



FOR IMMEDIATE RELEASE

FDA Approves Deltoid Injection Site for Abilify Maintena[®] (aripiprazole) for extended-release injectable suspension in the Treatment of Schizophrenia

- *Patients being treated for schizophrenia now have a new administration site option for Abilify Maintena*
- *Approval was based on data demonstrating pharmacokinetics, tolerability and safety of Abilify Maintena when injected in the deltoid muscle of the arm being comparable to gluteal administration*
- *The option for deltoid administration of Abilify Maintena provides patients and physicians more flexibility in the management and treatment of schizophrenia*

Princeton, N.J. and Deerfield, Ill. – JULY 30, 2015 – Otsuka America Pharmaceutical, Inc. (OAPI) and Lundbeck today announced that the U.S. Food and Drug Administration (FDA) has expanded the label of Abilify Maintena[®] (aripiprazole) for extended-release injectable suspension to include a new injection site, the deltoid muscle of the arm. Healthcare providers will now have the option for either a gluteal or deltoid injection site for administering Abilify Maintena to patients with schizophrenia.

Abilify Maintena is the first and only once-monthly injection of a dopamine D₂ partial agonist (the first injection is accompanied by 14 days of oral antipsychotic therapy) approved for the treatment of adults with schizophrenia. It was originally indicated for only gluteal injection when approved by the FDA in February 2013.^{1,2} The approval of the deltoid injection site was based on two studies that evaluated the safety and tolerability and pharmacokinetics of Abilify Maintena administered in the deltoid muscle compared to the gluteal muscle in adult patients with schizophrenia.^{1,3}

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“Having more choices and flexibility in the administration of Abilify Maintena for the treatment of schizophrenia may help strengthen the patient-physician alliance for the long-term management of the disease,” said study investigator David Walling, Ph.D., Chief Executive Officer and Principal Investigator, CNS Network. “It is important to offer an administration option for the deltoid muscle, in addition to the gluteal muscle, because some patients and physicians prefer the deltoid muscle site for injection.”

This new deltoid administration offering for Abilify Maintena is scheduled to be commercially available in the fall of 2015.

About the Clinical Trials^{1,3}

The pharmacokinetics, safety and tolerability of Abilify Maintena administered in the deltoid muscle compared to the gluteal muscle was evaluated in two, open-label studies in stable patients aged 18-64 years with a current diagnosis of schizophrenia. One study was a randomized, single-dose, parallel-arm, relative bioavailability study comparing the pharmacokinetic parameters of Abilify Maintena 400 mg after injection in the deltoid muscle of 17 patients, with the injection in the gluteal muscle of 18 patients. The second study was a multiple-dose, parallel-arm study designed to evaluate the safety and tolerability of Abilify Maintena 400 mg injections in the deltoid muscle, and to derive pharmacokinetic parameters following five monthly injections. In this study, 141 patients were randomized to the study and 138 received at least one dose of Abilify Maintena 400 mg injection either in the deltoid (N=71) or gluteal (N=67) muscle; subsequent doses were administered to all patients in the deltoid muscle. Of the patients who received at least one dose of Abilify Maintena, 97.1% of subjects had no dose adjustment; only four patients had a dose reduction to 300 mg.⁴

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. Furthermore, in the second study, multiple injections of Abilify Maintena 400 mg in the deltoid muscle resulted in comparable maximal- and minimal-plasma concentrations and comparable exposures of aripiprazole compared with injections in the gluteal muscle, as measured in earlier studies.

These data were presented earlier this year at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting in Miami, Florida.

About Abilify Maintena[®] (aripiprazole)

Abilify Maintena (aripiprazole) is available in the U.S. for the treatment of schizophrenia. Efficacy and safety for Abilify Maintena is supported by a short-term (12 weeks), randomized, double-blind, placebo-controlled trial in acutely relapsed adults, as well as a longer term (52 weeks) placebo-controlled, double-blind, randomized-withdrawal study for the maintenance treatment of schizophrenia.¹

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.^{5,6}

INDICATION

Abilify Maintena[®] (aripiprazole) 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.

See Full Prescribing Information for complete Boxed WARNING

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: 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. 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 – Non-Teratogenic Effects: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. 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 benefit justifies the potential risk 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.

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 [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 21 million people worldwide.^{7,8} In the U.S., there are approximately 2.4 million adults with schizophrenia, prevalent equally in both genders.^{8,9} While there is no cure for the disease, symptoms and risk of relapse – the re-emergence or worsening of psychotic symptoms¹⁰ – 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., a global healthcare company with the corporate philosophy: 'Otsuka-people creating new products for better health worldwide.'

Otsuka Pharmaceutical is a leading firm in the challenging area of mental health and also has products and research programs for several under-addressed diseases including tuberculosis, a significant global public health issue. These commitments illustrate more powerfully than words how Otsuka is a “big venture” company at heart, applying a youthful spirit of creativity in everything it does.

Otsuka Pharmaceutical and its affiliates employ approximately 30,000 people globally, and the company welcomes you to visit its global website at: <http://www.otsuka.co.jp/en/index.php>.

About Lundbeck

Based in Deerfield, Ill., Lundbeck US is an affiliate of H. Lundbeck A/S in Denmark, and focused solely on accelerating therapies for brain disorders. The company is 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 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).

References

1. Prescribing Information. ABILIFY MAINTENA[®] (aripiprazole) for extended-release injectable suspension, for intramuscular use. July 2015.

2. 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.
3. Peters-Strickland T., et al. Deltoid Injection of Aripiprazole Once-Monthly in the Treatment of Schizophrenia. Presented at the American Society of Clinical Psychopharmacology Annual Meeting (ASCP); 2015 June 22-25; Miami, Florida.
4. Data on File. ABIMAI-103
5. Kane J., et al. Aripiprazole Once-Monthly in the Acute Treatment of Schizophrenia: Findings From a 12-Week, Randomized, Double-Blind, Placebo-Controlled Study. *Journal of Clinical Psychiatry*. 2014;75 (11): 1254–1260.
6. Kane J., 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: 617-624.
7. Schizophrenia Fact Sheet. World Health Organization. 2014. Available at http://www.who.int/mental_health/management/schizophrenia/en/. Accessed on November 11, 2014.
8. National Institutes of Mental Health (NIMH). The Numbers Count: Mental Disorders in America. Available at <http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml>. Accessed May 14, 2013.
9. Mental Illness Facts and Numbers. National Alliance on Mental Illness. 2013. Available at: http://www.nami.org/factsheets/mentalillness_factsheet.pdf. Accessed October 29, 2014.
10. Almond, S., et al. Relapse in Schizophrenia: Costs, Clinical Outcomes and Quality of Life. *British Journal of Psychiatry*. 2004; 184: 346-351.

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