



ABILIFY MAINTENA[®] (aripiprazole) FOR EXTENDED-RELEASE INJECTABLE SUSPENSION APPROVED BY U.S. FDA FOR MAINTENANCE MONOTHERAPY TREATMENT OF BIPOLAR I DISORDER

- *First FDA approved, once-monthly, long-acting injectable for the maintenance monotherapy treatment of bipolar I disorder in adults^{1,2}*
- *New indication for ABILIFY MAINTENA is based on studies evaluating efficacy and safety in adult patients with bipolar I disorder¹*

(TOKYO, Japan & VALBY, Denmark, July 28, 2017) – Otsuka Pharmaceutical Co., Ltd. and H. Lundbeck A/S today announced ABILIFY MAINTENA[®] (aripiprazole) for extended-release injectable suspension was approved by the U.S. Food and Drug Administration for the maintenance monotherapy treatment of bipolar I disorder (BP-I) in adults.¹

ABILIFY MAINTENA is a once-monthly injectable formulation for intramuscular use created by Otsuka and has been co-developed and co-commercialized with Lundbeck. Based on Phase 3 study data, ABILIFY MAINTENA delayed the time to recurrence of any mood episode in adult patients experiencing a manic episode at screening compared to placebo.¹

“Bipolar I disorder is a recurrent chronic mental illness. ABILIFY MAINTENA provides healthcare professionals (HCPs) a new treatment option for their patients who have established tolerability with oral aripiprazole,” said Joseph Calabrese, MD, Director of the Mood Disorders Program at University Hospitals Cleveland Medical Center, and Professor of Psychiatry at Case Western Reserve University School of Medicine. “Receiving ABILIFY MAINTENA each month as prescribed and administered by a HCP, provides patients an opportunity to be free from taking their daily antipsychotic for bipolar I disorder; it is important to note that concomitant oral antipsychotic must be administered for 14 days after the first injection.”

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis. ABILIFY MAINTENA is contraindicated with a known hypersensitivity reaction to aripiprazole (see Important Safety Information below).

For more information about ABILIFY MAINTENA, please visit: <https://www.abilifymaintena.com/>.

About the Clinical Trial

The Phase 3 clinical trial supporting regulatory approval demonstrated the efficacy and safety of ABILIFY MAINTENA in the maintenance monotherapy treatment of BP-I. The study included patients who were experiencing a manic episode at trial entry and met DSM-IV-TR criteria for bipolar I disorder. In addition, patients had a history of at least one previous manic or mixed episode with manic symptoms of sufficient severity to require one of the following interventions: hospitalization and/or treatment with a mood stabilizer, and/or treatment with an antipsychotic agent. The clinical trial was a 52-week, double-blind, placebo-controlled, randomized withdrawal trial in adults with BP-I aged 18 to 65 years, who were stabilized with ABILIFY MAINTENA prior to randomization.¹ The primary endpoint demonstrated ABILIFY MAINTENA significantly delayed time to recurrence of any mood episode during a 52-week treatment study compared with

placebo.¹ The trial demonstrated significant differences between treatment groups in delaying time to recurrence of both manic and mixed episodes but no substantial difference in depressive mood episodes.¹

About ABILIFY MAINTENA® (aripiprazole)

ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension is an atypical antipsychotic for intramuscular use. It was created by Otsuka in Japan and has been co-developed and co-commercialized by the alliance between Otsuka and Lundbeck. ABILIFY MAINTENA was approved in the U.S. in 2013 for the treatment of adults with schizophrenia.¹ ABILIFY MAINTENA is a sterile lyophilized powder that when reconstituted with sterile water for injection, forms a suspension that can be administered by injection once a month (the initial injection is accompanied by an overlapping 14-day dosing of oral antipsychotic treatment). Subsequent doses of ABILIFY MAINTENA provide uninterrupted medication coverage for up to 30 days.¹ Depot formulations of antipsychotic agents provide patients with concentrations of active drug that remain at a therapeutic range for extended periods of time.¹⁻²

The most commonly observed adverse reactions with ABILIFY MAINTENA in patients with schizophrenia (incidence of 5 percent or greater and aripiprazole incidence at least twice that for placebo) were increased weight, akathisia, injection site pain, and sedation.¹

About Bipolar I Disorder

BP-I is a chronic mental illness with a 12-month and lifetime prevalence of 1.5 percent and 2.1 percent, respectively.^{3,4} People with BP-I experience one or more episodes of mania, and may have episodes of both mania and depression.^{3,5}

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

INDICATIONS

ABILIFY MAINTENA is an atypical antipsychotic indicated for:

- Treatment of schizophrenia in adults
- Maintenance monotherapy treatment of bipolar I disorder in adults

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 increased risk of death. 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): NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs including ABILIFY MAINTENA. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of ABILIFY MAINTENA, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, are believed to increase with duration of treatment and total cumulative dose of antipsychotic drugs. TD can develop after a relatively brief treatment period, even at low doses, or after discontinuation of treatment. Prescribing should be consistent with the need to minimize TD. If antipsychotic treatment is withdrawn, TD may remit, partially or completely.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of 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 have been reported less frequently. Prescribers should ask patients or their caregivers about 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.

