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ABILIFY[®] (aripiprazole) Approved for Maintenance Treatment of Bipolar I Disorder as an Adjunct to Either Lithium or Valproate

Data from 52-week maintenance trial showed superiority of adjunctive ABILIFY versus adjunctive placebo on primary study endpoint

PRINCETON, NJ and TOKYO, JAPAN, February 16, 2011 – [Bristol-Myers Squibb Company](#) (NYSE: BMY) and [Otsuka Pharmaceutical Co., Ltd.](#), a wholly owned direct subsidiary of Otsuka Holdings Co., Ltd., announced today that the U.S. Food and Drug Administration (FDA) has approved [ABILIFY[®]](#) (aripiprazole) as an adjunct to the mood stabilizers lithium or valproate for the maintenance treatment of Bipolar I Disorder.

ABILIFY was approved as an adjunct to lithium or valproate for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder in May 2008. ABILIFY is also approved as monotherapy for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder and for the maintenance treatment of Bipolar I Disorder. ABILIFY has a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis. Elderly patients treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

“Patients with Bipolar I Disorder often experience cycles of severe mood swings rather than a single episode¹,” said John Tsai, M.D., vice president, U.S. Medical, Bristol-Myers Squibb. “Because Bipolar Disorder is a lifelong and recurrent illness, this labeling update provides physicians with the option to prescribe ABILIFY as an add-on to either lithium or valproate as a long-term treatment to help manage symptoms of Bipolar I Disorder. Patients

should be periodically reassessed by their physician to determine the continued need for maintenance treatment.”

“Otsuka remains committed to developing products that are able to meet their fullest potential while helping physicians provide effective care for their patients,” said William H. Carson, M.D., President and CEO, Otsuka Pharmaceutical Development and Commercialization, Inc. “By updating the label to include maintenance treatment with ABILIFY as an add-on to lithium or valproate for patients with Bipolar I Disorder, we are helping to provide more options to physicians.”

The new indication is based on results from a 52-week maintenance trial of ABILIFY® (aripiprazole) and lithium or valproate in patients meeting DSM-IV criteria for Bipolar I Disorder. In this study, adjunctive ABILIFY was superior to adjunctive placebo on the primary study endpoint of time from randomization to relapse to any mood event. Mood events were defined as hospitalization for a manic, mixed or depressive episode, study discontinuation due to lack of efficacy (accompanied by Y-MRS and/or MADRS score >16)*, or a serious adverse event of worsening disease (accompanied by Y-MRS and/or MADRS score >16).

Through 52 weeks, the most commonly observed treatment-emergent adverse event associated with adjunctive ABILIFY and lithium or valproate (incidence $\geq 5\%$ and at least twice that of adjunctive placebo) in patients with Bipolar I Disorder was tremor (adjunctive ABILIFY: 6.0%; adjunctive placebo: 2.4%).

Study Design

This randomized, double-blind, placebo-controlled study enrolled adult patients meeting DSM-IV criteria for Bipolar I Disorder, who experienced a recent manic or mixed episode and who had a history of one or more manic or mixed episodes of sufficient severity to require hospitalization and/or treatment with a mood stabilizer or antipsychotic.

In this study, patients were initiated on open-label lithium (0.6 mEq/L to 1.0 mEq/L) or valproate (50 $\mu\text{g/mL}$ to 125 $\mu\text{g/mL}$) at therapeutic serum levels, and remained on stable doses for two weeks. After two weeks, patients who demonstrated an inadequate response (Y-MRS total score ≥ 16 and $\leq 35\%$ improvement on the Y-MRS total score) to lithium or valproate alone

* The Y-MRS, or Young-Mania Rating Scale, and the MADRS, or Montgomery-Åsberg Depression Rating Scale, are diagnostic questionnaires used to measure the severity of manic and depressive episodes, respectively.

received ABILIFY as adjunctive therapy with a starting dose of 15 mg/day, and the option to increase to 30 mg/day or reduce to 10 mg/day as early as day four. After 12 consecutive weeks of stability (Y-MRS and MADRS total scores ≤ 12) on adjunctive ABILIFY and lithium or valproate, 337 patients were randomized in a double-blind fashion to receive either the same dose of ABILIFY and lithium or valproate as they received at the end of the stabilization period or placebo and lithium or valproate. Patients were then monitored for manic, mixed or depressive relapse for a maximum of 52 weeks. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the ABILIFY group and 43 were from the placebo group. The number of observed manic episodes in the ABILIFY[®] (aripiprazole) group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (14) was similar to that in the placebo group (18).

About ABILIFY[®] (aripiprazole)

Discovered by Otsuka Pharmaceutical Co., Ltd. and jointly developed and commercialized by Otsuka and Bristol-Myers Squibb, ABILIFY is the first and only available dopamine partial agonist and is indicated for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults and pediatric patients (ages 10-17), the maintenance treatment of Bipolar I Disorder, treatment of Schizophrenia in adults and adolescents (ages 13-17), and as an adjunctive treatment to an antidepressant in adults with Major Depressive Disorder who have an inadequate response to antidepressant therapy. ABILIFY Tablets are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg strengths.

