U.S. FDA APPROVES THE LABELING UPDATE OF ABILIFY MAINTENA® (ARIPIPRAZOLE) FOR EXTENDED-RELEASE INJECTABLE SUSPENSION TO DESCRIBE NEW CLINICAL DATA FOR THE TREATMENT OF ACUTELY RELAPSED ADULTS WITH SCHIZOPHRENIA

- Labeling update provides description of controlled clinical study of Abilify Maintena for treating adult patients experiencing acute relapses of schizophrenia
- Approval was based on Abilify Maintena demonstrating efficacy, tolerability and safety in a 12-week study in acutely relapsed adults with schizophrenia
- Pivotal efficacy results were published in the November print edition of The Journal of Clinical Psychiatry

Tokyo, Japan and Valby, Denmark – December 6, 2014 – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announced that the U.S. Food and Drug Administration (FDA) approved the labeling update of Abilify Maintena® (aripiprazole) for extended-release injectable suspension. The approval was based on results from a controlled clinical study of acutely relapsed adults with schizophrenia. Efficacy was demonstrated in a 12-week randomized, double-blind, placebo-controlled study, which showed treatment with Abilify Maintena (with concomitant oral aripiprazole for the first two weeks) significantly improved symptoms with an acceptable safety and tolerability profile in adult patients experiencing an acute relapse of schizophrenia.¹ These data were published in the November print edition of The Journal of Clinical Psychiatry.²

Abilify Maintena, an atypical antipsychotic, was first approved by the FDA in February 2013 for intramuscular (gluteal) use for the treatment of schizophrenia. Efficacy was demonstrated in a placebo-controlled, randomized withdrawal maintenance trial in adult patients with schizophrenia, and additional support for efficacy was derived from oral aripiprazole trials.¹³
“An acute exacerbation of psychotic symptoms, also referred to as disease relapse, is a key consideration in the management of schizophrenia, and can occur when a patient no longer responds to or stops taking antipsychotic medication,” said study investigator John M. Kane, M.D., Chairman of Psychiatry, The Zucker Hillside Hospital, and Vice President, Behavioral Health Services, North Shore-LIJ Health System. “These data—and the updated product labeling—confirm the utility of Abilify Maintena in acutely relapsed adult patients, giving physicians an option to consider for both the initial and ongoing treatment of patients with schizophrenia.”

Clinical Trial Results

Efficacy of Abilify Maintena (aripiprazole) for the treatment of acutely relapsed adults with schizophrenia was demonstrated in a 12-week multicenter, randomized, double-blind, placebo-controlled trial. The primary measure used for assessing psychiatric signs and symptoms was the Positive and Negative Syndrome Scale (PANSS), a 30-item scale that measures positive and negative symptoms of schizophrenia and general psychopathology, using a rating scale of 1 (absent) to 7 (extreme); the primary endpoint was pre-specified to be measured as the change from baseline to week 10 of treatment. All patients entering the trial were inpatients who met DSM-IV-TR criteria for schizophrenia and experienced an acute psychotic episode as defined by both PANSS total score of 80 or higher, and a PANSS score greater than 4 on each of four specific psychotic symptoms (conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, unusual thought content). Patients had a mean PANSS total score of 103 at study entry.1

A total of 339 patients received double-blind treatment with Abilify Maintena 400 mg (n=167) or placebo (n=172), with 64.3% (Abilify Maintena) and 49.4% (placebo) of patients completing 10 weeks of treatment. The primary efficacy outcome was change from baseline to 10-week endpoint in PANSS total score and demonstrated greater improvement with Abilify Maintena than with placebo (-26.8 vs. -11.7, respectively, p<0.0001); statistically significant improvements with Abilify Maintena were shown at all time points measured from week 1-12.1 The key secondary efficacy outcome was change from baseline to 10-week endpoint in Clinical Global Impression Severity of Illness Scale (CGI-S) score and also showed statistically greater improvement with Abilify Maintena than with placebo (-1.4 vs. -0.6, respectively, p<0.0001).12

