

Meeting Minutes

Meeting Date: June 22, 2001
Location: WOCII - Rm 4028
IND:
Drug: Aripiprazole
Sponsor: Bristol-Myers Squibb / Otsuka
Type of Meeting: CMC PreNDA Meeting
Meeting Chair: Robert Seevers, Ph.D.
Meeting Recorder: Steven D. Hardeman, R.Ph.

Participants: see attached.

Discussion Points (bullets):

The following sponsor minutes (submitted 10-11-01) are generally accurate and will be archived as official minutes of this meeting, with the addition of the following comment:

[The only change is in the last item. The minutes state that stability data must be submitted no later than the 7 month point of the review clock. Actually that data "*should*" be submitted no later than the 7 month point of the review clock since submissions in the last three months of the review cycle run the risk of triggering a three month extension of the review clock, if they are deemed major amendments.]

APPEARS THIS WAY
ON ORIGINAL

OTSUKA MARYLAND RESEARCH INSTITUTE, LLC & BRISTOL-MYERS SQUIBB CO.

FDA MEETING MINUTES

Division of Neuropharmacological Drug Products

**ARIPIRAZOLE
OPC-14597**

ORAL TABLET FORMULATION

**CMC Pre-NDA Meeting
June 22, 2001**

Attendees from CDER, FDA:

Raman Baweja, Ph.D., Team Leader, OCPB
Steve Hardeman, RPh, Senior Regulatory Project Manager
Richard Lostritto, Ph.D., Chemistry Reviewer
Chandras Sahajwalla, Ph.D., Deputy Director, OCPB
Robert Seevers, Ph.D., Chemistry Team Leader
Hong Zhao, Ph.D., Reviewer, OCPB

Attendees from Bristol-Myers Squibb Company:

Shreeram Agharkar, Ph.D., Executive Director, Biopharmaceutics R&D
Michael Burnett, Director, CMC Regulatory Sciences
Norma Delaney, Ph.D., Assoc. Director, CMC Regulatory Sciences
Charles Wolleben, Ph.D., Director, Regulatory Sciences

Attendees from Otsuka Maryland Research Institute, LLC / Otsuka America Pharmaceutical Inc.:

Suresh Mallikaarjun, Ph.D., Assoc. Director, Clinical
Pharmacokinetics/Pharmacodynamics and Metabolism
Shinji Nishitani, Ph.D., Director, Manufacturing
Suva Roy, Ph.D., Senior Director, Regulatory Affairs CMC

Attendees from Otsuka Pharmaceutical Co., Ltd., Japan:

Tsutomu Fujimura, Director, Bulk Pharmaceutical Chemicals
Milton Severinsen, Manager, Manufacturing Process Development
Michiharu Sugawara, Director, Analytical Development, Formulation Research Institute

Meeting Summary

Prior to the meeting, background information was provided (Submission No. 352 to IND on June 6, 2001 and Submission No. 353 on June 8, 2001). A number of questions were submitted for discussion with FDA, of which five were highlighted in the cover letter as the main items requiring FDA feedback in order for our development program to proceed. As was agreed beforehand, the meeting was issues-driven and no presentation was made. After introductions, FDA proceeded directly to the questions. The issues discussed are provided below in italics followed by a summary of the ensuing discussion.

Does FDA concur with the proposal for biowaivers for the "new" 20- and 30-mg strengths?

The Agency does not agree with the biowaiver proposal. This is based upon a number of concerns that were discussed:

- It is their opinion that, based upon *in vitro* data, aripiprazole is not a Class 1 drug, and is more like a Class 4 drug (low solubility, low permeability).
- Although the linearity of aripiprazole pharmacokinetics was established, this was done, for doses greater than 15 mg, using multiples of lower strengths. Tablet strengths higher than 15 mg have not been tested *in vivo*.
- There is no IVIVC (*in vivo-in vitro* correlation) that includes data from the 30-mg tablet strength. An IVIVC established with lower strengths would not be adequate to grant biowaivers for the higher strengths (20 mg and 30 mg).
- Data from study CN138-035 indicate that the 15-mg tablet is not bioequivalent to 3X5 mg. Therefore, it is uncertain if strengths higher than 15 mg would perform well *in vivo*.

Based upon this, the Division is willing to grant a biowaiver for strengths of 15 mg and lower, but due to the issues stated above, cannot extend the waiver for higher dose strengths.

Dr. Mallikaarjun presented our rationale regarding the "new" 20- and 30-mg strengths which is based upon the fact that they are extensions of the 10-mg blend, and the dissolution data at pH 1.2 and 4.0 are as expected, i.e., rapid and almost complete dissolution. It was also pointed out that based on oral bioavailability of 87% in humans, aripiprazole is more like a Class 2 drug (i.e., low solubility and high permeability). The Agency responded that although the data appear satisfactory, there is no IVIVC. If an IVIVC were to be established, then they would be more accepting of granting biowaivers for the 20- and 30-mg strengths. However, they added that development of the IVIVC must include *in vivo* data for the 30-mg strength. Also, regardless of the fact that the new strengths are the same blend as the 10-mg strength, the lower C_{max} of the original 15-mg tablet compared to the 3X5 mg tablets gives them concern that dose strengths higher than 15 mg may not demonstrate dosage strength equivalency with lower strengths.

There was recognition that there is a problem conducting BE studies in subjects at doses of 30 mg due to tolerability issues. We were directed to the guidance regarding the demonstration of bioequivalence for clozapine, which has a similar problem of tolerability in subjects. (The guidance includes a strategy for evaluation of bioequivalence in patients at steady state.) Upon demonstration of bioequivalence of the 30-mg tablet strength to 3X10-mg tablets, FDA will grant a biowaiver for the 20-mg strength tablet.

Finally, it was noted that if bioequivalence is not demonstrated for the 30-mg strength, approval of this strength is still possible based upon the clinical experience that will exist in the NDA. This is an issue for the clinical reviewing division and would be based upon their review of the application.

With regard to the timing of submission of bioequivalence data to support the 20- and 30-mg dose strengths, submission of this data up to the time of the 120-day safety update would be acceptable and would not impact on the review clock. Just about any submission made during the last three months of the initial review clock will result in an extension of the clock by three months. In general, determination of whether or not to reset the review clock will be made based upon the time, number, and volume of the amendments.

Would FDA accept the NDA with Certificates of Analysis only at the time of filing for three batches each of the "new" 20- and 30-mg tablet formulations, manufactured at a scale representative of commercial production, along with a commitment to provide six-month stability data for the batches during the review?

Dr. Seevers responded that normally this could be a justification for a "refusal to file" recommendation. However, due to the fact that substantial stability information will be provided on lower strengths, this strategy is acceptable. Given this strategy, the understanding is that the tentative expiry for these dose strengths will be determined based upon the submitted six-month data. If no significant trend is seen in the data from both room temperature and accelerated conditions, a ——— expiry could be granted. Following a brief discussion it was agreed that we could make a case for extending the expiry in the NDA based upon our experience with the 10-mg clinical tablet formulation. This position would be considered during the review of the NDA.

Is the proposed regulatory dissolution method that has been developed in response to FDA's recommendation acceptable?

The proposed dissolution method was the following:

Medium: pH 1.2 USP buffer/900 mL
Apparatus: USP Dissolution Apparatus 2
Paddle Speed: 60 rpm

This varied from the Agency's original proposal in the paddle speed of 60 vs. 50 rpm. Initially, the Agency was not willing to accept an increase in the paddle speed to 60 rpm, which was proposed to decrease the variability seen at the lower paddle speed. A discussion followed on the implications of the lower paddle speed on specifications, including exploring the acceptability to the Agency of a low specification at 50 rpm rather than a tighter one at 60 rpm. FDA inquired as to whether or not we considered using a surfactant. Mr. Sugawara stated that the use of a surfactant at pH 1.2 has not been investigated. To fully explore the proposal to increase the paddle speed to 60 rpm, the Agency asked that we submit dissolution profiles for all strengths at 50 and 60 rpm at pH 1.2. (This was provided on June 25.)

On a related issue, it was noted that all stability is being monitored at pH 4.0, but this is not discriminating for bioavailability. As a result, before the commercial batches go on stability, there has to be an agreement on the dissolution testing. If there is a ruling that pH 1.2 is the appropriate pH, then that will be the QC test. It was recognized that both OPC/BMS and FDA do not want two QC dissolution tests (one at pH 1.2 and another at pH 4.0). This led to a discussion regarding the Agency's flexibility of going to a paddle speed of 60 rpm at pH 1.2. The Agency agreed to reconsider the issue of the paddle speed. [Post meeting note: After the requested dissolution data were provided (on June 25), FDA responded (on June 27) with their acceptance of the pH 1.2, 60-rpm dissolution method.]

Is the proposed bridging study between the original (pH 4.0) and new (pH 1.2) dissolution test methods to be used for the ongoing long-term stability studies acceptable to FDA?

The revised bridging study presented during the meeting was acceptable. A copy was submitted after the meeting. The open-dish protocol would be an acceptable link as long as nothing unusual surfaced during that test.

There was a discussion regarding monitoring for monohydrate. It was agreed that if the monohydrate is not formed, there is no need to set a specification for it. It was suggested that solid-state NMR could be used to limit monohydrate content, and that the specification could be dropped later if monohydrate were not detected. In the end it was agreed that monitoring formation of monohydrate by the pH 4.0 dissolution method through the duration of the NDA stability protocol can be used to demonstrate that formation of monohydrate is not an issue.

Does FDA agree that starting materials in the synthesis of aripiprazole?

can be considered

The Agency indicated that the starting materials seemed appropriate as long as they are commercially available and not obtained by sufficient to demonstrate commercial availability; COAs for these materials should be provided in the NDA. A catalog listing is not

Is the proposal to r

only for the same step acceptable to

FDA?

The proposal was acceptable to FDA.

Does FDA agree with the proposed regulatory tests for the drug substance?

The Agency advised us to follow the ICH guidance with regard to specifications for drug substance. Specified impurities should be identified, and our proposed limits should be in Dr. Lostritto asked why we had chosen the proposed particle size specification. Dr. Agharkar responded that this was chosen to be consistent with the particle size used in the clinical batches. Dr. Lostritto indicated that justification for the particle size specification should be provided in the NDA.

