FDA ACCEPTS FOR REVIEW A SUPPLEMENTAL NEW DRUG APPLICATION TO EXPAND LABELING OF ABILIFY MAINTENA® (aripiprazole) FOR THE TREATMENT OF BIPOLAR I DISORDER

- *Application seeks to expand ABILIFY MAINTENA label to include maintenance treatment for bipolar I disorder*
- *If the label expansion is approved, ABILIFY MAINTENA would offer prescribers a once-monthly long-acting injectable treatment option in the maintenance treatment of bipolar I disorder in adults*

(TOKYO, Japan & VALBY, Denmark, November 30, 2016) – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and Lundbeck today announced the U.S. Food and Drug Administration (FDA) has determined that the supplemental New Drug Application (sNDA) for the expanded labeling of ABILIFY MAINTENA® for the maintenance treatment of bipolar I disorder in adult patients is sufficiently complete to permit a substantive review and is considered filed. Under the Prescription Drug User Fee Act (PDUFA), the FDA has set a target date of July 28, 2017, to complete its review.

About ABILIFY MAINTENA

ABILIFY MAINTENA is an extended-release injectable suspension, for intramuscular use developed by Otsuka in Japan and is co-commercialized by the alliance between Otsuka and H. Lundbeck. ABILIFY MAINTENA was approved in the U.S. in 2013 for the treatment of adults with schizophrenia.[1] Efficacy and safety for ABILIFY MAINTENA is supported by a short-term (12-week), randomized, double-blind, placebo-controlled trial in acutely relapsed adults, as well as a longer term (52-week) placebo-controlled, double-blind, randomized-withdrawal study for the maintenance treatment of schizophrenia.[2]

ABILIFY MAINTENA, an atypical antipsychotic, is an intramuscular depot formulation of aripiprazole.[2] It is a sterile lyophilized powder that, when reconstituted with sterile water for injection, forms an injectable suspension that can be administered monthly.[2] After an initial injection of ABILIFY MAINTENA along with an overlapping 14-day dosing of oral antipsychotic treatment, subsequent injections of ABILIFY MAINTENA provide uninterrupted medication coverage for 30 days at a time.[2] It provides a treatment option to address two of the most important considerations in the management of schizophrenia — improving symptoms in patients with an acute relapse of their disease and reducing the risk of relapse or the re-emergence of worsening of symptoms.[2] Depot formulations of antipsychotic agents provide patients with concentrations of active drug that remain at a therapeutic range for an extended period of time.[3]

About Bipolar I Disorder

Bipolar I disorder (BP-I) is a chronic mental illness.[4] People with BP-I experience one or more episodes of mania, and may have episodes of both mania and depression; however, an episode of depression is not necessary for a BP-I diagnosis.[4] If left untreated, the manic and depressive symptoms may get worse.[4]

INDICATION and IMPORTANT SAFETY INFORMATION for ABILIFY MAINTENA® (aripiprazole)

INDICATION

ABILIFY MAINTENA is an atypical antipsychotic indicated for the treatment of schizophrenia.

IMPORTANT SAFETY INFORMATION

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 (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pathological Gambling and Other Compulsive Behaviors: Intense urges, particularly for gambling, and the inability to control these urges have been reported while taking aripiprazole. Other compulsive urges (e.g., eating, sexual, or shopping) have been reported less frequently. Prescribers should ask patients or their caregivers specifically about, and closely monitor for, the development of new or intense compulsive urges. Consider dose reduction or stopping aripiprazole, if such urges develop.

Orthostatic Hypotension: ABILIFY MAINTENA may cause orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. In patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) or history of drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. Consider discontinuing ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (ANC <1000/mm^3) and follow their WBC counts until recovery.

Seizures: ABILIFY MAINTENA should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: ABILIFY MAINTENA may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are certain ABILIFY MAINTENA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with ABILIFY MAINTENA; use caution in patients at risk for aspiration pneumonia.

Alcohol: Advise patients to avoid alcohol while taking ABILIFY MAINTENA.

