable.

IX. Use in Special Populations

This NDA provides no information about the use of Abilify Oral Solution 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 oral solution has been added to the following sections: DESCRIPTION, CLINICAL PHARMACOLOGY/ Pharmacokinetics, PRECAUTIONS (new section entitled "Sugar Content" is added), DOSAGE AND ADMINISTRATION, and HOW SUPPLIED.

The directions for taking Abilify Oral Solution 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

Abilify Oral Solution, when administered according to the directions in proposed labeling, is expected to be reasonably safe and effective. From a clinical perspective, it is recommended that this application be approved.

However, consultant reviews (biopharmaceutics, chemistry, and pharmacology/ toxicology) have not yet been completed. Thus, any significant issues raised by those reviews will need to be adequately addressed prior to approval.

Gregory M. Dubitsky, M.D.
March 27, 2004

cc: NDA 21-713
HFD-120/Division File
HFD-120/GDubitsky
 /TLaughren
 /PAndreason
 /SHardeman

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

/s/

Greg Dubitsky
3/27/04 07:48:51 PM
MEDICAL OFFICER

Thomas Laughren
9/18/04 01:51:50 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo
to file for more detailed comments--TPL