*Is the proposal to submit a _____
Mayaguez, P.R. acceptable?*

manufactured by BMS in

The proposal was accepted and _____ weeks ahead of the NDA. The DMF number and authorization letter should be provided in the NDA.

Other

- Dr. Seevers commented that we should make sure that the packaging materials that we propose in the NDA for commercial product are the same as those being used for stability.
- In order to facilitate the Agency's review of referenced DMFs, the letters of authorization should provide appropriate cross referencing to the exact location within the DMF of the specified items.
- It is acceptable to submit a stability update during the NDA review, but it must be received no later than the 1st day of the seventh month after NDA submission.

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

/s/

Steve Hardeman
1/10/02 07:02:05 AM
Signed for Robert SeEVERS, PhD

**APPEARS THIS WAY
ON ORIGINAL**

Advisory Committee Meeting: N/A

APPEARS THIS WAY
ON ORIGINAL

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

7 pages

MEMORANDUM

DATE: August 29, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-436

SUBJECT: Recommendation for Action on NDA 21-436, for the use of Aripiprazole in the treatment of patients with Schizophrenia

NDA 21-436, for the use of Aripiprazole, a so-called atypical antipsychotic drug, in the treatment of patients with schizophrenia, was submitted by Otsuka/Bristol-Myers Squibb, on 10/31/02. Aripiprazole has 5-HT_{1A} partial agonist activity and 5-HT_{2A/2C} antagonist activity, in addition to partial agonist activity at D₂ receptors. These activities are presumed to confer anti-schizophrenic activity, but to limit motor side effects by allowing sufficient dopamine to remain in nigro-striatal pathways while reducing dopamine activity in meso-limbic pathways.

The application contains the results of 7 controlled trials, 5 short-term placebo and active controlled trials, and 2 identically designed long-term active control trials comparing aripiprazole to haloperidol on time to relapse. The latter studies were analyzed, per protocol, as a single study. There was no difference between the 2 drugs in this trial, making it uninterpretable. In addition, the application contains safety data gathered in over 4700 patients in Phase 2/3 trials, and about 900 subjects in clinical pharmacology studies. Further, open label safety data in 769 aripiprazole treated patients in Japan was described.

The application has been reviewed by Drs. Greg Dubitsky and Rob Harris of the division (combined safety and efficacy review dated 6/12/02), Dr. Lois Freed, pharmacologist (review dated 8/29/02), Dr. Hong Zhao, Office of Clinical Pharmacology and Biopharmaceutics (review undated), Dr. Sherita McLamore, chemist (review dated 8/13/02), Dr. Yeh-Fong Chen, statistician (review dated 7/15/02), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 8/15/02). Dr. Laughren's memo provides a succinct, comprehensive overview of the relevant issues in the application. In this memo, I will briefly review the data, and offer the division's recommendation for action on the application.

EFFECTIVENESS

As noted above, the sponsor has presented the results of 5 short-term, placebo and active control studies. All but one study included an active control, and all but one study included multiple fixed doses of aripiprazole. The one study that did not employ multiple fixed doses was Study 93202, in which patients were

titrated up from 5 mg to 30 mg for the last 2 weeks of the study. Most of the trials designated more than one efficacy measure as primary, and all trials assessed multiple secondary outcomes. The following display presents the p-values for the drug-placebo contrasts on the primary outcome measures for all 5 short-term studies (Dr. Laughren's memo provides the actual change from baseline for all of these contrasts).

Study 93202 (4 weeks)

	Aripiprazole	Haloperidol 20 mg
BPRS	0.17	0.01
CGI-Severity	0.07	0.005

Study 94202 (4 weeks)

	Ari 2 mg	Ari 10 mg	Ari 30 mg	Haloperidol 10 mg
BPRS Core	0.7	0.9	0.12	0.05
CGI-Improvement	0.6	0.2	<0.01	0.08

Study 97201 (4 weeks)

	Ari 15 mg	Ari 30 mg	Haloperidol 10 mg
PANSS Total	<0.001	0.009	0.001
PANSS Positive	<0.001	0.001	<0.001
CGI-Severity	<0.001	0.02	0.002

Study 97202 (4 weeks)

	Ari 20 mg	Ari 30 mg	Risperidone 6 mg
PANSS Total	0.001	0.003	<0.001
PANSS Positive	0.001	0.02	<0.001
CGI-Severity	0.03	0.006	<0.001

Study 138001 (6 weeks)

	Ari 10 mg	Ari 15 mg	Ari 20 mg
PANSS Total	<0.001	0.004	<0.001
BPRS-Core	<0.001	0.014	<0.001
PANSS Negative	<0.001	0.002	<0.001

In the first 4 studies, the percentage of patients on aripiprazole who completed the trial ranged from 60-70%. In the last trial, the completion rate was between 30-40% in the drug-treated patients. Almost all of those who discontinued early discontinued at the end of weeks 3 or 4 (presumably by protocol, patients showing no improvement on the CGI were given the option of receiving open-label drug at the end of Week 3), and entered open-label treatment. There were no significant drug-placebo differences in the Observed Cases analyses in weeks 4, 5, and 6 on any of the 3 primary outcome measures, with the exception of Week 6, aripiprazole 10 mg, BPRS-Core, but there was nominal significance for the first 3 weeks in the 10 and 20 mg groups. This fact reassures Dr. Chen that the non-significant findings in the OC analysis for Weeks 4, 5, and 6 are not reflective of a serious bias.

However, in Study 97202, Dr. Chen notes that the Observed Cases analyses were essentially negative, and undertook an analysis of the various dropout cohorts by each week. Her concern was that the 25% of placebo patients who discontinued after Week 1 in this study could have biased the results. Her detailed review of this issue can be found in her review, pages 64-67.

Briefly, she discovered that the change in the PANSS Total Score in the placebo group of patients who discontinued during Week 1 was considerably larger (worse) than that in any of the other drug-treated Week 1 dropout cohorts. Further, she noted that an analysis of the rest of the placebo patients (with the dropout cohort removed) at Week 1 showed a fairly negative (good) response, much more consistent with the drug-treated OC Week 1 cohorts and that the OC placebo cohorts at Weeks 2, 3, and 4 further demonstrated that the placebo patients continued to improve with time. Additional analyses further confirmed that the early placebo dropouts did have considerably worse responses than the rest of the patients. These findings, taken together, raised the concern that both LOCF and OC analyses were potentially biased. That is, carrying forward such poor scores from so many early placebo discontinuations had the tendency to bias the analysis in favor of drug-placebo differences on the LOCF analysis, while utilizing the quite good scores in the placebo patients who remained in the trial potentially biased the OC analysis in the direction of diminishing any drug-placebo difference.

Studies 97201 and 97202 each enrolled patients with schizoaffective disorder in addition to patients with schizophrenia. Each study was analyzed with the schizoaffective patients removed, and each study retained the statistically significant between treatment differences described above.

SAFETY

As noted above, the application contains safety experience in about 900 subjects in clinical pharmacology studies, and in over 4700 patients, 3561 with schizophrenia. I will briefly review the relevant safety findings.

Deaths

There were no deaths in the short-term, placebo-controlled trials. In the overall Phase 2/3 experience, mortality was 23 deaths/1000 pt-yrs (61 deaths/2656 Pys). This compared to a mortality of 0 in the placebo patients (0 deaths/86 Pys), and 9.6/1000 Pys in the haloperidol treated patients (2 deaths/207 Pys). As Dr. Harris points out, 39/61 aripiprazole deaths were in elderly patients in Alzheimer's Disease studies (39 deaths/224 Pys, mortality of 174/1000 Pys). When these deaths are removed from the overall rate, the rate in non-AD patients was 9/1000 Pys (22 deaths/2433 Pys). This latter rate is comparable to the rate cited above for haloperidol. Examination of the deaths (non-AD) revealed no obvious drug-related cause, although there were 10 suicides, and 2 overdoses (? Intentional). The rate of suicide in this cohort was half that seen in the haloperidol-treated group.

Serious Adverse Events

There were 3 adverse events in the controlled trials that Dr. Harris considered serious: delirium in the setting of hyponatremia, syncope, and a generalized tonic-clonic seizure.

Further, the rate of serious ADRs in the larger database was no greater than that on placebo. One patient in the cohort of about 1700 patients still receiving blinded treatment at the time of the cut-off date for the Safety Update had ischemic colitis and GI bleeding on day 33 of treatment, 13 days after sustaining a head injury.

Discontinuations

In the short-term controlled trials, the rate of discontinuation for adverse events was greater in the placebo-treated patients than in the drug-treated patients. The only specific ADR that led to discontinuation in more than 1% of aripiprazole patients was psychosis: 3.6% in drug and 6.1% in placebo-treated patients.

According to Dr. Harris, there were no new "clinically important and possibly aripiprazole-related" adverse events that led to discontinuation in the larger Phase 2/3 database.

Other Adverse Events

As noted by Dr. Laughren, there were no adverse events that met standard frequently used criteria for inclusion in tabular form in labeling; that is, events with an incidence of at least 5% and twice that of placebo. There were only 2 ADRs with twice the incidence on drug compared to placebo: fever, 2% vs 1%, and blurred vision, 3% vs 1%.

As Dr. Harris points out, there were a number of adverse events that were seen more frequently on drug compared to placebo. The more important ones were:

Headache-32% vs 25%
Nausea-14% vs 10%
Vomiting-12% vs 7%
Insomnia-25% vs 19%
Lightheadedness-11% vs 7%
Blurred vision-3% vs 1%

Somnolence was the only ADR seen to be dose related (more on this below).

Laboratory Tests

There were no serum chemistry tests in which the number of patients with clinically significant changes was greater on drug compared to placebo, although there were isolated patients with clinically significant changes on several measures (the vast majority of tests in these patients became normal, or nearly so, with continued treatment. For a few patients, their last recorded values were abnormal; we will ask the sponsor for follow-up for these patients.

There was a median increase in ALT of about 9% in aripiprazole treated patients in controlled trials, compared to a 0% median change in placebo patients. In addition, there was a 22% increase in CPK in aripiprazole treated patients, compared to about 8.5% on placebo.

Regarding hematology, there was a 1% incidence of decreased hematocrit in drug treated patients, compared to a 0% incidence in the placebo patients. Only 1 aripiprazole treated patient had a decrease of significance; a drop from 43% to 20% on day 3 of treatment, with an associated drop in hemoglobin from 14 g/dL to 7 g/dL. He withdrew consent, and no follow-up is available.

