

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-866**

**PROPRIETARY NAME REVIEW(S)**

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**

**OFFICE OF DRUG SAFETY**

**(DMETS; WO22, Mail Stop Room 4447)**

**DATE RECEIVED:**

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**ODS CONSULT #: 06-0002**

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November 29, 2005

**TO:** Thomas Laughren, MD  
Acting Director, Division of Psychiatry Products  
HFD-130

**THROUGH:** Linda Kim-Jung, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support

**FROM:** Kristina C. Arnwine, PharmD, Safety Evaluator  
Division of Medication Errors and Technical Support

**PRODUCT NAME:**

**Abilify**  
(Aripiprazole Injection)  
9.75 mg

**NDA#: 21-866**

**NDA SPONSOR:** Otsuka America and Bristol-Myers Squibb

**RECOMMENDATIONS:**

DMETS has concerns with the proposed product concentration. Additionally, we recommend implementation of the label and labeling revisions outlined in section II of this review to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

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**Division of Medication Errors and Technical Support (DMETS)  
White Oak Bldg 22, Mail Stop Room 4447  
Center for Drug Evaluation and Research**

**LABEL AND LABELING REVIEW**

**DATE OF REVIEW:** January 24, 2005

**NDA#:** 21-866

**NAME OF DRUG:** Abilify (Aripiprazole Injection) 9.75 mg

**NDA HOLDER:** Otsuka America and Bristol-Myers Squibb

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Psychiatry Products (HFD-130), for a review of the container label, carton and insert labeling of Abilify Injection. The sponsor, Otsuka America, currently markets Abilify tablets (NDA 21-436) and oral solution (NDA 21-713) which were approved November 15, 2002 and December 10, 2004, respectively. Abilify injection is an extension of the existing product line. Abilify tablets and oral solution are indicated for the treatment of schizophrenia and bipolar disorder with a usual dose of 10 mg to 30 mg per day. Abilify injection is indicated for agitation associated with schizophrenia or bipolar mania with a usual dose of 15 mg to 30 mg per day. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. If ongoing Abilify therapy is indicated, Abilify tablets or oral solution may be initiated at a range of 10 mg to 30 mg per day as soon as clinically appropriate.

**II. ADVERSE EVENT REPORTING SYSTEM (AERS)**

DMETS conducted a search of the FDA Adverse Events Reporting System (AERS) for any medication errors associated with Abilify. The search was conducted using the high group level term "medication errors," and the preferred terms "medication error, pharmaceutical product complaint, accidental overdose, and overdose." The search did not identify any confusion between the brand name Abilify and any other currently marketed products or any safety issues related to the labels and/or labeling of Abilify. However, the search did identify four cases confusion between the established name, Aripiprazole, and the established names of various proton-pump inhibitors including Omeprazole, Pantoprazole, Lansoprazole. One case stated that an order for Abilify was switched to Protonix, that particular facility's formulary proton-pump inhibitor, after a pharmacist had seen Abilify advertisement material which included the established name, Aripiprazole. Three cases were potential medication errors in which healthcare practitioners stated concerns regarding the similarity between the established name Aripiprazole and the established names of proton-pump inhibitors.

**III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

In the review of the container labels, carton and insert labeling of Abilify, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

## A. SAFETY ISSUES WITH PROPOSED CONCENTRATION

DMETS is concerned with the potential for medication errors as a result of the misleading nature in which the concentration and total drug content are stated on the labels and labeling in addition to the actual milligram per milliliter concentration contained in each vial. Through a February 16, 2006 conversation with the chemistry reviewer for this NDA, DMETS was informed that the actual total drug content of each vial of Abilify is 10 mg/1.33 mL, with a milligram per milliliter concentration of 7.52 mg/mL. The current labels and labeling list the concentration as 7.5 mg/mL. Additionally, the container label and carton labeling do not list the total drug content at all, and the package insert labeling incorrectly lists the total drug content as 9.75 mg in the Dosage and Administration section.

