CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-729

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-729

Otsuka Pharmaceutical, Inc.
Attention: Kusuma Mallikaarjun, Ph.D.
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your new drug application (NDA) dated and received December 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions of January 13, March 31, July 8, August 4, and August 20, 2004.

We completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues.

1. Please provide compatibility data for aspartame with the active and other excipients in the drug product formulation, such as xylitol, to demonstrate that aspartame does not interact.

2. You stated that croscarmellose sodium is to be used [redacted] crospovidone. However, no rationale is provided for use of croscarmellose sodium as a [redacted] In addition, based on the Handbook of Pharmaceutical Excipients, croscarmellose sodium can show incompatibilities and requires special storage conditions. Please provide data to show its compatibility with the active and other excipients.

3. You have proposed using the [redacted] tablet press for the manufacture of commercial batches, however, you have provided no batch data derived from this tablet press. Please provide batch data using the [redacted] tablet press for one batch of each strength of Abilify ODT.

4. Please explain the testing results from the tablet compression of batch #2H56081 (10 mg) and batch #2G58279 (30 mg) where approximately [redacted] respectively, of [redacted] batches were rejected [redacted] Provide the sampling plans used for testing batches for tablet weight, potency, tablet hardness and disintegration during the compression process.

5. The specification that you have provided for the identification of aripiprazole in the drug product is "confirmed" for both the IR and HPLC test methods. This is not an acceptable specification as it is

vague and inconclusive. Please provide a more suitable specification for the identification of the drug product. You indicated that the [redacted] method for identification would not be part of the [redacted]. Identification tests should be specific for a drug substance (e.g., [redacted] Identification solely by a single [redacted] is not regarded as being specific. Provide an acceptable specification limit for the [redacted] method or a second identification test for aripiprazole in the drug product (e.g., [redacted] Refer to ICH Guidance Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products.

6. Your proposed disintegration time specification of NMT [redacted] is unacceptable. Please propose an updated disintegration time limit in the drug product specifications (refer to the Advisory Committee for Pharmaceutical Science, October 21- 22, 2003).

   In addition, the disintegration method states [redacted] Please provide updated criteria for the disintegration method and updated drug product release specifications.

7. The following pertain to the stability of the Aripiprazole ODT:

   a. The stability data provided for Abilify ODT batches (manufactured and packaged at Mayaguez, Puerto Rico) constitutes supportive stability data. Due to the possible softening and increased friability of the ODT, you will need to demonstrate that these tablets can be shipped in bulk containers and packaged at the proposed commercial sites in [redacted] Provide information on bulk containers, shipping conditions, and release data for the bulk batch at the packaging sites. Provide stability data from commercial packaging sites to demonstrate comparability with the stability data collected from Mayaguez, Puerto Rico.

   b. You have identified an unknown impurity at [redacted] under accelerated conditions. Have you identified and characterized this unknown impurity at [redacted]

   c. Please provide specification limits for each test method in the long-term stability protocol as well as the post-approval stability protocol. In addition, the post-approval stability protocol should monitor for water, hardness and friability.

8. Refer to your labeling for the following comments:

   a. Please provide labels for bulk containers for packaging and shipping and updated labels (containing trade name) for unit dose blisters and their cartons.

   b. The correct molecular weight for aripiprazole as per the USP Dictionary is 448.39. Please correct the molecular weight for aripiprazole in the Description section of the package insert.

9. During a recent inspection of the Bristol Myers Squibb drug product manufacturing and release testing facility for this application, located at Mayaguez, Puerto Rico (CFN # 2627673), our field investigator conveyed deficiencies to the facility representatives. Satisfactory resolution of these deficiencies is required, and this site will need to be found acceptable by the FDA's Office of Compliance, before this application may be approved.

10. We request that you adopt the following dissolution method and specification:

    Apparatus: USP Apparatus II (Paddle)
    Speed: 75 rpm
    Media: pH 4 Acetate Buffer
    Volume: 1000 mL

    Specification: Q NLT [redacted] in 30 minutes

11. We are granting your request for a waiver of *in vivo* bioequivalence studies for the 10 mg, 15 mg and 20 mg tablet strengths.

12. We have no objections to the use of the proprietary name, Abilify Discmelt.

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 note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

In addition, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the attached package insert.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). 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. Please individually mount ten of the copies on heavyweight paper or similar material.

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

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(s) directly to:

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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the

application under 21 CFR 314.65. 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}

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

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