A number of patients had low platelet counts, most of which returned to normal on treatment. However, 2 patients had only one on drug measurement; both were recorded as about 80,000 /cu mm, with no further values reported.

There was no evidence of abnormalities related to glucose metabolism, including assessment of random blood glucose levels (both mean and outlier assessments), and glycosylated hemoglobin.

Vital Signs/Orthostatic Changes

In the controlled trials, standing heart rate was increased in 19% of aripiprazole patients, compared to 13% of the placebo patients (p=0.012). There were no statistically or clinically significant differences between aripiprazole or placebo patients for other vital sign measurements.

There was no meaningful difference between the incidence of abnormal orthostatic blood pressure measurements in drug and placebo treated patients in the controlled trials.

In the short-term controlled trials, about 14% of drug treated and 9% of placebo treated patients had an orthostatic related adverse event (lightheadedness, faintness, etc.); 3 drug treated patients discontinued treatment for these events, compared to 0 placebo patients.

EKG

Dr. Laughren has discussed the EKG findings in detail.

Briefly, there were no meaningful differences between placebo and aripiprazole treated patients on any EKG parameters, including QT interval, in the controlled trials (in which the EKGs were not done in any systematic temporal relation to dosing).

The sponsor did perform a study evaluating the effects of higher doses (30-90 mg/day) on EKG intervals. This study evaluated cohorts of 10 patients (3 in each cohort received 30 mg, and 7 received either 45 mg, 60 mg, 75 mg, or 90 mg) 15 days after the initiation of dosing (steady state). A 5 day washout period followed each 15 day dosing period. The median change from baseline in QTc interval for the various doses is as follows:

30 mg	-12.5 msec
45 mg	-15.3 msec
60 mg	-5.9 msec
75 mg	-6.3 msec
90 mg	1.3 msec

Somnolence

As noted earlier, the only adverse event seen to be dose related was somnolence. In particular, the elderly seemed to be most susceptible to the occurrence of somnolence.

Specifically, in the controlled trial in patients with Alzheimer's Disease, which evaluated a flexible dose range of 2-15 mg/day over 10 weeks, the incidence of somnolence was about 8% in the drug and 1% in the placebo treated patients. In addition, in an open, uncontrolled rising dose tolerance study in elderly demented patients, the following incidence of somnolence was seen:

5-10 mg	0%
10-15 mg	60%
15-20 mg	80%
20-25 mg	100%
25-30 mg	100%

Weight Gain

In the controlled trials, about 8% of aripiprazole, and 3% of placebo treated patients experienced a weight gain of at least 7% of their body weight (this incidence in the drug group was less than that seen with the active comparators haloperidol and risperidone).

In a 52 week study comparing haloperidol to aripiprazole, 20% of the aripiprazole patients gained at least 7% of their body weight, compared to 13% of the haloperidol patients.

In a 6 month study comparing aripiprazole to olanzapine, 6% of the aripiprazole patients and 25% of the olanzapine patients had a weight gain of at least 7%. The aripiprazole patients had a mean decrease of about 0.9 kg, compared to a 3.6 kg gain in the olanzapine patients.

Seizures

In the controlled trials, one drug treated patient experienced a seizure (0 placebo patients). In the long-term haloperidol study, 3 aripiprazole patients (3/859, or 0.5%) had a seizure (0 haloperidol patients). In the 6 month olanzapine comparator study, 0 aripiprazole and 1 olanzapine treated patient had a seizure. I have no additional data on these patients.

EPS

In the controlled trials, 21% of aripiprazole treated patients had at least one EPS related AE, compared to 19% in the placebo group, and 44% in the haloperidol and 30% in the risperidone groups. A total of 0.2% of patients experienced tardive dyskinesia (TD) in the controlled trials in each of the aripiprazole and placebo groups. The incidence of akathisia was 10% in the drug, and 7% in the placebo treated patients.

In the long-term haloperidol controlled trials, 0.9% of the haloperidol and 0.6% of the aripiprazole patients developed TD. In the haloperidol group, 1.6% of patients developed dyskinesias, compared to 0.1% of the aripiprazole patients.

In the short-term controlled trials, patients on aripiprazole did better than placebo patients on the mean change from baseline on the AIMS total score (a standard EPS rating scale), but they did worse than placebo patients on the Barnes Akathisia Global Clinical Assessment score.

In the long-term haloperidol controlled trials, the aripiprazole patients did statistically significantly better than the haloperidol patients on the mean change from baseline on the AIMS total score.

Neuroleptic Malignant Syndrome (NMS)

One patient in the Phase 2/3 studies experienced NMS 17 days after his last dose of aripiprazole, and after having initiated haloperidol and risperidone.

There was one fairly unconfounded case of NMS in the Japanese cohort (out of 769 patients). In the Japanese cohort, 1/120 haloperidol treated patients experienced NMS.

Japanese Cohort

The application contains data from 769 aripiprazole treated patients in Japan.

In general, the Japanese data were consistent with the other data presented. In this open experience, there were one case each of severe renal injury (BUN 60 mg/dl and creatinine 9 mg/dl), hyponatremia (Na=116 mEq/L), NMS, and paralytic ileus. These events resolved with drug discontinuation and appropriate treatment.

COMMENTS

The sponsor has presented the results of 5 short-term, placebo and active controlled trials. In one trial, haloperidol was shown to be significantly superior to placebo, while aripiprazole in a dose range of 5-30 mg/day was not. In a second

study, fixed doses of aripiprazole of 2 and 10 mg/day were not distinguished from placebo, while aripiprazole 30 mg was distinguished from placebo on one of two primary outcome measures. In this study, haloperidol also only was distinguished from placebo on one of two primary outcomes.

In the other three controlled trials, fixed doses of 10, 15, 20, and 30 mg were shown to be statistically superior to placebo on all primary outcome measures as well as multiple secondary measures. In these studies, the lowest doses studied were invariably numerically superior to the higher doses. In one study, Dr. Chen, the statistician, expressed concern that the large number of dropouts early in the study could have introduced potential biases that could have affected the results either in favor of, or against, aripiprazole.

It is not clear why 2 studies did not distinguish aripiprazole from placebo. In the first study (Study 93202), it is clear that the estimate of the treatment effect for aripiprazole was very near that of haloperidol, which was shown to be statistically superior to placebo (see Dr. Laughren's memo, page 4), and the p-value for the aripiprazole-placebo contrast on the CGI-Severity (one of the two primary outcomes) was 0.066. While this study was "negative", I do not believe that the results are particularly damaging to the drug. In the second study in which aripiprazole was not consistently distinguished from placebo, haloperidol also was not consistently distinguished from placebo (and the aripiprazole 30 mg dose was significantly superior to placebo on one primary outcome). For these reasons, I also believe that this study is not critically damaging.

In the three remaining controlled trials, aripiprazole, at fixed doses between 10-30 mg, was clearly superior to placebo. In the one study of concern to Dr. Chen, the results are overwhelmingly in favor of aripiprazole in the standard ITT analysis, but the early dropouts complicate the interpretation. Given that the potential biases can go in either direction, and the clear result on the standard analysis, I believe it is reasonable to conclude that this trial contributes to a finding of substantial evidence of effectiveness; it certainly does not contradict the other "positive" data, and can be considered consistent with it. For these reasons, then, I conclude that the sponsor has provided substantial evidence of effectiveness for aripiprazole as a treatment for schizophrenia.

Dr. Dubitsky has concluded that 15 mg should be the recommended dose, because there is more evidence that this dose is effective than for the 10 mg dose. While it is true that there are 2 trials that establish the effectiveness of this dose, and only one such trial with 10 mg, I agree with Dr. Laughren that the data clearly establish the effectiveness of 10 mg, and therefore that it should be the recommended dose. I also agree that the sponsor has not established the lowest effective dose, and should be asked to do so. Finally, I also agree with Dr. Laughren that the sponsor should perform adequate trials to examine the long-term effectiveness of the drug.

Aripiprazole appears relatively safe in use. There appear to be no significant adverse events associated with its use, and on many outcomes it seems to cause fewer adverse events than the active comparators used in the controlled trials (I recognize that these comparisons do not definitively establish this fact).

There is, however, a signal for increased mortality in elderly patients with Alzheimer's Disease, possibly associated with aspiration pneumonia. This should be described in labeling, and, as Dr. Laughren notes, further evaluated in the post-marketing context. In addition, elderly patients with dementia seemed to be particularly susceptible to the occurrence of somnolence.

As Dr. Laughren notes, there seemed to be little evidence of EPS or abnormal glucose metabolism, important findings for a drug in this class, although some evidence suggests that aripiprazole can cause akathisia. There did, however, appear to be a signal that aripiprazole use was associated with weight gain, although not all the evidence supports this conclusion. There did appear to be one fairly clear, unconfounded case of NMS, in the Japanese experience.

In his review of the safety data, Dr. Harris presents data that suggest that higher doses of aripiprazole can prolong the QTc interval (page 109). The values presented are the median change from baseline to the maximum QTc value. As Dr. Laughren points out, this is not a standard way to present QT interval data, and a more traditional approach suggests that, at 30 mg, there is a marked decrease in QTc compared to baseline, and that this decrease becomes less with increasing dose, such that, at 90 mg, the change from baseline is +1.3 msec. The meaning of this finding is not at all clear, but I agree with Dr. Laughren that the fact that the QTc is not prolonged, compared to baseline, even at the higher doses, is reassuring. The remaining data do not suggest that aripiprazole causes QTc prolongation.

In particular, although the EKGs in the controlled trials were not timed to dosing, the C_{min} at steady state is about 60% the C_{max}, and the EKGs were likely taken closer to C_{max} than C_{min}. For this reason, I agree with Dr. Laughren that the timing of the EKGs is not an important consideration.

Aripiprazole is metabolized by CYP2D6 and 3A4. Patients deficient in 2D6 activity (poor metabolizers; PMs) have a net increase in circulating active moieties (parent and active metabolite, which ordinarily is present at about 40% of the parent) of about 60% compared to extensive metabolizers (EMs). We do not have information about the net change in levels of circulating active species when PMs (or EMs taking CYP2D6 inhibitors) are given a potent CYP3A4 inhibitor. However, it is reassuring to note that 893 patients have received daily doses of at least 25 mg for at least 6 months. This large exposure at doses close to 2-3 times the recommended dose provides reassurance that the levels achieved at the recommended dose in patients whose 2D6 and 3A4 isozymes are

inhibited/deficient should be well tolerated (although I do believe the sponsor should address the question of what levels are achieved in these maximally inhibited patients).