Falls: Antipsychotics may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

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: Use ABILIFY MAINTENA with caution in patients who may experience conditions that increase body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

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. Avoid concomitant use of CYP3A4 inducers with ABILIFY MAINTENA for greater than 14 days. 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: The most commonly observed adverse reactions with ABILIFY MAINTENA in patients with schizophrenia (incidence $\geq 5\%$ and at least twice that for placebo) were increased weight, akathisia, injection site pain, and sedation.

Injection Site Reactions: In a short-term, clinical trial with ABILIFY MAINTENA in patients with schizophrenia treated with gluteal administered ABILIFY MAINTENA, the percent of patients reporting any injection site-related adverse reaction was 5.4%, and 0.6% for placebo. In an open label study of ABILIFY MAINTENA administered in the deltoid or gluteal muscle, injection site pain was observed 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. Consider the benefits and risks of ABILIFY MAINTENA and possible risks to the fetus when prescribing ABILIFY MAINTENA to a pregnant woman. Advise pregnant women of potential fetal risk.

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**.

REFERENCES:

1. ABILIFY MAINTENA[®] (aripiprazole) 2017 full prescribing information.
2. RISPERDAL CONSTA[®] (risperidone) 2017 prescribing information. Janssen.
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3. Bipolar Disorder. National Alliance on Mental Illness website. <https://www.nami.org/Learn-More/Mental-Health-Conditions/Bipolar-Disorder>. Accessed September 27, 2016.
4. Epidemiology of DSM-5 bipolar I disorder: Results from the national epidemiologic survey on alcohol and related conditions - III. Blanco C, Compton WM, Saha TD et al. J Psychiatr Res 84 (2017) 310-317.
5. National Institute of Mental Health. Serious Mental Illness (SMI) Among U.S. Adults.
<https://www.nimh.nih.gov/health/statistics/prevalence/serious-mental-illness-smi-among-us-adults.shtml>. Accessed June 10, 2017.

About Otsuka Pharmaceutical Co., Ltd.

Otsuka Pharmaceutical Company 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 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 Company is a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan. The Otsuka group of companies employed 45,000 people worldwide and had consolidated sales of approximately USD 11 billion (€ 9.9 billion) in 2016.

All Otsuka stories start by taking the road less travelled. Learn more about Otsuka Pharmaceutical Company on its global website at <https://www.otsuka.co.jp/en>. Learn more about Otsuka in the U.S. at www.otsuka-us.com and connect with us on Twitter at [@OtsukaUS](https://twitter.com/OtsukaUS).

About Lundbeck

H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in psychiatric and neurological disorders. For more than 70 years, we have been at the forefront of research within neuroscience. Our key areas of focus are depression, schizophrenia, Parkinson's disease and Alzheimer's disease.

An estimated 700 million people worldwide are living with psychiatric and neurological disorders 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 psychiatric and neurological disorders — we call this Progress in Mind.

Read more at www.lundbeck.com/global/about-us/progress-in-mind.

Our approximately 5,000 employees in 55 countries are engaged in the entire value chain throughout research, development, production, marketing and sales. Our pipeline consists of several late-stage development programmes and our products are available in more than 100 countries. We have research centres in China and Denmark and production facilities in China, Denmark, France and Italy. Lundbeck generated revenue of DKK 15.6 billion in 2016 (EUR 2.1 billion; USD 2.3 billion).

For additional information, we encourage you to visit our corporate site www.lundbeck.com and connect with us on Twitter at @Lundbeck.

About Lundbeck in the U.S.

In the U.S., Lundbeck employs nearly 900 people focused solely on accelerating therapies for brain disorders. With a special commitment to the lives of patients, families and caregivers, Lundbeck U.S. actively engages in hundreds of initiatives each year that support our patient communities.

For additional information, we encourage you to visit our corporate site www.lundbeckus.com and connect with us on Twitter at @LundbeckUS.

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