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) [redacted] 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) [redacted] 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) [redacted] 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) [redacted] 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

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