There are a number of patients on whom additional data should be obtained (patients whose last laboratory value was abnormal, patients with seizures).

PRE-CLINICAL ISSUES

Dr. Freed has identified 2 issues that she believes need further evaluation.

In a 26 week study in albino rats, aripiprazole has been shown to produce retinal degeneration in a few animals at the highest dose. The finding was also seen at the 2 highest doses (40 and 60 mg/kg) in the carcinogenicity study in Sprague-Dawley rats. Although the sponsor has not examined this finding further, it appears to be similar to lesions produced by ropinerole and pramipexole, 2 dopamine agonists approved for the treatment of Parkinson's Disease. According to Dr. Freed, the AUC at the NOEL for this finding is about 6 times that at the recommended dose of 10-15 mg/day in humans (her review actually says that the margin is about 3, but she calculated this on the basis of a recommended dose in humans of 30 mg). She notes that the finding in pramipexole occurred in albino rats at exposures much closer to the recommended dose in humans, although she also notes that the margin of 6 cited above for aripiprazole will be less in PMs. She recommends that the sponsor further evaluate the mechanism of the rat retinal findings, and we will ask them to do this in the letter. In addition, we have added a subsection to the Precautions section of labeling, called Retinal Pathology in Albino Rats, that briefly describes the finding and states that the significance to humans is unknown (this is analogous to statements in the ropinerole and pramipexole labeling).

In addition, Dr. Freed has concluded that aripiprazole may have abuse liability. Specifically, one of 4 monkeys trained to self-administer cocaine continued self-administration when aripiprazole was substituted, and 4/4 monkeys experienced withdrawal symptoms upon abrupt discontinuation of treatment. We will therefore also ask the sponsor to address this issue.

CMC

There are a number of CMC issues that need to be resolved and these will be communicated to the sponsor. In addition, one manufacturing plant has failed inspection; we will give the sponsor the option of removing this site, given that there are other sites in the application that perform these functions.

RECOMMENDATION

For the reasons stated above, I recommend that the sponsor be issued the attached Approvable letter, with appended draft labeling.

Russell Katz, M.D.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Russell Katz
8/29/02 01:16:46 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 15, 2002

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

SUBJECT: Recommendation for Approvable Action for
Product Name (aripiprazole) capsules for the treatment of schizophrenia

TO: File NDA 21-436
[Note: This overview should be filed with the 10-31-01
original submission.]

1.0 BACKGROUND

Aripiprazole is a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5HT2 receptors. This class of compounds is referred to as "dopamine system stabilizers," based on the hope that they will permit sufficient nigrostriatal DA activity to prevent EPS while at the same time reducing excessive DA activity in the mesolimbic pathways. However, it can be thought of more generally as another member of the class of atypical antipsychotics, which now include the following marketed products in the US: clozapine; risperidone; olanzapine; quetiapine; and ziprasidone. This development program and NDA focus on aripiprazole's use in the treatment of schizophrenia. However, it should be noted that programs in mania and psychosis of Alzheimer's disease are also underway. The proposed dose range in schizophrenia is 15 to 30 mg/day.

An EOP2 meeting was held with the sponsor on 2-19-97:

-We generally discussed the requirements for an NDA. Of note, the sponsor wanted to discuss a time of onset claim and comparative claims. We noted the lack of an accepted approach for a time of onset claim and the higher standard set for comparative claims.

A second EOP2 meeting was held with the sponsor on 2-2-00:

schizophrenia.

A preNDA meeting was held with the sponsor on 7-2-01:

-The meeting focused on both format issues and content of the planned NDA. The plan was to submit data to support claims in both schizophrenia _____ however, we learned on 9-24-01 that the second _____ and, therefore, the NDA would include only the schizophrenia efficacy data.

This NDA required reviews by all disciplines. The CMC review was conducted by Sherita McLamore, Ph.D. The pharmacology/toxicology review was conducted by Lois Freed, Ph.D. The biopharmaceutics review was conducted by Hong Zhao, Ph.D. The primary review of the efficacy data was done by Greg Dubitsky, M.D., from the clinical group, and Yeh-Fong Chen, Ph.D., from the Division of Biometrics. The primary review of safety data was done by Robert Harris, M.D. from the clinical group.

The studies supporting this supplement were conducted under _____ submitted 6-10-93. The original NDA was submitted 10-31-02, and a safety update was submitted 2-27-02.

We decided not to _____

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

The sponsor had originally proposed the name Abilitat for this product, however, this name was rejected by DMETS because of possible confusion with other similar names. The sponsor subsequently proposed the name _____ and this name was also rejected by DMETS because of possible confusion with other similar names. The sponsor has now proposed 2 new names, i.e., Abilify and _____. DMETS has concluded that the name Abilify is acceptable, and _____ is not. Thus, we have included Abilify as the product name in our proposed labeling.

3.0 PHARMACOLOGY

The pharmacology/toxicology review is not finalized at the time of completing this memo, however, I am not aware of any pharmacology/toxicology concerns that would preclude an approvable action for this NDA.

4.0 BIOPHARMACEUTICS

The pharmacokinetics of aripiprazole have been adequately characterized and I am not aware of any biopharmaceutics concerns that would preclude an approvable action on this NDA.

Aripiprazole is cleared by both 2D6 and 3A4, and has an elimination half-life of about 75 hours. Steady state is reached in 14 days. Absorption is not affected by food, and the PK does not appear

to be affected by age, gender, race, smoking status, hepatic or renal impairment. The primary active metabolite appears to have similar pharmacological activity and potency as the parent, and is present at about 40% of the parent levels; thus, it clearly contributes to the overall efficacy. Potent inhibitors of 3A4 (ketoconazole) and 2D6 (quinidine) had only modest effects on the clearance of aripiprazole (reductions of 38% and 52%, respectively), but enough of an effect to recommend dosage adjustments. Carbamazepine reduces plasma aripiprazole levels, and thus also requires dose adjustment.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 5 short-term, placebo-controlled trials in patients with schizophrenia or schizoaffective disorder. Results from 2 identically designed longer-term trials (31-98-217 & 31-98-304-01) were included in the NDA. These involved randomization of acute patients to either aripiprazole or haloperidol (2:1 ratio) for up to 52 weeks. The primary outcome was time to relapse in "responders" during acute treatment, and an analysis of a pool of the two studies (apparently the planned analysis) failed to show a difference between drugs on this outcome. Thus, these data were not reviewed in depth, and will not be further discussed.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 93202

This was a randomized, double-blind, parallel group, 4-week, flexible-dose study (10 US sites) comparing aripiprazole (in a range of 5 to 30 mg/day, given on a qd basis, after breakfast), haloperidol (in a range of 5 to 20 mg/day, given on a qd basis, after breakfast), and placebo. The study was conducted in adult (18-65) inpatients meeting DSM-III-R criteria for schizophrenia. Patients must have had an acute relapse. Dosing followed a fixed titration, e.g., aripiprazole patients were started on 5 mg/day for days 1-2, then 10 mg for days 3-4, then 15 mg for days 5-6, then 20 mg for days 7-12, and finally 30 mg for days 13-28. Haloperidol patients were similarly moved from 5, 10, 15, and to 20 mg/day by day 7, and until day 28. The modified ITT samples for aripiprazole, haloperidol, and placebo were 33, 33, and 35, respectively. Completion for aripiprazole, haloperidol, and placebo were 62%, 59%, and 43%, respectively. The patients were mostly male, about 50% white, and the mean age was about 40 years.

The efficacy assessments included the BPRS and the CGI, administered weekly, and the primary outcomes were (1) change from baseline to endpoint in the BPRS total score, and (2) the proportion of patients having improved by at least 1 point on the CGI-severity scale. As is usually the case, the modified ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup BPRS and CGI assessment. The LOCF analysis

was considered primary, but OC was also done. Wilcoxon's and Fisher's exact tests were the models used for BPRS and CGI, respectively. The results were as follows:

Efficacy Results on BPRS for Study 93202 (LOCF)

	Mean Baseline BPRS	Mean Obaseline BPRS	[P-value(vs pbo)]
Aripiprazole	53.0	-7.2	0.173
Haloperidol	50.3	-8.1	0.010
Placebo	50.0	-2.1	

Efficacy Results on CGI-Sev for Study 93202 (LOCF)

	Mean Baseline CGI-S	% ≥ 1 pt improve	[P-value(vs pbo)]
Aripiprazole	4.8	42%	0.066
Haloperidol	4.7	55%	0.005
Placebo	4.5	20%	

Comment: Both Drs. Dubitsky and Chen considered this a negative study for aripiprazole, and I agree. The results were particularly damaging for aripiprazole since haloperidol, the positive control, was superior to placebo on both primary outcomes.

5.1.2.2 Study 94202

This was a randomized, double-blind, parallel group, 4-week, fixed-dose study (22 US sites) comparing aripiprazole (at fixed doses of 2, 10, or 30 mg/day, given on a qd basis, after breakfast), haloperidol (at a fixed dose of 10 mg/day, given on a qd basis, after breakfast), and placebo. The study was conducted in adult (18-65) inpatients meeting DSM-IV-R criteria for schizophrenia. Patients must have had an acute relapse. Patients were titrated to their fixed doses rapidly, i.e., over 1-2 days. The modified ITT samples for aripiprazole, haloperidol, and placebo were 51, 51, 54, 54, and 57, respectively. Completion for aripiprazole, haloperidol, and placebo were 66%, 65%, 69%, 56%, and 50%, respectively. The patients were mostly male, about 50% white, and the mean age was about 40 years.

