CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-436

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 and received October 31, 2001, 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 of September 18, October 8, and October 16, 2002.

Your submission of September 18, 2002 constituted a complete response to our action letter of August 29, 2002.

This new drug application provides for the use of Abilify (aripiprazole) tablets for the treatment of schizophrenia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We note your agreement to the attached labeling as well as the Phase 4 commitments and their corresponding time frame completion dates in an e-mail communication dated November 7, 2002.

The final printed labeling (FPL) must be identical to the attached labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. For administrative purposes, designate this submission "**FPL for approved NDA 21-436.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your agreed-upon commitments of September 28, and November 7, 2002, to conduct the following postmarketing studies:

1. A food effect study on the highest strength (30 mg).

   Protocol Submission: Within 2 months of the date of this letter
   Study Start: Within 4 months of the date of this letter
   Final Report Submission: Within 15 months of the date of this letter

   We acknowledge that this timeline assumes that there is no need for Agency feedback on the protocol (standard food effect design will be employed) and that the 30 mg strength is tolerated by healthy volunteers. If this strength is not tolerated by healthy volunteers resulting in the need to conduct this study in schizophrenics, the timeline will be impacted and need to be re-negotiated with the Agency.

2. Studies to determine whether or not doses lower than 10 mg are effective.

   Protocol Submission: Within 6 months of the date of this letter
   Study Start: Within 12 months of the date of this letter
   Final Report Submission: Within 42 months of the date of this letter

   This timeline incorporates 2 months for Agency review of the design of the protocol. If this study demonstrates that lower doses are effective in the treatment of schizophrenia, the results should be submitted to the NDA in the form of an efficacy supplement.

3. Studies to further characterize (e.g., reversibility, functional correlates) and, if possible, to determine the mechanism(s) underlying the retinal degeneration observed in the 26-week and 2-year carcinogenicity studies in Sprague-Dawley rat.

   Protocol Submission: Within 5 months of the date of this letter
   Study Start: Within 8 months of the date of this letter
   Final Report Submission: Within 42 months of the date of this letter

   Since the retinal lesion observed in (b) Sprague-Dawley (SD) albino rats administered high doses of aripiprazole has morphologic features characteristic of light-induced retinopathy, it is critical that the potential for aripiprazole-related ocular changes be investigated in a pigmented rat strain that is less susceptible to light-induced retinal degeneration to rule out a direct effect of drug. Therefore, a one-month oral tolerability and toxicokinetic study in female (b) rats will be initiated in November, 2002 to determine the suitability of this pigmented rat strain for studying the pathogenesis of the retinal degeneration in SD rats. If the clinical tolerability and systemic exposure to aripiprazole in (b) rats are comparable to that observed in Sprague-Dawley rats at doses resulting in re)--al changes, then a draft protocol for the definitive study evaluating the functional consequences, reversibility, and pathogenesis of retinal degeneration will be submitted within 5 months of the approval letter. If clinical tolerability or systemic exposure to aripiprazole is lower in (b) ats than in SD rats at comparable doses, then an additional TK/tolerability study in alternate strains of pigmented rats will be conducted prior to initiation of the definitive study. We acknowledge that this additional pilot study will add approximately 3 to 4 months to the timeline for protocol submission, study start, and final report dates each.

4. Studies investigating the abuse liability of aripiprazole.

Protocol Submission:	N/A
Study Start:	July 22, 2002
Final Report Submission:	Within 5 months of the date of this letter

We acknowledge that you are currently conducting an abuse liability study in monkeys in Japan. The timeline above incorporates roughly 2 months needed to translate the protocol into English.

5. Submit the results of Study 138047 to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia.

We acknowledge that this study has already been completed and that the safety data were reported as part of the 120 Day Safety Update. However, a formal submission of the results of this study will be submitted within 30 days of the date of the approval letter. This submission should be submitted to the NDA as an efficacy supplement.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

The text in italics below addresses the application of FDA's Pediatric Rule at [21 CFR 314.55/21 CFR 601.27] to this NDA. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we are deferring submission of pediatric studies until January 1, 2007.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

Please note that we have approved an expiration date of 24 months for all strengths of this drug product.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Enclosure

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

/s/

Robert Temple
11/15/02 03:41:12 PM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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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^0
- Specification: ——— in 30 min

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. [redacted] " 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

attachment - labeling

Number of Pages Redacted 29

Draft Labeling
(not releasable