Safety of Abilify Maintena

The overall safety and tolerability profile of Abilify Maintena in this study was generally consistent with
that observed in previous double-blind phase III studies.\textsuperscript{4,5} The most common reason for discontinuation at week 10 was patient withdrawal of consent in the Abilify Maintena group (19\% vs. 9\% for placebo) and lack of efficacy in the placebo group (29\% vs. 7\% for Abilify Maintena). Discontinuations due to adverse events occurred in 4\% of patients receiving Abilify Maintena vs. 8\% of patients receiving placebo.\textsuperscript{2} Common adverse reactions (≥5\% and with an incidence at least 2-times greater than placebo) were increased weight (16.8\% vs. 7.0\%), akathisia (11.4\% vs. 3.5\%), sedation (5.4\% vs. 1.2\%) and injection site pain (5.4\% vs. 0.6\%).\textsuperscript{1}

**About Abilify Maintena® (aripiprazole)**

Abilify Maintena (aripiprazole once-monthly) is the first and only once-monthly injection of a dopamine D\textsubscript{2} 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.\textsuperscript{2,4}

**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 phosphokinese, 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 reaction:** 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% of 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. In the U.S., there are approximately 2.4 million adults with schizophrenia, prevalent equally in both genders. While there is no cure for the disease, symptoms and risk of relapse – the re-emergence or worsening of psychotic symptoms – can be managed in most patients with appropriate antipsychotic treatment.

**About Otsuka Pharmaceutical Co., Ltd.**
Otsuka Pharmaceutical Co., Ltd. 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 and original 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 leading firm 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 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 Co., Ltd., which employees approximately 28,700 people worldwide, is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group that is headquartered in Tokyo, Japan. The Otsuka Group has business operations in 26 countries and regions around the world, with consolidated sales of approximately USD 14.1 billion for fiscal year 2013 (4/1/2013-3/31/2014.) Otsuka Pharmaceutical welcomes you to visit its global website at https://www.otsuka.co.jp/en.

About Lundbeck
H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in brain diseases. For more than 50 years, we have been at the forefront of research within neuroscience. Our key areas of focus are alcohol dependence, Alzheimer's disease, bipolar disorder, depression/anxiety, epilepsy, Huntington's disease, Parkinson's disease, schizophrenia, stroke and symptomatic neurogenic orthostatic hypotension (NOH).

An estimated 700 million people worldwide are living with brain disease 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 brain disease — we call this Progress in Mind.

Our approximately 6,000 employees in 57 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, Denmark and the United States and production facilities in China, Denmark, France and Italy. Lundbeck generated revenue of approximately DKK 15.3 billion in 2013 (EUR 2.1 billion; USD 2.7 billion).

Lundbeck's shares are listed on the stock exchange in Copenhagen under the symbol "LUN". Lundbeck has a sponsored Level 1 ADR program listed in the US (OTC) under the symbol "HLUYY". For additional information, we encourage you to visit our corporate site www.lundbeck.com.

**References:**

1. Prescribing Information. ABILIFY MAINTENA® (aripiprazole) for extended-release injectable suspension, for intramuscular use. December 2014.


Otsuka Contacts

Media:

NORTH AMERICA
Rose Weldon
Otsuka America Pharmaceutical, Inc.
rose.weldon@otsuka-us.com
+1 609 524 6879, +1 215 801 7644 (cell)

JAPAN/ASIA
Jeffrey Gilbert
Otsuka Pharmaceutical Co., Ltd.
gilbert.jeffrey@otsuka.co.jp
+81 3 6361 7379, +81 80 8728 6039 (cell)

EUROPE
Alison Ross
Otsuka Pharmaceutical Europe, Ltd.
+44 7768 337 128
Aross@otsuka-europe.com

Investors:
Yoko Ishii
Investor Relations Dept.
Otsuka Holdings Co, Ltd.
Ishiiyo@Otsuka.jp
+81 3 6361 7411

Lundbeck Contacts

Media:

U.S.
Ashleigh Duchene
Lundbeck
aduc@lundbeck.com
+1 847 282 1164

EUROPE
Mads Kronborg
Lundbeck
mavk@lundbeck.com
+45 36 43 28 51
Investors:

Palle Holm Olesen
Chief Specialist, Investor Relations
palo@lundbeck.com
+45 36 43 24 26

Jens Høyer
Specialist, Investor Relations
JSHR@Lundbeck.com
+45 36 43 33 86