The efficacy assessments included the BPRS and the CGI, administered weekly, and the primary outcomes were (1) change from baseline to endpoint in the BPRS core score (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content), and (2) CGI-Improvement at the last visit. The modified ITT data set included all randomized patients who had baseline and at least one followup BPRS and CGI assessment (regardless of whether or not they received assigned treatment). The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with Dunnett's to adjust for multiple doses. The results were as follows:

Efficacy Results on BPRS Core Score (C) for Study 94202 (LOCF)

i.e., 30 vs placebo was looked at first, and only if significant was 15 vs placebo looked at. Haloperidol was included only for assay sensitivity. The results were as follows:

Efficacy Results on PANSS Total Score (T) for Study 97201 (LOCF)

	Mean BL PANSS-T	Mean Obaseline PANSS-T	[P-value(vs pbo)]
Aripiprazole 15	97.9	-15.5	<0.001
Aripiprazole 30	98.5	-11.4	0.009
Haloperidol 10	99.6	-13.8	0.001
Placebo	100.2	-2.9	

Efficacy Results on PANSS Positive Score (P) for Study 97201 (LOCF)

	Mean BL PANSS-P	Mean Obaseline PANSS-P	[P-value(vs pbo)]
Aripiprazole 15	24.6	-4.2	<0.001
Aripiprazole 30	24.4	-3.8	0.001
Haloperidol 10	25.1	-4.4	<0.001
Placebo	24.9	-0.6	

Efficacy Results on CGI-Severity Score for Study 97201 (LOCF)

	Mean BL CGI-S	Mean Obaseline CGI-S	[P-value(vs pbo)]
Aripiprazole 15	4.9	-0.6	<0.001
Aripiprazole 30	4.8	-0.4	0.019
Haloperidol 10	4.9	-0.5	0.002
Placebo	4.9	-0.1	

A separate analysis of the subgroup of patients with schizophrenia also favored all 3 drug groups over placebo for all 3 outcomes.

Comment: Both Drs. Dubitsky and Chen considered this a positive study for aripiprazole, and I agree. There was no advantage of the 30 mg dose over the 15 mg dose; in fact, numerically, the 15 mg dose was superior.

5.1.2.4 Study 97202

This was a randomized, double-blind, parallel group, 4-week, fixed-dose study (40 US sites) comparing aripiprazole (at fixed doses of 20 or 30 mg/day, given on a qd basis, after breakfast), risperidone (at a fixed dose of 6 mg/day, given on a bid basis), and placebo. The study was conducted in adult (18-65) inpatients meeting DSM-IV-R criteria for schizophrenia or schizoaffective disorder.

About 2/3 of patients met criteria for schizophrenia. Patients must have had an acute relapse. Patients assigned to aripiprazole were given their full assigned dose from the first day of treatment, i.e., no titration. Patients assigned to risperidone were titrated to 3 mg bid over 3 days. The modified ITT samples for aripiprazole, risperidone, and placebo were 98, 96, 95, and 103, respectively. Completion for aripiprazole, risperidone, and placebo were 62%, 71%, 64%, and 50%, respectively. The patients were about 2/3 male, about 60% white, and the mean age was about 39 years.

The efficacy assessments included the PANSS and the CGI, administered weekly, and the primary outcomes were (1) change from baseline to endpoint in the PANSS total score, (2) change from baseline to endpoint in the PANSS positive subscale, and (3) change from baseline to endpoint in the CGI-Severity score. The modified ITT data set included all randomized patients who had baseline and at least one followup PANSS and CGI assessment (regardless of whether or not they received assigned treatment). The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with a step-down procedure to deal with the 2 aripiprazole doses, i.e., 30 vs placebo was looked at first, and only if significant was 15 vs placebo looked at. Risperidone was included only for assay sensitivity. The results were as follows:

Efficacy Results on PANSS Total Score (T) for Study 97202 (LOCF)

	Mean BL PANSS-T	Mean Obaseline PANSS-T	[P-value(vs pbo)]
Aripiprazole 20	94.0	-14.5	0.001
Aripiprazole 30	92.3	-13.9	0.003
Risperidone 6 93.6		-15.7	<0.001
Placebo	95.0	-5.0	

Efficacy Results on PANSS Positive Score (P) for Study 97202 (LOCF)

	Mean BL PANSS-P	Mean Obaseline PANSS-P	[P-value(vs pbo)]
Aripiprazole 20	24.8	-4.9	0.001
Aripiprazole 30	24.0	-3.9	0.018
Risperidone 6 23.9		-5.2	<0.001
Placebo	24.5	-1.8	

Efficacy Results on CGI-Severity Score for Study 97202 (LOCF)

	Mean BL CGI-S	Mean Obaseline CGI-S	[P-value(vs pbo)]
Aripiprazole 20	4.8	-0.5	0.030
Aripiprazole 30	4.7	-0.6	0.006
Risperidone 6 4.8		-0.7	<0.001
Placebo	4.8	-0.2	

A separate analysis of the subgroup of patients with schizophrenia also favored all 3 drug groups over placebo for all 3 outcomes. Dr. Chen expressed some concern about bias, based on her analysis of dropout cohorts (this was done due to discrepancies between LOCF & OC results), but, nevertheless, she considered this a positive study.

Comment: Both Drs. Dubitsky and Chen considered this a positive study for aripiprazole, and I agree. There was no advantage of the 30 mg dose over the 20 mg dose; in fact, numerically, the 20 mg dose was superior on PANSS measures.

5.1.2.5 Study 138001

This was a randomized, double-blind, parallel group, 6-week, fixed-dose study (53 US sites and 4 Canadian sites) comparing aripiprazole (at fixed doses of 10, 15, or 20 mg/day, given on a qd basis), and placebo. The study was conducted in adult (18-65) inpatients meeting DSM-IV criteria for schizophrenia. Patients must have had an acute relapse. Patients assigned to aripiprazole were given their full assigned dose from the first day of treatment, i.e., no titration. The modified ITT samples for aripiprazole and placebo were 103, 103, 97, and 107, respectively. Completion for aripiprazole and placebo were 41%, 33%, 40%, and 28%, respectively. The patients were about 3/4 male, about 50% white, and the mean age was about 40 years.

The primary efficacy assessment was the PANSS, administered weekly, and the primary outcome was change from baseline to endpoint in the PANSS total score. A protocol amendment defined 2 key secondary outcomes as follows: (1) change from baseline to endpoint in the BPRS Core Score, derived from the PANSS, and (2) change from baseline to endpoint in the PANSS Negative Subscale score. The modified ITT data set included all randomized patients who took at least 1 dose of their assigned treatment and had baseline and at least one followup PANSS. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with a step-down procedure to deal with the 2 key secondary outcomes, i.e., first BPRS Core Score and second PANSS Negative Subscale. Hochberg's procedure was used for adjusting for the 3 dose groups. The results were as follows:

Efficacy Results on PANSS Total Score (T) for Study 138001 (LOCF)

	Mean BL PANSS-T	Mean Obaseline PANSS-T	[P-value(vs pbo)]
Aripiprazole 10	92.8	-15.0	<0.001
Aripiprazole 15	93.3	-11.73	0.004
Aripiprazole 20	92.3	-14.4	<0.001
Placebo	92.4	-2.3	

Efficacy Results on PANSS-Derived BPRS Core Score (BPRS-C) for Study 138001 (LOCF)

	Mean BL BPRS-C	Mean Obaseline BPRS-C	[P-value(vs pbo)]
Aripiprazole 10	16.9	-3.9	<0.001
Aripiprazole 15	16.8	-2.9	0.014
Aripiprazole 20	16.7	-3.6	<0.001
Placebo	16.8	-1.4	

Efficacy Results on PANSS Negative Score (N) for Study 138001 (LOCF)

	Mean BL PANSS-N	Mean Obaseline PANSS-N	[P-value(vs pbo)]
Aripiprazole 10	23.4	-3.5	<0.001
Aripiprazole 15	23.4	-2.7	0.002
Aripiprazole 20	23.3	-3.3	<0.001
Placebo	22.7	+0.1	

Comment: Both Drs. Dubitsky and Chen considered this a positive study for aripiprazole, and I agree. This superiority was observed for the primary outcome and both key secondary outcomes. There was

no advantage of the 15 or 20 mg dose groups over the 10 mg dose; in fact, numerically, the 10 mg dose was superior on all 3 PANSS measures.

5.1.3 Comment on Other Important Clinical Issues Regarding Aripiprazole for Schizophrenia

Evidence Bearing on the Question of Dose/Response for Efficacy

All 3 positive studies involved fixed aripiprazole doses, and among the 3 studies, the doses included were: 10, 15, 20, and 30 mg/day. There was no indication of dose response across this range of doses. Dr. Dubitsky has recommended a target dose of 15 mg/day, largely because there was more support for this dose than for the 10 mg dose. I would prefer targeting 10 mg, with the possibility of titrating up to 15 mg in treatment failures. Labeling will need to be clear in noting the lack of demonstrated benefit for doses larger than 10 to 15 mg/day.

Clinical Predictors of Response

Exploratory analyses were done by the sponsor to detect subgroup interactions on the basis of gender, age, and race. There was no clear indication of differences in response based on these variables. Dr. Chen performed an analysis based on subgrouping patients ≤ 50 and > 50 , and found results suggestive of a smaller treatment effect in the older group, due almost entirely to a much larger placebo response in this subgroup. I don't think this isolated finding is readily interpretable, and I would not recommend mentioning this finding in labeling.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the PANSS total score observed in the positive studies was similar to that seen in other positive schizophrenia trials, and I consider this a sufficient effect to support an efficacy claim for this product in schizophrenia.

Duration of Treatment

The data presented in this supplement pertinent to the question of the long-term efficacy of aripiprazole in schizophrenia showed no difference between aripiprazole and haloperidol, and were thus uninterpretable. The sponsor has recently completed a randomized withdrawal trial (138047) which may be capable of addressing the question of longer-term efficacy when analyzed.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy for aripiprazole in schizophrenia. While there was 1 negative study for aripiprazole, and in fact haloperidol demonstrated the assay sensitivity of that trial, I still feel that the 3 positive trials overcome this negative outcome. The sponsor has not adequately explored the lower end of the dose response

curve for aripiprazole, and they should be encouraged to commit to doing this in phase 4. The issue of longer-term efficacy will need to be addressed in the future.

5.2 Safety Data

5.2.1 Safety Database

Dr. Harris' safety review of this NDA was based on an integrated database covering 71 trials in the non-Japanese development program for aripiprazole (35 clinical pharmacology studies and 36 phase 2-3 safety and efficacy trials). This included data from the original submission and also a 4-month safety update (with a cutoff date of 11-30-01). This program included 924 aripiprazole-exposed subjects in the clinical pharmacology trials and 4710 aripiprazole-exposed subjects in the phase 2-3 trials (representing 2656 patient-years of exposure in the phase 2-3 program). The patient distribution for the 4710 sample was as follows: schizophrenia-3561; bipolar-645; dementia-504. The ICH criteria for duration of exposure were easily met, with n=1513 exposed for ≥ 6 mo and n=902 exposed for ≥ 12 mo. The phase 2-3 programs included studies of schizophrenia, mania, and psychosis of Alzheimer's disease. Patients in the schizophrenia program were about 75% male, about 55% white and 31% black, and the mean age was about 39. The Alzheimer's patients were, of course, considerably older (mean age = 82), 75% female, and 89% white.

