



FOR IMMEDIATE RELEASE

**U.S. FDA ACCEPTS FOR REVIEW SUPPLEMENTAL NEW DRUG APPLICATION
FOR DELTOID ADMINISTRATION OF ABILIFY MAINTENA[®] (aripiprazole)
EXTENDED-RELEASE INJECTABLE SUSPENSION**

Princeton, N.J. and Deerfield, Ill. – December 15, 2014 – Otsuka America Pharmaceutical, Inc. (OAPI) and Lundbeck today announced the U.S. Food and Drug Administration (FDA) has accepted for review a supplemental New Drug Application (sNDA) for a proposed new injection site—the deltoid muscle of the arm—for Abilify Maintena[®] (aripiprazole) for extended-release injectable suspension. If approved, healthcare providers will have both a gluteal and deltoid option for administering Abilify Maintena to patients with schizophrenia. Under the Prescription Drug User Fee Act (PDUFA), the FDA has set a target date of July 30, 2015 to complete its review.

About Abilify Maintena[®] (aripiprazole)

Abilify Maintena (aripiprazole once-monthly) is the first and only once-monthly injection of a dopamine D₂ partial agonist. It is available in the U.S. for the treatment of schizophrenia and in a number of European countries for maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole. In Canada it is available for the maintenance treatment of schizophrenia in stabilized adult patients and in Australia for maintenance of clinical improvement in the treatment of schizophrenia.

Abilify Maintena, an atypical antipsychotic, is an intramuscular depot formulation of aripiprazole. It is a sterile lyophilized powder that, when reconstituted with sterile water for injection, forms an injectable suspension that can be administered monthly. 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. 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. Depot formulations of antipsychotic agents provide patients with concentrations of active drug that remain at a therapeutic range for an extended period of time.^{1,2}

**IMPORTANT SAFETY INFORMATION for ABILIFY MAINTENA[®] (aripiprazole)
for extended-release injectable suspension**

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). Analyses of 17 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 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. Clinical monitoring of weight is recommended.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension. Abilify Maintena 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. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving Abilify Maintena. In such patients, consider discontinuation of Abilify Maintena at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions: 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 aripiprazole (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.

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

Pregnancy/Nursing: Based on animal data, may cause fetal harm. Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Please see accompanying [FULL PRESCRIBING INFORMATION](#), including Boxed WARNING, for ABILIFY MAINTENA.

About Schizophrenia

Schizophrenia is a disease characterized by a distortion in the process of thinking and of emotional responsiveness. It most commonly manifests as hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and is accompanied by significant social or occupational dysfunction. Onset of symptoms typically occurs in young adulthood and the condition is chronic, often requiring life-long treatment to mitigate symptoms. It has been estimated that schizophrenia affects approximately 1% of the adult population in the U.S., and approximately 24 million people worldwide.^{3,4} In the U.S., there are approximately 2.4 million adults with schizophrenia, prevalent equally in both genders.^{5,6} While there is no cure for the disease, symptoms and risk of relapse – the re-emergence or worsening of psychotic symptoms⁷ – can be managed in most patients with appropriate antipsychotic treatment.

About Otsuka America Pharmaceutical, Inc.

Otsuka America Pharmaceutical, Inc. (OAPI) is an innovative, fast-growing healthcare company that commercializes Otsuka-discovered and in-licensed products in the U.S., with a strong focus on neuroscience, oncology, cardio-renal and medical devices. For more information, visit www.otsuka-us.com.

OAPI is a subsidiary of Otsuka America, Inc. (OAI), a holding company established in the U.S. in 1989. OAI is wholly owned by Otsuka Pharmaceutical Co., Ltd., based in Japan. The Otsuka Group employs approximately 42,000 people globally and its products are available in more than

80 countries worldwide. Otsuka welcomes you to visit its global website at

<https://www.otsuka.co.jp/en/>.

About Lundbeck

Based in Deerfield, Ill., Lundbeck U.S. was formed in 2009 as a wholly-owned subsidiary of H. Lundbeck A/S in Denmark. With a focus on accelerating advances in brain disorders, employees are engaged in the research, development, production, marketing and sale of innovative therapies that fulfill unmet medical needs among people living with challenging and sometimes rare neurologic and psychiatric disorders. In its late-stage research pipeline, the company has neurology compounds under investigation for Alzheimer's disease, stroke and epilepsy, in addition to therapies in development for mental health disorders. With a special commitment to the lives of patients, families and caregivers, Lundbeck 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](https://twitter.com/LundbeckUS).

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Media Contacts:

Otsuka Contacts

U.S.

Rose Weldon

Otsuka America Pharmaceutical, Inc.

rose.weldon@otsuka-us.com

+1 609 524 6879, +1 215 801 7644 (cell)

Lundbeck Contacts

U.S.

Ashleigh Duchene

Lundbeck

aduc@lundbeck.com

+1 847 282 1164

December 2014 09US14EBC0163