DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 / S-002

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 dated June 23, 2003, received June 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Tablets.

We also acknowledge receipt of your submissions dated May 26, 2004, July 19, 2004, and July 28, 2004. Your submission of July 28, 2004, as cross-referenced to the May 26 and July 19, 2004 submissions, constituted a Complete Response to our April 23, 2004 action letter.

This supplemental new drug application provides for the use of Abilify® Tablets in the treatment of acute manic or mixed episodes associated with Bipolar Disorder. We have completed our review of this supplemental application as amended. It is approved effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling text.

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 for children below the age of 10 years. We are deferring submission of your pediatric studies for ages 10 to 17 years (children and adolescents) under PREA until September 30, 2008.

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.*
   You are required to assess the safety and effectiveness of Abilify as a treatment for bipolar disorder in pediatric patients ages 10 to 17 (children and adolescents).

   Final Report Submission: September 30, 2008

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 and your secure email of the same date. The commitments are summarized below.

2. *Clinical Efficacy and Safety: Adult clinical study to address 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 acute efficacy and safety of aripiprazole as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate).

   Final Report Submission: September 30, 2007

3. *Clinical Efficacy and Safety: 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).

   Final Report Submission: September 30, 2009

4. *Pharmacology / Toxicology: 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.

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

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**."

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 NDA 21-436 / S-002**." 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
9/29/04 07:17:27 AM