In addition, as of 10-31-01, 9 phase 1 studies and 10 phase 2-3 studies with aripiprazole had been conducted in Japan, including a total of 901 patients exposed to aripiprazole. Serious adverse events were available from these trials.

There were no postmarketing data since aripiprazole is not approved anywhere in the world.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

One approach that we have used to identify the adverse event profile for a drug is to identify in the adverse events table for the drug those events that can be considered common and drug-related; we have generally used 5% as the cutoff for "common" and a risk for drug that is twice the placebo risk as a criterion for being considered "drug-related." For most drugs, this approach yields a set of events that might reasonably be considered to represent the common adverse events profile for that drug. Oddly, this approach, when applied to the pool of short-term placebo-controlled trials for aripiprazole, did not identify any events. However, there were several events that, while not strictly meeting these criteria, did appear to occur at a higher rate for aripiprazole vs placebo: headache; nausea; vomiting; insomnia; lightheadedness; and blurred vision.

5.2.2.2 Vital Signs Changes (Blood Pressure and Heart Rate)

Aripiprazole is associated with a small mean increase in heart rate of about 3 bpm (after subtracting placebo effect, i.e., +4 for aripiprazole and +3 for placebo). There was also a measurable difference from placebo in orthostatic changes and a slight excess of orthostatic related adverse events, e.g., syncope, lightheadedness, and dizziness (14% for aripiprazole vs 9% for placebo). This may be a result of the alpha-1 antagonist effect of aripiprazole. Otherwise, aripiprazole did not appear to have vital signs effects.

5.2.2.3 Mortality and Pneumonia in Elderly Patients

The only signal for excess mortality that emerged for aripiprazole was in the subgroup of elderly patients treated for psychosis of Alzheimer's disease. In a 10 week placebo-controlled trial in this population there were 4/105 (4%) deaths for aripiprazole vs 0/102 for placebo. In the pool of all 504 aripiprazole-exposed elderly patients there were 39 deaths (174 per 1000 PY). 10 of the 39 deaths were attributed to pneumonia, including 5 for aspiration pneumonia. Of course, the background mortality rate is high in this population; nevertheless, the difference in mortality between aripiprazole and placebo in the controlled trial raises a concern.

5.2.2.4 Somnolence

Another approach to identifying possibly drug-related events is to look for evidence of dose-relatedness for adverse events. When this approach was used, the only event that turned up as possibly dose-related was somnolence. This event was even more pronounced in elderly patients, where the risk ratio (drug:placebo) was almost 8.

5.2.2.5 QTc Findings

Aripiprazole was evaluated for repolarization problems in 2 in vitro models, i.e., the isolated canine heart and the isolated right atrium from male Hartley guinea pigs, and in 2 in vivo models, i.e., anesthetized mongrel and Beagle dogs. Apparently data were not provided for the 2 in vitro models. For the mongrel dog, the sponsor provided only quantitative data, i.e., a slight prolongation of QT interval for both aripiprazole and the control drug, chlorpromazine. They commented that chlorpromazine had 3 times the potency as aripiprazole in this assay. In the Beagle dog, apparently aripiprazole actually decreased the QT interval (no change in QTc), compared to the control, haloperidol, which increased both QT and QTc. They also reported no early after depolarizations with aripiprazole, but did see EADs with haloperidol. To my knowledge, they have not looked at IKR or reported on other in vitro studies. Thus, overall, there is no signal from the admittedly limited preclinical assessment of QT.

The human ECG data for this application come primarily from a pool of the 5 phase 2-3 clinical trials, and were collected at baseline, and after 2 and 4 weeks in these trials. Timing with regard to dosing for the 2 on treatment values for each patient appears to have been random, however, given the very long half-lives for aripiprazole and its active metabolite, it was likely not critical when these were done, since both would have been at steady state, and fluctuation would likely have been minimal. An analysis of these data for proportions of patients having specific ECG abnormalities revealed no signals for aripiprazole vs placebo. These data were also analyzed regarding median and mean

change from baseline in various ECG parameters, including QTc. The sponsor used several different correction methods, including (1) Bazett's; (2) an exponential method, based on deriving an exponent from the baseline data (QT_{cE}), and (3) $QT_{cN} = QT/RR^{0.37}$, where the N refers to the fact that this was another approach suggested by DNDP. Either QT_{cE} or QT_{cN} is appropriate, given the slight increase in HR with this drug. The results for mean change from baseline in QT_{cE} by dose group are as follows:

<u>Placebo</u>	<u>Aripiprazole</u>						
	<u>Hpl</u>	<u>Rsp</u>	<u>2</u>	<u>10</u>	<u>15</u>	<u>20</u>	<u>30</u>
-3.5	-1.0	+2.2	-4.9	-5.3	-3.3	-3.9	-4.4

These data suggest a slight tendency for aripiprazole to decrease the QTc interval, compared to placebo. The data were also assessed for outliers, i.e., proportions going over 450 msec, over 500 msec, and those increasing from baseline by 30 or 60 msec. Again, there was no signal for increased outliers for aripiprazole. These data give no indication of a QTc prolonging effect for aripiprazole. A PK/PD analysis of these clinical trials data by Gene Williams of OCPB also found no relationship between plasma concentration and QTc.

However, an early study exploring doses up to 90 mg/day did reveal some findings suggesting that perhaps the QTc effect of aripiprazole might change over this broader dose range. This was a randomized safety and tolerability study involving multiple doses (15 days) of 30, 45, 60, 75, and 90 mg/day. Each cohort had 10 patients; 3 received the 30 mg control dose, and the other 7 got the maximum dose received in the previous cohort, i.e., the study was done with gradually increasing doses, as tolerated. ECGs were done at baseline, and at predose and at 4-6 hours postdose on days 1, 8, and 15. ECGs were centrally read for this study, as for all the studies. The results for median change from baseline in QT_{cN} by dose group are as follows (unclear if these are predose or 4-6 hours postdose, but given the very long half-life, may not make much difference):

<u>Aripiprazole</u>				
<u>30</u>	<u>45</u>	<u>60</u>	<u>75</u>	<u>90</u>
-12.5	-15.1	-6.0	-6.3	+1.3

Dr. Harris presented in his review, alternatively, the median change from baseline to maximum value, revealing what appeared to be a signal for substantial QTc prolongation at the 75 and 90 mg doses. However, I disagree. I think the mean or median change from baseline data are more meaningful, and don't suggest a potential for prolongation, even at the highest dose. Rather, they suggest that the QTc shortening effect seen with lower doses may be lost as the dose increases. Gene Williams also did an analysis of these data (dose vs QTc), and reached a similar conclusion, i.e., that the QTc shortening effect is lost as the dose increases from 30 to 90mg/day. Of course, if one looks at outliers on the high side, i.e., maximal changes from baseline, one will see larger excursions at the higher doses. It is very difficult to know what this means clinically. One might worry that, as the dose is pushed even higher, e.g., in overdose, there might be an actual prolonging effect on the QTc interval, but this is pure speculation. Nevertheless, I think it would be useful to recommend ECG monitoring in overdoses.

5.2.3 Conclusions Regarding Safety of Aripiprazole in Schizophrenia and the Other Indications for Which it Might be Used

There were no drug-related adverse events that would preclude the approvability of aripiprazole for schizophrenia. Of note, there is no indication thus far of _____

Those events that can be confidently considered drug-related can be adequately addressed in labeling. I agree with Drs. Harris and Dubitsky that the possible signal for excess mortality in elderly patients with dementia deserves some mention in labeling and certainly deserves postmarketing followup.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

The sponsor indicated that they discovered 161 literature references in their literature search, and they provided a warrant that a careful review of the full text articles revealed no findings that would affect conclusions about the safety of aripiprazole. Dr. Harris reviewed that reference list and reached a similar conclusion, i.e., that none of the references appeared to have relevance to the safety of aripiprazole.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, aripiprazole is not approved for any indication in any country at this time. We will ask for an update on the regulatory status of aripiprazole for the treatment of schizophrenia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS

We decided _____

9.0 DSI INSPECTIONS

Inspections were conducted at 4 sites for the 3 positive schizophrenia trials, and all data from these sites were considered acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft labeling.

10.2 Foreign Labeling

Aripiprazole is not approved for the treatment of schizophrenia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of schizophrenia. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:

Orig NDA 21-436

HFD-120

HFD-120/TLaughren/RKatz/GDubitsky/RHarris/SHardeman

HFD-101/RTemple

DOC: MMARIPIP.AE1

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/s/

Thomas Laughren
8/15/02 10:53:45 AM
MEDICAL OFFICER

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MEMORANDUM

To: File, NDA 21-436

Through: Robert Temple, M.D., ODE I Office Director
Barry Rosloff, Ph.D., Pharmacology Supervisor, HFD-120
Lois Freed, Ph.D., Pharmacology Reviewer, HFD-120
Steven Hardeman, R.Ph., Regulatory Project Manager

From: Jeri El-Hage, Ph.D., ODE I Associate Director for Pharmacology/Toxicology

Subject: NDA 21-436, Abilify (aripiprazole)
Tertiary Pharmacology/Toxicology Review

Date: August 29, 2002

A complete toxicologic evaluation of aripiprazole has been completed and the toxicity profile supports the recommendation of the pharmacology reviewer for NDA approval. This tertiary review is based on a Draft Review provided by Dr. Lois Freed. The preclinical evaluation includes a complete genotoxicity battery, oral toxicity studies in rats (4, 13, 26, and 52 weeks duration) and monkeys (4, 13, 39 and 52 weeks duration), a complete reproductive toxicity battery, and 2-year carcinogenicity bioassays in mice and rats. Dietary carcinogenicity studies were conducted in CD-1 mice and Fischer rats. Due to inadequacy of the dose levels in the initial studies (maximum tolerated dose not evaluated), the carcinogenicity bioassays were repeated utilizing dietary dosing in CD-1 mice and oral dosing in Sprague Dawley rats.