About Bipolar Disorder

Different from the normal ups and downs that everyone goes through, the symptoms of bipolar disorder are severe.² People who have this illness tend to experience extreme mood swings, along with other specific symptoms and behaviors.³ The classic form of the illness is called Bipolar I Disorder which affects approximately one percent of the population in the U.S.
1,4

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY[®] (aripiprazole)

INDICATIONS:

ABILIFY is indicated for:

- Acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and as an adjunct to lithium or valproate for adults and pediatrics 10 to 17 years of age
- Maintenance treatment of Bipolar I Disorder, both as monotherapy and as an adjunct to lithium or valproate
- Use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Treatment of Schizophrenia in adults and in adolescents 13 to 17 years of age
- Treatment of irritability associated with Autistic Disorder in pediatric patients 6 to 17 years of age

Special Considerations for Pediatric Uses:

Treatment for pediatric patients should be initiated only after a thorough diagnostic evaluation and careful consideration of the risks and benefits of treatment. Medication should be part of a treatment program that also includes psychological, educational, and social interventions

ABILIFY[®] (aripiprazole) Injection is indicated for:

- Acute treatment of agitation associated with Schizophrenia or Bipolar Disorder, manic or mixed in adults

IMPORTANT SAFETY INFORMATION

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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS

Contraindication – Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

- **Cerebrovascular Adverse Events, Including Stroke** – Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY
- **Neuroleptic Malignant Syndrome (NMS)** – As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems
- **Tardive Dyskinesia (TD)** – The risk of developing TD 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. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn
- **Hyperglycemia and Diabetes Mellitus** – Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY® (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

Orthostatic Hypotension – ABILIFY may be associated with 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 with antipsychotics, including ABILIFY. Patients with history of a clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions – As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold (eg, Alzheimer’s dementia)

Potential for Cognitive and Motor Impairment – Like other antipsychotics, ABILIFY may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

Body Temperature Regulation – Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Suicide – The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Dysphagia – Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY® (aripiprazole); use caution in patients at risk for aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia.

Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with Major Depressive Disorder.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

Commonly observed adverse reactions ($\geq 5\%$ incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Adult patients with Major Depressive Disorder (adjunctive treatment to antidepressant therapy): akathisia (25% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)
- Adult patients (monotherapy) with Bipolar Mania: akathisia (13% vs 4%), sedation (8% vs 3%), tremor (6% vs 3%), restlessness (6% vs 3%), and extrapyramidal disorder (5% vs 2%)
- Adult patients (adjunctive therapy with lithium or valproate) with Bipolar Mania: akathisia (19% vs 5%), insomnia (8% vs 4%), and extrapyramidal disorder (5% vs 1%)
- Pediatric patients (10 to 17 years) with Bipolar Mania: somnolence (23% vs 3%), extrapyramidal disorder (20% vs 3%), fatigue (11% vs 4%), nausea (11% vs 4%), akathisia

(10% vs 2%), blurred vision (8% vs 0%), salivary hypersecretion (6% vs 0%), and dizziness (5% vs 1%)

- Adult patients with Schizophrenia: akathisia (8% vs 4%)
- Pediatric patients (13 to 17 years) with Schizophrenia: extrapyramidal disorder (17% vs 5%), somnolence (16% vs 6%), and tremor (7% vs 2%)
- Pediatric patients (6 to 17 years) with irritability associated with Autistic Disorder: sedation (21% vs 4%), fatigue (17% vs 2%), vomiting (14% vs 7%), somnolence (10%; vs 4%), tremor (10% vs 0%), pyrexia (9% vs 1%), drooling (9% vs 0%), decreased appetite (7% vs 2%), salivary hypersecretion (6% vs 1%), extrapyramidal disorder (6% vs 0%), and lethargy (5% vs 0%)
- Adult patients with agitation associated with Schizophrenia or Bipolar Mania: nausea (9% vs 3%)

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: 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® (aripiprazole) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please see FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, and Medication Guide for ABILIFY® (aripiprazole) at www.abilify.com.

About Otsuka Pharmaceutical Co., Ltd. and Bristol-Myers Squibb

Otsuka Pharmaceutical Co., Ltd. and Bristol-Myers Squibb are collaborative partners in the development and commercialization of ABILIFY in the United States and major European countries.

ABILIFY was discovered by Otsuka Pharmaceutical Co., Ltd. Founded in 1964, 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 consumer products for the maintenance of everyday health. Otsuka is committed to being a corporation that creates global value, adhering to the high ethical standards required of a company involved in human health and life, maintaining a dynamic corporate culture, and working in harmony with local communities and the natural environment.

Otsuka Pharmaceutical Co., Ltd. is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group. The Otsuka Group comprises 145 companies and employs approximately 39,000 people in 23 countries and regions worldwide. Otsuka and its consolidated subsidiaries earned ¥1,084.2 billion (approx. US \$11.7 billion) in annual revenues in fiscal 2009.

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases.

Visit Otsuka Pharmaceutical Co., Ltd. at: <http://www.otsuka.co.jp/en/>

Visit Bristol-Myers Squibb at: www.bms.com

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¹ Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington DC, American Psychiatric Association, 2000.

² National Institute of Mental Health Web site. Bipolar disorder. Available at: <http://www.nimh.nih.gov/publicat/bipolar.cfm#intro>. Accessed March 2010.

³ National Institute of Mental Health. Bipolar disorder. Bethesda (MD): National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services; Printed 2001, Reprinted September 2002. (NIH Publication No 02-3679).

⁴ Merikangas, K., Akiskal, H.S., Angst, J., Greenberg, M.S., Hirschfeld, R.M.A., Petukhova, M., Kessler, R.C., 2007. Lifetime and 12month prevalence of bipolar spectrum disorder in the National Comorbidity Survey-Replication. *Arch. Gen. Psychiatry* 65, 543–552.