



## OTSUKA AND LUNDBECK PRESENT DATA AT ACNP ANNUAL MEETING ON LONG-ACTING INJECTABLE ARIPIPRAZOLE AS A POTENTIAL MAINTENANCE TREATMENT FOR BIPOLAR I DISORDER

- Phase III investigational study results present efficacy, tolerability and safety profile of long-acting injectable aripiprazole (ABILIFY MAINTENA®) in maintenance treatment of bipolar I disorder<sup>1</sup>
- Study data demonstrate long-acting injectable aripiprazole (ABILIFY MAINTENA) delayed time to recurrence of mood episodes in recently manic patients, as compared with placebo<sup>1</sup>

**PRINCETON, N.J. & DEERFIELD, Ill., December 7, 2016** - Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) and Lundbeck presented data on aripiprazole for extended-release injectable suspension for intramuscular use (hereinafter ABILIFY MAINTENA®) in the maintenance treatment of bipolar I disorder (BP-I) at the 2016 Annual Meeting of the American College of Neuropsychopharmacology (ACNP) in Hollywood, Florida.

Study data demonstrate that ABILIFY MAINTENA delayed time to recurrence of mood episodes in adult patients<sup>1</sup>. Treatment was compared with placebo and demonstrated a safety profile consistent with that observed with ABILIFY MAINTENA in the treatment of patients with schizophrenia.

“Patients with bipolar I disorder can benefit from a long acting injectable, which may help provide longer term stability in patients who have difficulty in taking a daily pill,” said Joseph Calabrese, M.D., Director of Mood Disorders Program at University Hospitals Cleveland Medical Center, and professor of psychiatry at Case Western Reserve University School of Medicine.

### Study results

Results were from a 52-week, phase III, double-blind, randomized withdrawal trial in adults with BP-I aged 18 to 65 years.<sup>1</sup> The primary endpoint demonstrated ABILIFY MAINTENA significantly delayed time to recurrence of any mood episode (see recurrence criteria below) during a 52-week treatment study compared with placebo (Hazard Ratio: 0.451; 95 percent Confidence Interval: [0.299-0.678];  $p < 0.0001$ ).<sup>1</sup> The key secondary endpoint, the proportion of patients with recurrence of any mood episode in the randomized phase, was significantly lower ( $p < 0.0001$ ) in the ABILIFY MAINTENA group (35/132; 26.5 percent) compared to the placebo group (68/133; 51.1 percent); results were driven primarily by reductions in manic recurrences.<sup>1</sup>

The study also demonstrated a statistically significant improvement vs. placebo on the Clinical Global Impression – Bipolar Version – Severity (CGI-BP-S) Mania Score ( $p = 0.0011$ ) and a time to hospitalization that was significantly delayed in participants randomized to ABILIFY MAINTENA vs. placebo ( $p = 0.0002$ ; secondary endpoints, see below).<sup>1</sup> Serious adverse events in the randomized phase were reported by 10/132 (7.6 percent) patients in the ABILIFY MAINTENA group vs. 25/133 (18.8 percent) patients in the placebo group. Treatment emergent adverse events (TEAEs) in the randomized phase were 101/132 (76.5 percent) on ABILIFY MAINTENA and 107/133 (80.5 percent) on placebo.<sup>1</sup>

### About the Study

Patients in the “*Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study*” were required to be experiencing a manic episode (per DSM-IV-TR criteria) with a Young-Mania Rating Scale (YMRS) total score  $\geq 20$  at study entry, as well as at least one previous manic or mixed episode requiring hospitalization or treatment with a mood stabilizer or antipsychotic agent.<sup>1</sup> The

study was composed of multiple phases: following screening for eligibility, subjects entered a conversion phase to oral aripiprazole monotherapy, if needed, followed by an oral aripiprazole stabilization phase, a single-blind ABILIFY MAINTENA stabilization phase, and, a double-blind, placebo-controlled randomized withdrawal phase. The primary endpoint was the time from randomization to recurrence of any mood episode defined by any of the following criteria: hospitalization for any mood episode, YMRS total score  $\geq 15$ , Montgomery Asberg Depression Rating Scale total score  $\geq 15$ , Clinical Global Impression – Bipolar Version-Severity (CGI-BP-S) score  $>4$ , serious treatment-emergent adverse event (TEAE) of disease worsening, discontinuation due to lack of efficacy/disease worsening, clinical worsening with need for pharmacological treatment of symptoms, or active suicidality.<sup>1</sup>

The proportion of patients with recurrence of any mood episode was the key secondary endpoint.<sup>1</sup> Other secondary endpoints included: 1) adjusted mean change from baseline to week 52 in CGI-BP-S mania scores was significantly better with ABILIFY MAINTENA vs. placebo (least squares mean difference:  $-0.43$ ; 95% CI  $[-0.69$  to  $-0.17]$ ;  $P=0.0011$ ); and 2) time to recurrence as defined by hospitalization for a mood disorder was delayed with ABILIFY MAINTENA vs. placebo (Hazard Ratio: 0.137; 95 percent Confidence Interval:  $[0.040-0.465]$ ;  $p=0.0002$ ).<sup>1</sup>