Aripiprazole tested negative for genotoxic potential in the *in vitro* Ames assay, bacterial DNA repair assay, mouse lymphoma assay, and unscheduled DNA synthesis assay. Aripiprazole tested positive for clastogenicity in the *in vivo* mouse micronucleus assay. There was some disagreement between myself and the reviewer on the interpretation of the *in vitro* chromosome aberration assays in Chinese hamster lung cells. The reviewer interpreted the results of several studies as demonstrating clastogenic potential. I agree that statistically significant increases in aberrations were observed in several assays. However, when cell survival was assessed in conjunction with the definitive assays, statistically significant increases in aberrations were observed primarily with the highest dose tested when doses were associated with excessive cytotoxicity. Adequate assays should assess doses producing up to 50% cytotoxicity (i.e., 50% decreases in relative survival). While analysis of data at doses producing 60-70% cytotoxicity may be appropriate, I have difficulty interpreting chromosome aberrations at severe cytotoxicity (>80%) as being attributable to direct genotoxic effects. Dr Freed stated that her interpretation of the data was based on previous discussions of similar study results with Dr. Rosalie Elespuru of CFSAN, a recognized expert in genotoxicity and member of the CDER genotoxicity committee. In addition, Dr. Freed contacted Dr. Elespuru today to specifically discuss the results of the chromosome aberrations assays with aripiprazole. Dr. Elespuru confirmed previous discussions and Dr. Freed's interpretation of the data. Therefore, the genotoxicity labeling (p. 227) is acceptable as written.

The remainder of the preclinical sections of the labeling are acceptable as written. I concur with the reviewer that the retinal degeneration observed in chronic rat studies (6-month and 2-year) was drug-related and warrants the addition of an animal toxicology section to the labeling. This is consistent with the discussion of similar findings in the Mirapex (pramipexole) label.

Regarding the recommendations for Phase IV evaluations in the action letter, the request for further assessment of abuse liability is reasonable.

I question the recommendation for further preclinical characterization of the retinal degeneration in the rat based on feasibility. There were no retinal findings in subchronic (4 or 13 week) rat studies. The finding was infrequent (3/40 rats) at six months and clearly observed with increased incidence and severity in the 2-year rat study. Other toxicities, including mortality, signs, and weight loss at 60 mg/kg, prevent designing a study with higher doses to induce the retinal toxicity within a reasonable study duration. The toxicity was only observed with doses producing reasonable exposure multiples relative to therapeutic exposures (13 – 19 times MRHD based on body surface area) administered chronically. Therefore, a discussion of the findings in the labeling appears adequate. Mechanistic studies were performed for pramipexole demonstrating the mechanism involved in induction of the toxicity is relevant to humans.

Dr Freed also stated that she was following up to determine if clinical monitoring for retinal degeneration had been recommended for related products.

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/s/

Jeri El Hage
9/5/02 09:43:22 AM
PHARMACOLOGIST

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA 21-436

Abilify (aripiprazole) 2, 5, 10, 15, 20, and 30 mg Tablets

Stamp Date: October 31, 2001

Final Action Due Date: November 19, 2002

Approval Date:

HFD-120

Applicant: Otsuka Pharmaceutical Co., Ltd.

Therapeutic Class: Antipsychotic

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: Treatment of Schizophrenia

Is there a full waiver for this indication? No -- Deferred

Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 13 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral -- Adult studies ready for approval.

Date studies are due (mm/dd/yy): January 1, 2007

This page was completed by:

Steven D. Hardeman, R.Ph.

{See appended electronic signature page}

Senior Regulatory Project Manager

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: May 28, 2002

TO: Steven D. Hardeman, R. Ph., Senior Regulatory Project Manager
Gregory Dubitsky, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-436

APPLICANT: Bristol-Myers Squibb/Otsuka

DRUG: Abilitat (aripiprazole)

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

CHEMICAL CLASSIFICATION: 1S

INDICATION: Schizophrenia

CONSULTATION REQUEST DATE: December 18, 2001

ACTION GOAL DATE: June 31, 2002

I. BACKGROUND:

Aripiprazole, a quinolone derivative, is a novel antipsychotic drug and being developed for treatment of schizophrenia. Although the mechanism of action of aripiprazole in schizophrenia is unknown, it has been proposed that aripiprazole's efficacy is mediated through a combination of partial agonism at dopamine D₂ and serotonin 5-HT_{1A} receptors and antagonism of 5-HT₂ receptors.

In this NDA application, the sponsor has requested the use of aripiprazole in treatment of schizophrenia. The application was based on clinical efficacy and safety data in three double-blind, placebo-controlled trials (protocols CN138-001; 31-97-201; and 31-97-202). Inspection assignment was issued on January 8, 2002 for 4 domestic sites, Drs. Tran-Johnson, Zimbrotff, Fabre and Seibel.

II. RESULTS (by site):

NAME	CITY	STATE	PROTO- COLS	ASSIGNED DATE	RECEIVED DATE	CLASSIFI- CATION
Tran-Johnson, Pharm.D.	San Diego	CA	CN138-001; and 31-97- 201	01-08-2002	04-04-2002	VAI*
Zimbrotff, MD	Upland	CA	31-97-201	01-08-2002	05-09-2002	NAI
Fabre, MD, Ph.D	Houston	TX	31-97-202	01-08-2002	05-20-2002	VAI*
Seibel, MD	Washington	DC	31-97-202	01-08-2002	03-06-2002	VAI

* Final classification pending; the letters to the investigators are currently with Office of General Counsel (GC) for review.

Dr. Tran-Johnson, Pharm.D.

At this clinical site, two studies were inspected: protocol CN-138-001 using three fixed doses (10mg, 15mg or 20mg) of aripiprazole for treatment of acute schizophrenia, and protocol 31-97-201 using two fixed doses (15mg or 30mg) of aripiprazole for treatment of psychosis.

For protocol CN-138-001, 34 subjects were screened; 28 subjects were randomized into the double blind phase of the study to receive either aripiprazole or placebo. Of the 28 subjects, 10 subjects discontinued and 18 subjects completed the protocol. The reason for discontinuation included lost to follow up (1), adverse event (akathisia in one subject, dystonia in one subject) and personal reasons/conflict.

For protocol 31-97-201, 32 subjects were screened; 28 subjects were randomized into the double blind phase of the study to receive either aripiprazole, haloperidol 10mg or placebo. Of the 28 subjects, 15 subjects discontinued and 13 subjects completed the protocol. The reason for discontinuation included lack of efficacy (3), adverse event (akathisia in two subjects) and personal reasons.

Inspectional findings:

Protocol CN-138-001: 1) prohibited medication, cogentin, was used by subject 00301/R-L 12 hours prior to administration of rating scales for efficacy or safety; and 2) 5 of 28 subjects did not sign an amended informed consent form, approved by the IRB, in a timely manner.

Protocol 31-97-201: No major deviation from regulation noted.

Signed and dated informed consents were present for all participants except for finding #2 under

protocol CN-138-001. Overall, data seem acceptable.

Dr. Zimbroff, MD

At this clinical site, Dr. Zimbroff conducted protocol 31-97-201 using two fixed doses (15mg or 30mg) of aripiprazole for treatment of schizophrenia. Thirty-eight subjects were screened; 28 subjects were randomized into the double blind phase of the study to receive aripiprazole, haloperidol 10mg or placebo and 27 subjects completed the protocol. A total of 11 subjects discontinued among which one subject withdrew consent (subject # 97201-43-28) after randomization. The reasons for discontinuation were listed as failed screen, withdrew consent and unable to comply.

Inspectional findings showed no significant deviation from regulation. One discrepancy was noted in that subject #97201-43-24 was listed with adverse experience among the discontinued subjects while source documents indicated that the subject was enrolled on 11/13/97 and completed the study on 12/16/97.

Signed and dated informed consents were present for participants. Data appear acceptable.

Dr. Fabre, MD, PhD

At this clinical site, the conduct of protocol 31-97-202, using two fixed doses (20 or 30mg) of aripiprazole, risperidol 6 mg as active control or placebo for treatment of psychosis, was inspected. Thirty subjects were screened; 26 subjects were randomized into the double blind phase of the study. 7 subjects discontinued and 19 subjects completed the protocol. The reason for discontinuation included lack of effect (1 subject), adverse event (1 subject) and personal reasons/subject withdrew consent (5 subjects).

An audit of 10 records was conducted. Inspectional findings included: 1) there was inconsistent history of psychiatric medication (eg. no prior treatment vs thiorazine for subject _____ no medications taken vs medication discontinued for subject _____), and prior hospitalization (the presence or absence of hospitalization for subjects _____); as per staff notes; and illegible history/diagnosis by the P.I. for these 3 subjects; and 2) lack of documentation of prior neuroleptic drug use for 2 subjects _____) as required by the protocol to determine enrollment eligibility.

Signed and dated informed consents were present for all participants. Overall, data appear acceptable.

Dr. Seibel, MD

At this site, thirty-three subjects were screened; thirty subjects enrolled. Twenty-eight subjects were randomized to receive placebo, aripiprazole (20 or 30 mg daily) or risperidol in the double-blind phase of the protocol (31-97-202). Of the 28 subjects, 22 subjects completed the study and 6 subjects were discontinued. Reasons for discontinuations included adverse event for one

subject _____, lack of efficacy in 2 subjects (_____), withdrawal of consent by 2 subjects (_____) and exacerbation of schizophrenia (_____).

An audit of 6 subjects' records was conducted. Observations included: 1) protocol violations in that two subjects _____, who did not meet all the inclusion/exclusion criteria were enrolled in the study; 2) failure to perform laboratory testing after returning from a pass for four subjects; 3) failure to perform pregnancy test for three female subjects; 4) delay in reporting certain adverse events to the IRB; and 5) missing certain vital sign measures for five subjects within the first 5 days of dosing.

All subjects signed the consent forms prior to dosing with the study drug.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Although some deficiencies were noted in the areas of protocol violations, IRB reporting and minor deficiencies in record keeping, the data from these sites appear acceptable for use in support of this NDA.

There were no limitations to these inspections.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAIr = Deviation(s) from regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:

NDA 21-436

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/c/t/s

HFD-47/Khin/Friend

HFD-45/RF

rd: NK 05/28/02

reviewed: AEH 5/28/02

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Michele Balser

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Original CIS signed by Drs. Khin and ElHage on 5/28/02.

