



NDA 21-436/S-026, 21-713/S-019, 21-729/S-012, 21-866/S-013

Otsuka Pharmaceutical Development & Commercialization, Inc.  
Attn: Dr. Kusuma Mallikaarjun, Senior Director – Regulatory Affairs  
2440 Research Blvd.  
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug application dated and received July 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) tablets, Abilify Discmelt (aripiprazole) orally disintegrating tablets, Abilify (aripiprazole) oral solution, and Abilify (aripiprazole) injection.

Reference is also made to an FDA letter dated June 16, 2008 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antipsychotic drugs. This information pertained to the warning regarding use of antipsychotics and increased mortality in elderly patients with dementia-related psychosis.

Your supplemental application provides for revisions to the labeling for Abilify (aripiprazole) tablets, Abilify Discmelt (aripiprazole) orally disintegrating tablets, Abilify (aripiprazole) oral solution, and Abilify (aripiprazole) injection, consistent with our June 16, 2008 letter.

This supplemental new drug application provides for the following changes to product labeling:

Under the **BOXED WARNING** section, the addition of a warning regarding increased mortality in elderly patients with dementia-related psychosis. [This new section will be added to the beginning of the label with bolded font and enclosed in a black box.]

**WARNING**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**—

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed

to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Abilify is not approved for the treatment of patients with dementia-related psychosis (*see* **WARNINGS**).

Under **WARNINGS** the language below will be implemented in bolded font in the **WARNINGS** section as the first paragraph in this section.

## **WARNINGS**

### **Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Abilify is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

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

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved supplement NDAs 21-436/SLR-026, 21-713/SLR-019, 21-729/SLR-012, 21-866/SLR-013.**”

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in these applications.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter and that the revised labeling be reflected in the next printing of the labeling. While you may use labeling already printed, we request that revised labeling accompany any newly shipped product within 60 days from the date of this letter.

Failure to make these changes promptly could make your product misbranded under Sections 201(n) and 502(a) of FDCA.

## **PROMOTIONAL MATERIALS**

You must promptly revise all promotional labeling and advertising for this product to make it consistent with the labeling changes described above. These revisions should include prominent disclosure of the important new information described in the **BOXED WARNING** section that appear in the revised package labeling.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Psychiatry Products and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important information about this drug 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  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

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 LCDR Sonny Saini, Pharm. D., Safety Project Manager, at (301) 796-0532.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Thomas Laughren  
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