DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Lois M. Jessen, MS, PharmD.
Associate Director
Otsuka Pharmaceutical Development & Commercialization, Inc.
1 University Square Drive, Suite 500
Princeton, NJ 08540

RE: NDA 021436
ABILIFY (aripiprazole) Tablets
MA #1541

Dear Dr. Jessen:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a pharmacology aid (03US13EP0314) for ABILIFY (aripiprazole) Tablets (Abilify) submitted by Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) under cover of Form FDA 2253. The pharmacology aid is false or misleading because it makes misleading claims and presentations about the drug. Thus, the pharmacology aid misbrands Abilify within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 331(a). *C.f.* 21 CFR 202.1(e)(6)(ii).

Background

Below are the indications (in pertinent part) and summary of the most serious and most common risks associated with the use of Abilify.[1]

According to its FDA-approved product labeling (PI), Abilify is indicated for the acute treatment of manic and mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate.

Abilify is indicated for the maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to either lithium or valproate.

Abilify is also indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD).

Abilify is associated with a number of serious risks. The PI for Abilify contains Boxed Warnings regarding increased mortality in elderly patients with dementia-related psychosis and the increased risk of suicidality and antidepressant drugs. Abilify is contraindicated in

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

patients with a known hypersensitivity to Abilify. The PI also contains several warnings and precautions regarding the risks of cerebrovascular adverse events, including stroke, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension, leukopenia, neutropenia, and agranulocytosis, seizures and convulsions, potential for cognitive and motor impairment, body temperature regulation, suicide, and dysphagia. The most common adverse reactions associated with the use of Abilify as monotherapy in patients with bipolar mania include akathisia, sedation, restlessness, tremor, and extrapyramidal disorder. The most common adverse reactions associated with the use of Abilify as adjunctive therapy in patients with bipolar mania include akathisia, insomnia, and extrapyramidal disorder. The most common adverse reactions associated with Abilify in patients with MDD include akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

Misleading Claims and Presentations

The pharmacology aid includes the following claims and presentations (emphasis original):

Page 1:

- "**ABILIFY® (aripiprazole)…modulates both synaptic dopamine and serotonin**," in conjunction with:
  - An image labeled "**Full Antagonist**" depicting a light dimmer switch set to "LOW" against dark background wallpaper with graphics of human brains that are difficult to visualize.
  - An image labeled, "**Full Agonist**" depicting a light dimmer switch set to "HIGH" against brightly-lit background wallpaper with graphics of human brains that are difficult to visualize.

Page 2:

- A graph labeled "**Theoretical action of partial agonist compared to full agonist and antagonist**" [2] depicting the maximum percentage response *in vitro* versus the concentration (M) in conjunction with the claim, "A partial agonist may have the same potency as a full agonist, but at a lower maximal level of response."

Page 3:

- "**Modulating dopaminergic and serotonergic activity sets ABILIFY® (aripiprazole) apart**"[3]
- "Help modulate dopamine and serotonergic activity with ABILIFY"
- "ABILIFY… modulating neuronal activity in both hypoactive and hyperactive environments[4]"
  - These claims are presented in conjunction with images of light dimmer switches for dopamine and serotonin full antagonist and full agonist (same image as page one), with the superimposed image of a third light dimmer switch set halfway between "HIGH" and "LOW."

[2] Green B. Focus on aripiprazole. *Curr Med Res Opin.* 2004; 20(2): 207-213. Review.
[3] Fleischhacker WW, Aripiprazole. *Expert Opin Pharmacother.* 2005; 6(12): 2091-2101.
[4] Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 2: illustrating their mechanism of action. J Clin Psychiatry. 2001; 62(12): 923-924.

Page 6:

- "**Unique pharmacology sets ABILIFY® (aripiprazole) apart**"
- "ABILIFY
  - Is thought to increase neuronal activity in hypoactive conditions[4]
  - Is thought to decrease neuronal activity in hyperactive conditions[4]
  - Has a high affinity for both dopamine and serotonin receptors…."
- These claims are presented in conjunction with the image of the light dimmer switch set halfway between "HIGH" and "LOW," presented against well-lit background wallpaper, with clearly defined graphics of human brains.

The totality of these claims and presentations misleadingly implies a greater degree of certainty about the mechanism of action of Abilify in humans than is currently known. Specifically, the claims and presentations suggest a definitive understanding of Abilify's ability to modulate dopaminergic and serotonergic activity in humans. However, the impact of the partial agonist properties of Abilify on its mechanism of action in patients with bipolar disorder or MDD has not been established. According to the CLINICAL PHARMACOLOGY section of the PI (emphasis added):

> The mechanism of action of aripiprazole…is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D2 and 5-HT_{1A} receptors, and antagonist activity at 5-HT_{2A} receptors.

The references [2-4] cited in support of the claims described above are articles which provide overviews of the pharmacology, efficacy, and safety of aripiprazole. The Stahl (2001)[4] article is a general discussion of a new class of antipsychotic medications, which includes aripiprazole, the Green (2004)[2] article provides a summary of published research on aripiprazole from 1995 through 2003, and the Fleischhacker (2005)[3] article is an opinion piece on the pharmacology, safety, and efficacy of aripiprazole. These references are not sufficient to support claims and presentations suggesting that Abilify has been demonstrated to modulate dopaminergic and serotonergic activity, or modulate neuronal activity in both hypoactive and hyperactive environments in humans. If you have data to support these claims, please submit them to FDA for review. We acknowledge that the bolded headline claims on pages one through three and six include a footnote more accurately describing what is known about the mechanism of action[5] for Abilify. However, this footnote does not mitigate the misleading nature of the claims and presentations described above.

Furthermore, the totality of these claims and presentations is also misleading because it implies that Abilify offers advantages over other currently approved treatments for bipolar disorder or MDD when this has not been demonstrated. Specifically, the comparative presentations of dimmer switches described above in conjunction with claims such as Abilify's "unique pharmacology sets [it] apart" misleadingly imply that Abilify has a clinical advantage due to its pharmacology. FDA is not aware of any evidence to support the implication that Abilify offers significant advantages over other prescription drugs already approved for the treatment of bipolar disorder or MDD because of its pharmacology. If you have such data, please submit them to FDA for review.

[5] According to the footnote, "Although the mechanism of action of ABILIFY is unknown, the efficacy of ABILIFY could be mediated through a combination of partial agonist activity at the dopamine D_2 and serotonin 5-HT_{1A} receptors, and antagonist activity at the serotonin 5-HT_{2A} receptors."

Conclusion and Requested Action

For the reasons discussed above, the pharmacology aid misbrands Abilify within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 331(a). *C.f.* 21 CFR 202.1(e)(6)(ii).

OPDP requests that Otsuka immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before May 1, 2015, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Abilify that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #1541 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Abilify complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Lisa M. Hubbard, RPh, RAC
Deputy Division Director
Office of Prescription Drug Promotion

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/s/

SUSANNAH O'DONNELL
04/17/2015

LISA M HUBBARD
04/17/2015