Concomitant Medication: Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the ABILIFY MAINTENA dosage may need to be increased. Avoid the concomitant use of CYP3A4 inducers with ABILIFY MAINTENA for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels. Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

Most Commonly Observed Adverse Reactions: Based on the placebo-controlled trial of ABILIFY MAINTENA in schizophrenia, the most commonly observed adverse reactions associated with the use of ABILIFY MAINTENA (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were increased weight (16.8% vs 7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs 0.6%), and sedation (5.4% vs 1.2%).

Injection Site Reactions: In the data from the short-term, double-blind, placebo-controlled trial with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction (all reported as injection site pain) was 5.4% for patients treated with gluteal administered ABILIFY MAINTENA and 0.6% for placebo. In an open label study comparing bioavailability of ABILIFY MAINTENA administered in the deltoid or gluteal muscle, injection site pain was observed in both groups at approximately equal rates.

Dystonia: Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Neonates exposed to antipsychotic drugs, including ABILIFY MAINTENA, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. These complications have varied in severity, from being self-limited to requiring intensive care and prolonged hospitalization. ABILIFY MAINTENA should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Lactation: Aripiprazole is present in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and any potential risks to the infant.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see accompanying FULL PRESCRIBING INFORMATION, including **BOXED WARNING,** for ABILIFY MAINTENA (aripiprazole).

REFERENCES:

1. Drug Approval Reports. U.S. Food and Drug Administration (FDA). 2013. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.MonthlyApprovalsAll. Accessed November 11, 2014.
2. ABILIFY MAINTENA US (aripiprazole) 2016 Full prescribing information. Tokyo: Otsuka Pharmaceutical Co., Ltd.
3. Kane JM, Sanchez R, Perry PP, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double- blind, placebo-controlled study. Journal of Clinical Psychiatry. 2012; 73(5): 617-624.
4. Bipolar Disorder. National Alliance on Mental Illness website. https://www.nami.org/Learn-More/Mental-Health-Conditions/Bipolar-Disorder. Accessed September 27, 2016.

About Otsuka Pharmaceutical Co., Ltd.

Otsuka Pharmaceutical is a global healthcare company with the corporate philosophy: “Otsuka – people creating new products for better health worldwide.” Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and nutraceutical products for the maintenance of everyday health.

In pharmaceuticals, Otsuka is a leader in the challenging area of mental health and also has research programs on several under-addressed diseases including tuberculosis, a significant global public health issue. These commitments illustrate how Otsuka is a “big venture” company at heart, applying a youthful spirit of creativity in everything it does.

Otsuka Pharmaceutical and related companies, which employ approximately 31,000 people worldwide, is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group that is headquartered in Tokyo, Japan. The Otsuka Group has business operations in 28 countries and regions around the world, with consolidated sales of approximately 1.45 trillion yen (or USD 11.9 billion or EUR 10.8 billion) in 2015. Otsuka welcomes you to visit its global website at https://www.otsuka.co.jp/en.

About Lundbeck

Lundbeck is a global pharmaceutical company specialized in brain diseases. For more than 70 years, we have been at the forefront of research within neuroscience. The key areas of focus are Alzheimer's disease, depression, Parkinson's disease and psychosis. An estimated 700 million people worldwide are living with brain disease and far too many suffer due to inadequate treatment, discrimination, a reduced number of working days, early retirement and other unnecessary consequences. Every day, we strive for improved treatment and a

better life for people living with brain disease – we call this Progress in Mind. Our approximately 5,500 employees in 57 countries are engaged in the entire value chain throughout research, development, production, marketing and sales. Our pipeline consists of several late-stage development programs and our products are available in more than 100 countries. We have research centers in China and Denmark and production facilities in China, Denmark, France and Italy. Lundbeck generated core revenue of DKK 14.6 billion in 2015 (EUR 2 billion; USD 2.2 billion). For additional information, we encourage you to visit our corporate site www.lundbeck.com and connect with us on Twitter at @Lundbeck. Lundbeck in the U.S. In the U.S., Lundbeck employs more than 800 people focused solely on accelerating therapies for brain diseases. With a special commitment to the lives of patients, families and caregivers, Lundbeck US actively engages in hundreds of initiatives each year that support our patient communities. To learn more, visit us at www.LundbeckUS.com and connect with us on Twitter at @LundbeckUS.

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