ABILIFY MAINTENA exhibited a tolerability profile in patients with bipolar I disorder similar to that in treatment of patients with schizophrenia. During the ABILIFY MAINTENA stabilization phase, the TEAEs ( $\geq 5$  percent) were akathisia (17.4 percent), weight increased (11.1 percent), insomnia (9.6 percent), anxiety (7.1 percent), restlessness (5.6 percent), fatigue (5.2 percent) and nasopharyngitis (5.2 percent).<sup>1</sup> In the randomized phase, specific TEAEs reported by greater than or equal to 5 percent of patients and greater in the ABILIFY MAINTENA group than in the placebo group respectively, were increased weight (23.5 percent vs. 18.0 percent), akathisia (21.2 percent vs. 12.8 percent), insomnia (7.6 percent vs. 7.5 percent) and anxiety (6.8 percent vs. 4.5 percent).<sup>1</sup>

### About ABILIFY MAINTENA<sup>®</sup> (long-acting injectable aripiprazole)

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.<sup>2</sup> 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.<sup>3</sup>

ABILIFY MAINTENA, an atypical antipsychotic, is an intramuscular depot formulation of aripiprazole.<sup>3</sup> It is a sterile lyophilized powder that, when reconstituted with sterile water for injection, forms an injectable suspension that can be administered monthly.<sup>3</sup> 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.<sup>3</sup> 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.<sup>3</sup> Depot formulations of antipsychotic agents provide patients with concentrations of active drug that remain at a therapeutic range for an extended period of time.<sup>4,5</sup>

### About Bipolar I Disorder

Bipolar I disorder is a chronic mental illness.<sup>6</sup> People with bipolar I disorder 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 bipolar I disorder diagnosis.<sup>6</sup> The lifetime prevalence estimate of bipolar I disorder in the U.S. is 1.0 percent and 12-month prevalence is 0.6 percent.<sup>7</sup> If left untreated, the manic and depressive symptoms may get worse.<sup>6</sup>

## 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<sup>3</sup>) 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](http://www.fda.gov/medwatch)).

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

### About Otsuka Pharmaceutical Development & Commercialization, Inc.

Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) is an innovative, fast-growing healthcare company that discovers and develops new compounds that address unanswered medical needs and advance human health. With a 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](http://www.otsuka-us.com) and follow us on Twitter at @OtsukaUS. 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 [www.otsuka.com](http://www.otsuka.com).

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

Lundbeck 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 research 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.

Our approximately 5,000 employees in 57 countries are engaged in the entire value chain throughout research, development, manufacturing, 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).

In the U.S., Lundbeck employs nearly 1,000 people focused solely on accelerating therapies for brain disorders, including epilepsy. 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](http://www.lundbeckus.com) and connect with us on Twitter at @LundbeckUS.

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### Safe Harbor/Forward-Looking Statements

The above information contains forward-looking statements that provide our expectations or forecasts of future events such as new product introductions, product approvals and financial performance.

Such forward-looking statements are subject to risks, uncertainties and inaccurate assumptions. This may cause actual results to differ materially from expectations and it may cause any or all of our forward-looking statements here or in other publications to be wrong. Factors that may affect future results include interest rate and currency exchange rate fluctuations, delay or failure of development projects, production problems, unexpected contract breaches or terminations, government-mandated or market-driven price decreases for Lundbeck's products, introduction of competing products, Lundbeck's ability to successfully market both new and existing products, exposure to product liability and other lawsuits, changes in reimbursement rules and governmental laws and related interpretation thereof, and unexpected growth in costs and expenses.

Certain assumptions made by Lundbeck are required by Danish Securities Law for full disclosure of material corporate information. Some assumptions, including assumptions relating to sales associated with product that is prescribed for unapproved uses, are made taking into account past performances of other similar drugs for similar disease states or past performance of the same drug in other regions where the product is currently marketed. It is important to note that although physicians may, as part of their freedom to practice medicine in the US, prescribe approved drugs for any use they deem appropriate, including unapproved uses, at Lundbeck, promotion of unapproved uses is strictly prohibited.

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- <sup>1</sup> Calabrese J., et al. (2016 December). *Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study*. Poster session at the Annual Meeting of the American College of Neuropsychopharmacology, Hollywood, FL.
- <sup>2</sup> Drug Approval Reports. U.S. Food and Drug Administration (FDA). 2013. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2013/202971Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2013/202971Orig1s000ltr.pdf). Accessed November 11, 2014.
- <sup>3</sup> ABILIFY MAINTENA (aripiprazole) 2016 Full Prescribing Information. Tokyo: Otsuka Pharmaceutical Co., Ltd.
- <sup>4</sup> 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.
- <sup>5</sup> Patel MX, et. Al. Why aren't depot antipsychotics prescribed more often and what can be done about it? *Advances in Psychiatric Treatment*. 2005; (11) 203-213
- <sup>6</sup> Bipolar Disorder. National Alliance on Mental Illness website. <http://www.nami.org/Learn-More/Mental-Health-Conditions/Bipolar-Disorder>. Accessed September 27, 2016.
- <sup>7</sup> Merikangas, KR, et. Al. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2007; 64(5) 543-552.