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**U.S. FOOD AND DRUG ADMINISTRATION APPROVES ABILIFY<sup>®</sup> (aripiprazole) FOR THE ACUTE TREATMENT OF MANIC AND MIXED EPISODES ASSOCIATED WITH BIPOLAR I DISORDER IN PEDIATRIC PATIENTS (10 TO 17 YEARS OF AGE)**

***- Otsuka-sponsored Study Evaluated Use of ABILIFY In This Patient Population -***

TOKYO, JAPAN and PRINCETON, NJ, February 29, 2008 – Otsuka Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Company (NYSE: BMY) announced today that the U.S. Food and Drug Administration (FDA) approved the supplemental New Drug Application for ABILIFY<sup>®</sup> (aripiprazole) for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder, with or without psychotic features in pediatric patients (10 to 17 years old). ABILIFY has been approved for the acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults since September 2004 and March 2005, respectively.

“Pediatric bipolar illness is a serious condition,” said Christoph Correll, M.D., Medical Director, Recognition and Prevention Program, The Zucker Hillside Hospital and Assistant Professor of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Glen Oaks, New York. “The availability of an additional treatment option that can help guide decisions in managing Bipolar I Disorder in children and adolescents is welcome news.”

The approval is based on results from a four-week, multicenter, randomized, double-blind, placebo-controlled study in pediatric patients (10 to 17 years old) with Bipolar I Disorder that demonstrated efficacy with ABILIFY compared to placebo on the primary efficacy endpoint, mean change from baseline to Week 4 on the Young-Mania Rating Scale (Y-MRS) Total Score.

“We are pleased that the FDA has approved ABILIFY® (aripiprazole) to treat pediatric patients aged 10 to 17 years suffering from Bipolar I Disorder,” said Taro Iwamoto, Ph.D., Chief Executive Officer, President and Chief Operating Officer, Otsuka Pharmaceutical Development and Commercialization, Inc. “The approval of this new indication for ABILIFY provides clinicians with expanded treatment options that can help address the therapeutic needs of this population.”

“We are committed to developing innovative new medicines to their fullest potential,” said Elliott Sigal, M.D., Ph.D., Executive Vice President, Chief Scientific Officer and President, Research and Development, Bristol-Myers Squibb. “Expanding the clinical use of an important therapy such as ABILIFY gives pediatric patients with Bipolar I Disorder and their caregivers a new treatment option in their fight against this serious disease.”

### **Clinical Trial Design and Findings**

These findings are from a four-week, multicenter, randomized, double-blind, placebo-controlled study, which evaluated the efficacy and safety of ABILIFY in 296 pediatric patients (10 to 17 years old) with a *DSM-IV* diagnosis of Bipolar I Disorder, manic or mixed episodes, with or without psychotic features. Diagnosis was made by a trained child and adolescent psychiatrist and confirmed by a separate diagnostic interview. This study was conducted on an outpatient basis with the possibility of inpatient hospitalization, as needed. This clinical trial was sponsored by Otsuka Pharmaceutical Co., Ltd. and its U.S. subsidiary, Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ) with enrollment at 54 U.S. centers.

After a screening period of up to four weeks, pediatric patients (10 to 17 years old) who scored greater than or equal to 20 on the Y-MRS\* were randomly assigned to receive one of two fixed doses of ABILIFY [10 mg/day (n=98) or 30 mg/day (n=99)] or placebo (n=99). ABILIFY was initiated at a starting dose of 2 mg/day and titrated to the target dose of 10 mg/day or 30 mg/day.

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\* The Y-MRS is a standard measure that is an 11-item rating scale used by healthcare providers to assess the scope and severity of manic symptoms.<sup>1</sup> Y-MRS Total Scores range from 0 (no manic symptoms) to 60 (severe mania).<sup>2</sup>

<sup>1</sup> Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry*. 1978; 133:429-435.

<sup>2</sup> Rush AJ, et al. *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association;2000.

The primary efficacy endpoint was the mean change in the Y-MRS Total Score from baseline to Week 4. Safety evaluations included incidence of adverse reactions, discontinuation due to adverse reactions, laboratory measures and body weight.

For the primary endpoint, both doses of ABILIFY<sup>®</sup> (aripiprazole) demonstrated statistically significant improvement in symptoms when compared to placebo (p-value less than 0.0001) as measured by the mean change from baseline to endpoint (Week 4) on the Y-MRS Total Score. The efficacy of ABILIFY for the maintenance treatment of Bipolar I Disorder in the pediatric population has not been evaluated.

Approximately 80% of patients completed the four-week study (ABILIFY 10 mg: 86%; ABILIFY 30 mg: 78%; placebo: 77%). There was a low rate of discontinuation due to adverse reactions at Week 4 (ABILIFY: 7%; placebo: 2%).

During the study, the most commonly observed adverse reactions (greater than or equal to 5% in combined ABILIFY groups and at least twice the rate of placebo) associated with ABILIFY were: somnolence (ABILIFY: 23%; placebo: 3%), extrapyramidal disorder (ABILIFY: 20%; placebo: 3%), fatigue (ABILIFY: 11%; placebo: 4%), nausea (ABILIFY: 11%; placebo: 4%), akathisia (ABILIFY: 10%; placebo: 2%), blurred vision (ABILIFY: 8%; placebo: 0%), salivary hypersecretion (ABILIFY: 6%; placebo: 0%) and dizziness (ABILIFY: 5%; placebo: 1%). Four common adverse reactions had a possible dose-response relationship at Week 4: extrapyramidal disorder (ABILIFY 10 mg: 12.2%; ABILIFY 30 mg: 27.3%; placebo: 3.1%), somnolence (ABILIFY 10 mg: 19.4%; ABILIFY 30 mg: 26.3%; placebo: 3.1%), akathisia (ABILIFY 10 mg: 8.2%; ABILIFY 30 mg: 11.1%; placebo: 2.1%) and salivary hypersecretion (ABILIFY 10 mg: 3.1%; ABILIFY 30 mg: 8.1%; placebo: 0%). Children and adolescents might be more sensitive than adults in developing antipsychotic-related adverse events.<sup>1</sup>