1. The misleading nature of the milligram per milliliter concentration and the total drug content statements increase the potential for medication errors. The prominence of the concentration on the container label and carton labeling leads practitioners to believe that each vial only contains 7.5 mg of Abilify, which is incorrect. The vial contains a total of 10 mg. The total volume (i.e. 1.3 mL) is listed on the labels and labeling, however, it is not prominent enough for a practitioner to readily recognize that each vial contains more than one milliliter. Furthermore, both statements (i.e. 7.5 mg/mL and 1.3 mL) are incorrect. The actual milligram per milliliter concentration is 7.52 mg/mL and the actual total volume is 1.33 mL. Additionally, the correct total drug content per vial (i.e. 10 mg) is not listed anywhere in the labels and labeling. The Dosage and Administration Section of the package insert incorrectly states that \_\_\_\_\_, meanwhile the Description Section describes Abilify Injection as a \_\_\_\_\_. These inconsistent statements are both incorrect and confusing with regard to how much drug is contained in each vial. Thus, practitioners are left wondering whether each vial contains 9.75 mg or 7.5 mg, when in actuality it contains 10 mg. In addition, based on the information on the labels and labeling practitioners are led to believe the total volume is either 1 mL or 1.3 mL, when in actuality it is 1.33 mL. Thus, without the correct milligram per milliliter concentration or total drug content per total volume listed on the labels and labeling it is impossible for practitioners to correctly administer the desired dose to patients.
2. Moreover, the proposed milligram per milliliter concentration increases the potential for medication errors as a result of calculation and/or administration errors. With a concentration of 7.52 mg/mL and a total volume of 1.33 mL, neither of these numbers, 7.52 or 1.33, facilitate easy calculations, or calculations which result in numbers that can be easily measured. Since the range of dosing for the proposed product is 1 mg to 15 mg, healthcare practitioners would be required to calculate the volume to be administered and this volume will always result in a volume that utilizes two decimal places. For example, if a physician orders a dose of 5 mg, the pharmacist would require a calculation based on the labeled amount. This calculation would result in a 0.665 mL volume. Additionally, this volume is not easily measured using syringes commonly used in a healthcare setting. Although tuberculin syringes are calibrated in tenths, a 0.665 mL volume would be difficult to measure since the syringe is not calibrated in hundredths. Moreover, doses of more than 10 mg could not be measured using a tuberculin syringe and larger syringes are generally not calibrated in tenths or hundredths. Thus, any doses greater than 10 mg would either require more than one shot (using a tuberculin syringe) or would require that the healthcare practitioner approximate the dose using a larger syringe. The proposed concentration and total volume make the administration of varied doses impossible to accurately measure and could potentially lead to underdoses or overdoses.

We anticipate confusion with the proposed concentration and total volume leading to medication errors. DMETS recommends reformulating Abilify Injection so that the total volume that the 10 mg Abilify is contained in is a whole number (i.e. 2 mL). Thus, the resultant milligram per milliliter concentration will be a whole number as well (i.e., 5 mg/mL). The use of whole numbers will allow for easier calculations and accurate measurement and administration of prescribed doses.

## B. LABELING COMMENTS

1. See Safety Comments concerning the proposed product concentration outlined in Section A.

### 2. GENERAL COMMENTS

- a. The total drug content in each vial is 10 mg and not 7.5 mg as labeled. Post marketing evidence has shown that when the total drug content is not included on the labels and labeling, practitioners assume that the amount listed on the labels and labeling (i.e. 7.5 mg/mL) is the total amount included in the vial/syringe. This assumption may lead to overdoses. Additionally, see our concerns with respect to this proposed concentration in Section III-A. Revise the total drug content statement to include the total amount of drug per total volume followed by the milligram per milliliter concentration. For example:

**10 mg/1.33 mL**  
(7.52 mg/mL)

- b. Revise the statement ~~\_\_\_\_\_~~ to read, "For Intramuscular Use Only." DMETS does not recommend the use of abbreviations on labels and labeling in order to prevent medication errors due to misinterpretation.
- c. Revise the statement ~~\_\_\_\_\_~~ to read "Single use container. Discard any unused portion."
- d. Remove the statement, ~~\_\_\_\_\_~~ from labels and labeling.

### 3. VIAL LABEL

- a. See General Comments B-1-a through B-1-d.
- b. The color scheme used for "7.5 mg/mL" (i.e. blue font on light blue background) does not provide adequate contrast and makes the information difficult to read. Change the color scheme to provide more contrast and make the information easier to read.
- c. If the product strength is not revised per Section III-A, include a total volume statement (i.e. 1.33 mL vial) at the top of the label.
- d. Relocate the "Rx only" to the bottom portion of the vial in order to increase the prominence of the "Rx only" statement as well as the product strength and concentration.

#### 4. CARTON LABELING

- a. See General Comments B-1-a through B-1-d.
- b. Revise the "See package insert for indications..." statement to read, "Usual Dosage: See package insert," per 21 CFR 201.55.

#### 5. INSERT LABELING

- a. See General Comment B-1-a.
- b. Revise the statement of strength throughout the insert labeling to read 10 mg/1.33 mL instead of 7.5 mg/mL.
- c. Description Section, Third Paragraph

Revise the statement, "Abilify Injection is available in single-dose vials..." to read, \_\_\_\_\_

- d. Dosage and Administration Section, Administration of Abilify Injection Sub-Section

- i. Revise the statement, "~~\_\_\_\_\_~~" to read, "~~\_\_\_\_\_~~"

- ii. Delete the statement "~~\_\_\_\_\_~~," as it will no longer be necessary after revision of labels and labeling to reflect the total drug content of 10 mg .

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/s/  
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