U.S. FDA APPROVES DUAL-CHAMBER SYRINGE FOR ABILIFY MAINTENA® (aripiprazole) EXTENDED-RELEASE INJECTABLE SUSPENSION FOR THE TREATMENT OF SCHIZOPHRENIA

- Dual-chamber syringe offers healthcare providers more flexibility during patient office visits
- First of several anticipated product enhancements to Abilify Maintena

**Princeton, N.J. and Deerfield, Ill.** – September 29, 2014 – Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) and Lundbeck announced today that the U.S. Food and Drug Administration (FDA) has approved a new formulation of Abilify Maintena® (aripiprazole) for extended-release injectable suspension – a pre-filled dual-chamber syringe. Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia; efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials. The companies expect the dual-chamber syringe will be available in the U.S. in January 2015.

“Since March 2013, Abilify Maintena has been an important treatment option for people living with schizophrenia. Otsuka and Lundbeck continue to be committed to ongoing innovation to address the challenges associated with treating this population,” said Robert McQuade, Ph.D., Executive Vice President and Chief Strategic Officer of Otsuka. “With the approval of the dual-chamber syringe, we are pleased to introduce the first of several anticipated product enhancements that can simplify the delivery of care for patients receiving Abilify Maintena, as compared to the current formulation; and it offers healthcare providers a new, easier to use option during their office visits with patients.”

The Abilify Maintena dual-chamber syringe will be available in 300 mg and 400 mg doses for deep intramuscular gluteal injection only by healthcare professionals.
About Abilify Maintena® (aripiprazole)

Abilify Maintena (aripiprazole) for extended-release injectable suspension is indicated for the treatment of schizophrenia. Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia. It is the first and only once-monthly injection of a dopamine D₂ partial agonist and was approved by the U.S. Food and Drug Administration (FDA) on February 28, 2013.²³

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 one of the most important considerations in the management of schizophrenia – reducing the risk of relapse, or the re-emergence or 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.¹² Abilify Maintena became available for prescribing in the U.S. on March 18, 2013. Abilify Maintena is not approved for the treatment of patients with dementia-related psychosis.

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

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 (aripiprazole) 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. There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).

- **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

**Orthostatic Hypotension:** Aripiprazole may cause orthostatic hypotension. ABILIFY MAINTENA (aripiprazole) 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 (aripiprazole) 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 reaction:** The safety profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs. placebo, respectively, was:

- Akathisia (8% vs. 4%) in adult patients with schizophrenia.

**Injection Site Reactions:** In the open-label, stabilization phase of a study with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for ABILIFY MAINTENA-treated patients.

**Dystonia** is a class effect of antipsychotic drugs. 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 (aripiprazole) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Aripiprazole is excreted 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 Otsuka Pharmaceutical Development & Commercialization, Inc.

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) is an innovative, fast-growing healthcare company that discovers and develops new compounds that address unanswered medical needs and advance human health. With a strong focus on neuroscience, oncology, and cardio-renal treatments, OPDC is dedicated to improving the health and quality of human life. For more information, visit www.otsuka-us.com.

OPDC 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. 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 in the U.S.

Lundbeck in the U.S., headquartered in Deerfield, Illinois, is a wholly-owned subsidiary of H. Lundbeck A/S in Denmark. Globally, our mission is to help people suffering from psychiatric and neurologic disorders. To drive this mission in the U.S., nearly 800 employees are engaged in the research, development, production, marketing and sale of innovative specialty therapies that fulfill unmet medical needs. We see the person behind the disease and how it affects the lives of patients, families and caregivers. Lundbeck is actively involved with hundreds of local and national U.S. events each year that support our patient communities. To learn more, visit us at www.LundbeckUS.com and connect with us on Twitter at @LundbeckUS.

References


2. Prescribing Information. ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension, for intramuscular use. February 2013.

3. U.S. Food and Drug Administration (FDA). FDA Approved Drug Products: All approvals February 2013. Available at:

**Media Contacts:**

**Otsuka:**

**U.S.**

Rose Weldon  
Corporate Communications  
Otsuka America Pharmaceuticals, Inc.  
[rose.weldon@otsuka-us.com](mailto:rose.weldon@otsuka-us.com)  
+1 609 524 6879

**Lundbeck:**

**U.S.**

Ashleigh Duchene  
Lundbeck  
[aduc@lundbeck.com](mailto:aduc@lundbeck.com)  
+1 847 282 1164

September 2014 09US14EBC0126