In the study, weight gain greater than or equal to 7% change from baseline was seen in 3.2%, 9.4% and 3.3% for the ABILIFY 10 mg, ABILIFY 30 mg and placebo groups, respectively. The mean change from baseline to Week 4 in body weight was 0.6 kilograms (kg) for ABILIFY 10 mg, 0.9 kg for ABILIFY 30 mg and 0.5 kg for placebo.

In this study, ABILIFY demonstrated no clinically important differences on prolactin and the following metabolic parameters: triglyceride, HDL-C, LDL-C and total cholesterol. All

treatment groups showed a reduction in mean serum prolactin levels at last visit relative to baseline.

### **About ABILIFY® (aripiprazole)**

The first and only available dopamine partial agonist, ABILIFY is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults and pediatric patients (10 to 17 years old). ABILIFY® (aripiprazole) Injection is indicated for the treatment of adults with agitation associated with Bipolar I Disorder, manic or mixed.

Initially approved in November 2002, over 14.9 million prescriptions have been written for ABILIFY in the U.S.<sup>2</sup> through December 2007.

ABILIFY is available by prescription only. ABILIFY Tablets should be taken once daily with or without food and are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg strengths. ABILIFY® DISCMELT™ (aripiprazole) Orally Disintegrating Tablets are available in 10 mg and 15 mg strengths. In addition, ABILIFY is available in a 1 mg/mL nonrefrigerated Oral Solution and as a single-dose, ready-to-use solution for intramuscular injection 7.5 mg/mL. In adult patients, the recommended ABILIFY® (aripiprazole) Oral target dose is 15 mg/day to 30 mg/day in Bipolar I Disorder. In pediatric patients (10 to 17 years old) with Bipolar I Disorder, the recommended ABILIFY Oral target dose is 10 mg/day (with a starting dose of 2 mg/day which was titrated to 5 mg/day after 2 days and to the target dose of 10 mg/day after 2 additional days). In adult patients with agitation associated with bipolar mania, the ABILIFY Injection initial dose is 9.75 mg/1.3 mL. If ongoing ABILIFY therapy is clinically indicated, oral ABILIFY in a range of 10 mg/day to 30 mg/day should replace ABILIFY Injection as soon as possible. The safety of doses of ABILIFY Oral or ABILIFY Injection above 30 mg/day has not been evaluated in clinical trials.

## **IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY**

### **INDICATIONS:**

- ABILIFY is indicated for acute and maintenance treatment of adults with manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features
- ABILIFY is indicated for acute treatment of pediatric patients (10 to 17 years old) with manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features
- ABILIFY Injection is indicated for the treatment of adults with agitation associated with Bipolar I Disorder, manic or mixed.

**IMPORTANT SAFETY INFORMATION:**

**Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). ABILIFY® (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).**

**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 for the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression (See Boxed WARNING).**

Contraindications: Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

**Cerebrovascular adverse reactions** (eg, stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence 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. If signs and symptoms appear, immediate discontinuation is recommended

**Tardive dyskinesia (TD)**—The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely

**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. Patients with diabetes should be monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY

ABILIFY® (aripiprazole) 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.

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.

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.

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.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia.

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.

Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 or CYP2D6 inhibitors increase ABILIFY drug concentrations when used concomitantly.

CYP3A4 inducers decrease ABILIFY drug concentrations when used concomitantly.

**Commonly observed adverse reactions** (greater than or equal to 5% incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Adult patients with bipolar mania: constipation (13% vs 6%), akathisia (15% vs 3%), sedation (8% vs 3%), tremor (7% vs 3%), restlessness (6% vs 3%), and extrapyramidal disorder (5% vs 2%)
- Pediatric patients (10 to 17 years) with Bipolar I Disorder: 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 agitation associated with bipolar mania: nausea (9% vs 3%)

Please see FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, for ABILIFY.

## **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<sup>®</sup> (aripiprazole) 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. The Otsuka Pharmaceutical Group comprises 99 companies and employs approximately 31,000 people in 18 countries and regions worldwide. Otsuka and its consolidated subsidiaries earned U.S. \$7.2 billion in annual revenues in fiscal 2006.

Bristol-Myers Squibb is a global biopharmaceutical and related healthcare products company whose mission is to extend and enhance human life.

*For more information and FULL PRESCRIBING INFORMATION,*

*including **Boxed WARNINGS**, visit: [www.abilify.com](http://www.abilify.com)*

*Visit Otsuka Pharmaceutical Co., Ltd. at: [www.otsuka-global.com](http://www.otsuka-global.com)*

*Visit Bristol-Myers Squibb at: [www.bms.com](http://www.bms.com)*

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### **References**

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- <sup>1</sup> Kumra S, Oberstar JV, Sikich L, Findling RL, McClellan JM, Vinogradov S, Schulz SC. Efficacy and Tolerability of Second-Generation Antipsychotics in Children and Adolescents With Schizophrenia. *Schizophrenia Bulletin*. Published online October 8, 2007.
  - <sup>2</sup> IMS Auditrac NGPS: ABILIFY total monthly retail prescriptions: Data accessed December 2007.