Ni Aye Khin

5/28/02 04:17:01 PM

MEDICAL OFFICER

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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 7, 2002

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

SUBJECT: Recommendation for Approval Action for
Product Name (aripiprazole) capsules for the treatment of schizophrenia

TO: File NDA 21-436
[Note: This overview should be filed with the 9-18-02 response to our 8-29-02-
approvable letter.]

We issued an approvable letter for this NDA on 8-29-02, including requests for the following: (1) comments on several clinical issues, (2) adoption of alternative dissolution specifications, (3) responses to CMC deficiencies, (4) literature update; (5) foreign regulatory update; (6) safety update; and (7) commitments on several postapproval requests. We also provided draft labeling.

The sponsor responded on 9-18-02.

Clinical Issues

Patients Lacking Followup for Laboratory Abnormalities

-We had asked the sponsor to obtain followup data on 6 patients for whom abnormalities were present at the final visit. They were able to obtain additional information on one of these patients (138001-7-458), suggesting that the elevated CPK values were declining. No additional information could be obtained for the remaining patients.

Adoption of Alternative Dissolution Specifications

-The sponsor has agreed to accept our proposed dissolution specifications.

CMC Deficiencies

-To my knowledge, all remaining CMC issues have been resolved.

Literature Update

-An updated literature review identified 56 articles in the published literature (only a list of these references was provided), and the sponsor has warranted that these articles revealed no important new safety information regarding aripiprazole.

Foreign Regulatory Update

-The sponsor reported that aripiprazole has been approved in Mexico, and applications are pending in _____ They warrant that no negative regulatory actions have been taken with regard to aripiprazole anywhere.

Safety Update

-The sponsor provided a safety update with a new cutoff date of 6-30-02, including the following numbers of new patients exposed to aripiprazole:

- 882 in non-Japanese ph 2/3 studies
- 59 in non-Japanese ph 1 studies
- 55 in Japanese studies

-The total number of non-Japanese patients/subjects exposed to aripiprazole as of this safety update is 5,592. None of the new data came from short-term placebo-controlled trials.

-The review of the new data, conducted by Drs. Dubitsky and Harris, focused on deaths and SAEs. There were 43 new deaths, the vast majority coming from Alzheimer's patients (39), and the causes of death were the typical background events seen with the earlier deaths in this program. There were 264 new SAEs in the non-Japanese ph 2/3 studies. Overall, the pattern of SAEs seen was similar to that seen in the original NDA, and no important new SAEs were revealed.

Commitments on Postapproval Requests

-We had asked for commitments to conduct studies, postapproval, to address the following issues:

- Food Effect Study at Highest Strength
- Studies to Explore Dose/Response for Efficacy Below 10 mg
- Longer-Term Efficacy Data
- Further Studies of Retinal Degeneration in Rat
- Further Studies of Abuse Liability

-The sponsor agreed to conduct such studies, and submit the data needed to address these issues. They indicated that they will contact us postapproval regarding study design issues.

Draft Labeling

-We have reached agreement with the sponsor on final labeling as of 11-7-02.

Conclusions and Recommendations:

-I believe that the sponsor has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of schizophrenia. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:

Orig NDA 21-436

HFD-120

HFD-120/TLaughren/RKatz/GDubitsky/RHarris/SHardeman

HFD-101/RTemple

DOC: MMARIP.P1

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Draft Labeling
(not releasable)



NDA 21-436

Otsuka Pharmaceutical Co., Ltd.
Attention: Gary Ingenito, M.D., Ph.D.
President and Chief Operating Officer
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Ingenito:

Please refer to your new drug application (NDA) dated October 31, 2001, received October 31, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) 2, 5, 10, 15, 20 and 30 mg Tablets.

We acknowledge receipt of your submissions as follows:

December 21, 2001	January 17, 2002	February 1, 2002	February 12, 2002
February 25, 2002	February 27, 2002	March 15, 2002	March 20, 2002
March 22, 2002	March 29, 2002	April 4, 2002	April 10, 2002
April 15, 2002	April 16, 2002	April 29, 2002	May 8, 2002
May 9, 2002	May 10, 2002	May 15, 2002	May 31, 2002
June 3, 2002	June 7, 2002	June 24, 2002	July 10, 2002
July 29, 2002			

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Clinical Pharmacology and Biopharmaceutics

Please adopt the following dissolution method and specification for all strengths of aripiprazole tablets (2, 5, 10, 15, 20 and 30 mg):

- Apparatus: USP Apparatus 2 (paddles) at 60 rpm

- Medium: 900 mL of 0.1 N HCl (pH 1.2) at 37±0.5 C°
- Specification: _____

Clinical

We note that, for several patients, there were abnormal laboratory findings present at the last visit, but no followup information. We ask that you attempt to find and provide followup laboratory and other information on the following patients:

138001-33-102	elevated SGOT
97201-36-18	elevated SGOT
138001-7-458	elevated CPK
97202-89-6	low platelet count
138001-7-281	low platelet count
97202-71-19	low platelet count

Chemistry

Establishment Inspections:

The Bristol drug product manufacturing, packaging, and release testing facility located in Mayaguez, PR (CFN #2627673) was found to be unacceptable by the FDA's Office of Compliance. We note that your application describes other facilities that perform these functions. If you plan to utilize the Mayaguez, PR site (CFN #2627673), a satisfactory inspection will be needed, otherwise the site should be withdrawn from the NDA.

Drug Substance and Drug Product:

1. Please provide detailed methodology for the identification of aripiprazole drug substance by IR.
2. Please provide detailed information supporting the use of your drug substance packaging. Any relevant DMF information should include appropriate letters of authorization (LOAs), which clearly indicate (by name, part number, etc.) the item(s) referenced in the DMF, and their precise location and date of inclusion in the DMF.
3. Please include a sample of the label to be used for the drug substance during shipping and storage. The label should clearly indicate the name of the bulk substance, the identifying lot or control number, and the storage condition for the drug substance.
4. Please provide the limit of detection and the limit of quantitation for _____ in the method for the Determination of Impurities and Degradation Products.

5. Please provide a certificate of analysis for each of the drug product excipients.
6. Specifications for the Impurities and Degradation Products are _____ and _____
The batch analyses results for _____ and _____
_____ for at least two batches were "not counted." Please explain.
7. Please provide a complete and detailed description of the secondary packaging systems for the HDPE bottles and blister strips. Your response should include specifications and in-process controls.
8. On page 50 of volume 1.4 you state "In the case of the aluminum/aluminum cold-form blisters, the primary packaging components are identical to those employed in the primary stability batches, except for the foil lidding. In this case, paper-backed aluminum foil laminate was used for the primary stability batches, whereas the batches intended for marketing will use either the same...or a plain (non-paper-backed) aluminum foil laminate of identical structure, composition and moisture and oxygen barrier properties." Please provide the appropriate data to demonstrate that these packaging systems are equivalent.
9. On page 101 in the drug product stress stability section, you indicated that you would include data for the 2, 5, 10, 15, 20 and 30 mg tablets at 25C/60% RH and 40C/75% RH in the open petri dish, however, you only included data for the 15, 20 and 30 mg tablets. Please provide stability data for the 2, 5 and 10 mg tablets at 25C/60% RH and 40C/75% RH in the open petri dish.
10. Please provide updated drug substance stability data.
11. Please provide updated stability data for the 2, 5, 10, 15, 20 and 30 mg tablets manufactured at the Mayaguez, Puerto Rico facility.
12. Please provide updated drug product release specifications which reflect the biopharm dissolution recommendation.
13. The 1987 FDA Guidance for Submitting Samples and Analytical Data for Methods Validation indicates that four copies of the Methods Validation Package should be included with your original submission. Accordingly, we request that you submit two additional copies of the Methods Validation Package.
14. The proposed carton and blister backing for the drug product has the name Abilitat (aripiprazole) Tablets listed as the name of the drug product. This name was not accepted by the Office of Post-Marketing Drug Risk Assessment (OPDRA). Please commit to submitting revised container closure information for the new proprietary name, Abilify.
15. Labels for the secondary packaging of the cold-form blisters were provided, however, you did not provide labels for folding cartons (30, 60, 90 and 500 count bottles) of the drug product. Please indicate if you plan to use secondary packaging for these bottles and if so please provide draft labeling for each strength.

Foreign Regulatory Update/Labeling

We require a review of the status of all aripiprazole actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If

aripiprazole has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for aripiprazole along with English translations when needed.

World Literature Update

Prior to the approval of aripiprazole, we require an updated report on the world archival literature pertaining to the safety of aripiprazole. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of aripiprazole. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in pre-clinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Update

Our assessment of the safety of aripiprazole is based on our review of all safety information provided in your original and subsequent submissions, including your safety update of February 27, 2002. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

Post Approval (Phase 4) Commitments

1. Due to the limited solubility of aripiprazole and non-rapid dissolving nature of the tablet in gastric pH (pH 1.2), we ask that you commit to conducting a food effect study on the highest strength (30 mg).
2. In each of the 3 positive fixed dose studies, the lowest dose (10, 15, or 20 mg) was numerically superior to all the higher doses. You have thus not adequately explored the lower end of the dose response curve for effectiveness. We ask that you commit to conducting, postapproval, additional studies to determine whether or not doses lower than 10 mg are effective.
3. To address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia, we request that you submit, post-approval, the results of Study 138047.

4. We ask that you commit to conducting, postapproval, additional studies in order to further characterize (e.g., reversibility, functional correlates) and, if possible, to determine the mechanism(s) underlying the retinal degeneration observed in the 26-wk and 2-yr carcinogenicity studies in Sprague-Dawley rat.
5. The data from studies conducted in rhesus monkey suggest that aripiprazole may have some abuse liability. One of 4 monkeys trained to self-administer cocaine continued to self-administer when aripiprazole was substituted for cocaine. In addition, 4 of 4 monkeys exhibited withdrawal symptoms following abrupt cessation of dosing with aripiprazole. Although self-stimulation was not observed in rats when aripiprazole was substituted for cocaine, there was a tendency for animals to exhibit withdrawal symptoms following abrupt cessation of dosing. Therefore, we ask that you commit to conducting, postapproval, additional studies investigating the abuse liability of aripiprazole.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Number of Pages
Redacted 28 + 26 = 54



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