DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 / S-005, S-008
NDA 21-713 / S-003

Otsuka Maryland Research Institute
Attn: Dr. Kusuma Mallikaarjun
Director, Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug application (NDA 21-436 / S-005) dated January 28, 2004, received January 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Tablets.

We also acknowledge receipt of your submission dated January 3, 2005 and your secure electronic mail transmissions dated January 18, 2005 (2). Your submission of January 3, 2005 constituted a Complete Response to our November 30, 2004 action letter.

Reference is also made to your supplemental new drug application (NDA 21-436 / S-008) dated December 27, 2004, received December 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Tablets, and to your supplemental new drug application (NDA 21-713 / S-003) dated February 16, 2005, received February 16, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Oral Solution.

Supplemental new drug application NDA 21-436 / S-005 provides for the use of Abilify® Tablets as maintenance therapy in Bipolar I Disorder; supplemental new drug application NDA 21-713 / S-003 is a labeling supplement to provide for similar use of Abilify® Oral Solution.

We have completed our reviews of these supplemental applications. They are approved effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling text.

Supplemental new drug application NDA 21-436 / S-008 provided for the addition of a statement on cerebrovascular adverse events (CVAEs), reported in ABILIFY clinical studies, to the WARNINGS section of labeling. CVAE Warning language, as agreed to on January 19, 2005 between representatives of your firm and members of this Division, is also included in the enclosed agreed-upon labeling text. S-008 is therefore superseded by the inclusion of this language in the approved labeling for S-005 and S-003.

Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitment: Partial Waiver, Partial Deferral

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We are waiving this requirement entirely for NDA 21-713 / S-003. We are also waiving it for children below the age of 10 years with regard to NDA 21-436 / S-005. We are deferring submission of pediatric studies under PREA for NDA 21-436 / S-005, for children aged 10 to 17 years (children and adolescents), until April 1, 2009. PREA requirements do not apply to NDA 21-436 / S-008.

The deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitments are listed below.

1. *Deferred pediatric studies under PREA (NDA 21-436 / S-005).*
   You are required to assess the safety and effectiveness of Abilify as long-term maintenance treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents).

   Final Report Submission: April 1, 2009

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

Pediatric Exclusivity

Please note that Proposed Pediatric Study Requests and Pediatric Written Requests, which apply to pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act, are distinct from, and may need to be developed ***in addition to,*** pediatric studies under PREA as described above. Satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Additional Phase 4 Commitments (Clinical):

We remind you of your additional postmarketing commitments, agreed upon in two teleconferences on September 28, 2004 with reference to Supplement S-002 for acute treatment of bipolar I disorder, and confirmed in your submission of January 3, 2005 and your secure emails of January 18, 2005, with reference to S-005. The commitments are summarized below.

2. *Clinical Efficacy and Safety, S-002 and S-005: Adult clinical study to address longer-term efficacy and safety of aripiprazole as add-on therapy in bipolar disorder.*
   You have agreed to submit the results of a clinical study in adults examining the longer-term efficacy and safety of aripiprazole as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate). Fulfillment of this commitment for S-002 will also fulfill it for S-005.

   Final Report Submission: September 30, 2009

3. *Pharmacology / Toxicology, S-002 and S-005: Juvenile animal toxicity study/ies to support pediatric studies of aripiprazole in bipolar disorder.*
   You have agreed to conduct and submit a juvenile animal study or studies to support pediatric studies of aripiprazole in bipolar disorder. This study will support both S-002 and S-005 when submitted.

   Final Report(s) Submission: June 30, 2006.

4. *Drug-Drug Interaction, S-005: Drug interaction studies with lithium and valproate.*
   You have agreed to conduct and submit drug interaction studies examining the interaction of aripiprazole with lithium and with valproate (two separate studies). These studies will support S-005 as a Phase 4 commitment.

   Final Reports Submission: June 30, 2005.

Submit clinical protocols to your IND for this product. Submit nonclinical protocols and all final study reports to this NDA, including any final reports intended to support clinical efficacy claims or changes in labeling. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary for each commitment in your annual report to this NDA. The status summary should include:

- expected summary completion dates,
- expected final report submission dates,
- any changes in plans since the last annual report,
- and, for clinical studies, the 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**." Please clearly mark all submissions with the supplement number or numbers that they support, for database management purposes.

Labeling
The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplemental NDAs 21-436 / S-005 and 21-713 / S-003**." Approval of this submission by FDA is not required before the labeling is used.

Introductory Promotional Materials
In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in this indication. 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(s) directly to:

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

If you issue a letter communicating important information about this product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: agreed-upon labeling

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

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