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**U.S. FOOD AND DRUG ADMINISTRATION APPROVES ABILIFY<sup>®</sup> (aripiprazole)  
FOR ADD-ON TREATMENT TO LITHIUM OR VALPROATE IN THE ACUTE  
TREATMENT OF ADULTS WITH MANIC AND MIXED EPISODES OF  
BIPOLAR I DISORDER WITH OR WITHOUT PSYCHOTIC FEATURES**

PRINCETON, NJ and TOKYO, JAPAN, May 8, 2008 – Bristol-Myers Squibb Company (NYSE: BMY) and Otsuka Pharmaceutical Co., Ltd. announced today that the U.S. Food and Drug Administration (FDA) approved updated labeling for ABILIFY<sup>®</sup> (aripiprazole) as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults. ABILIFY has been approved as monotherapy for the treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults since September 2004.

In addition to this new indication, the FDA also approved a new recommended starting and target dose of 15 mg daily for ABILIFY monotherapy in the treatment of Bipolar I Disorder in adults.

The approval of ABILIFY used in combination with lithium or valproate is based on results from a six-week, randomized, double-blind, placebo-controlled study in adults with manic or mixed episodes of Bipolar I Disorder who had an inadequate response to a two-week, lead-in phase of mood stabilizer monotherapy (lithium or valproate).<sup>1</sup> At study endpoint (Week 6), add-on ABILIFY was superior to lithium or valproate with adjunctive placebo in the reduction of the Young-Mania Rating Scale (Y-MRS) Total Score and the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) Severity of Illness Score for Mania.

The approval of the starting dose of 15 mg daily for ABILIFY® (aripiprazole) is based on results from two three-week, randomized, double-blind, placebo-controlled studies in adults with manic or mixed episodes of Bipolar I Disorder. At study endpoint (Week 3), ABILIFY was superior to placebo in the reduction of the Y-MRS Total Score and CGI-BP Severity of Illness Score for Mania.

“Expanding the clinical use of ABILIFY gives patients with Bipolar I Disorder a new treatment option,” said Elliott Sigal, M.D., Ph.D., Executive Vice President, Chief Scientific Officer and President, Research and Development, Bristol-Myers Squibb.

“Our mission at Otsuka is to develop products to their fullest potential,” said Hiromi Yoshikawa, Chairman and Chief Executive Officer, Otsuka America Pharmaceutical, Inc. “The approval of this new indication for ABILIFY provides another option for physicians that helps address the needs of their patients.”

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

The findings of adjunctive use of ABILIFY in Bipolar I Disorder are from a six-week, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of add-on ABILIFY in 384 adult patients with a *DSM-IV* diagnosis of Bipolar I Disorder, manic or mixed episodes, with or without psychotic features.<sup>1</sup>

During the two-week lead-in phase, adult patients received stable doses of lithium or valproate to achieve therapeutic blood levels. Patients demonstrating an inadequate response (Y-MRS Total Score greater than or equal to 16 and less than or equal to 25% improvement on the Y-MRS Total Score) to lithium or valproate were randomized to receive either adjunctive ABILIFY (15 mg/day or an increase to 30 mg/day as early as day seven based on clinical response) or adjunctive placebo.

The primary efficacy endpoint was the mean change in the Y-MRS Total Score.<sup>1</sup> The CGI-BP Severity of Illness Score for Mania from baseline to Week 6 was the key secondary endpoint. Safety evaluations included incidence of adverse reactions, body weight and discontinuation due to adverse reactions.<sup>1</sup>

For the primary endpoint, adjunctive ABILIFY demonstrated statistically significant improvement in symptoms when compared to adjunctive placebo (p-value equals 0.002) as measured by the mean change from baseline to endpoint (Week 6) on the Y-MRS Total Score.<sup>1</sup>

For the secondary endpoint, CGI-BP Severity of Illness Score for Mania also demonstrated statistically significant improvement in symptoms (p-value equals 0.014).<sup>1</sup> Seventy-one percent of the patients co-administered valproate and 62% of the adult patients co-administered lithium, were on 15 mg/day at endpoint.

For patients already tolerating either lithium or valproate as monotherapy, the rate of discontinuation due to adverse reactions with adjunctive ABILIFY<sup>®</sup> (aripiprazole) was 12% compared to 6% for adjunctive placebo. The most common adverse reactions associated with discontinuation in adjunctive ABILIFY-treated patients compared to adjunctive placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

During the study, the most commonly observed adverse reactions (incidence of greater than or equal to 5% for adjunctive ABILIFY and at least twice the rate of adjunctive placebo) associated with adjunctive ABILIFY were: akathisia (adjunctive ABILIFY: 19%; adjunctive placebo: 5%), insomnia (adjunctive ABILIFY: 8%; adjunctive placebo: 4%) and extrapyramidal disorder (adjunctive ABILIFY: 5%; adjunctive placebo: 1%).

Mean weight gain was low and was 0.6 kilograms (kg) for adjunctive ABILIFY and 0.2 kg for adjunctive placebo. In the study, there was a low rate of weight gain greater than or equal to 7% of body weight for adjunctive ABILIFY (3%) compared to adjunctive placebo (4%).

### ***Label Update on ABILIFY and Lamotrigine***

The ABILIFY label was also updated to include new pharmacokinetic information on the co-administration of 10 mg/day to 30 mg/day doses of ABILIFY with 100 mg/day to 400 mg/day lamotrigine. No dosage adjustment of lamotrigine is required when ABILIFY is added to lamotrigine.

### **About ABILIFY**

The first and only available dopamine partial agonist, ABILIFY is indicated for acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults, and for acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients (aged 10-17). ABILIFY is also indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or

without psychotic features in adults. ABILIFY® (aripiprazole) Injection is indicated for the acute treatment of agitation associated with Bipolar I Disorder, manic or mixed, in adults.

Initially approved in November 2002, over 20 million prescriptions have been written for ABILIFY in the U.S.<sup>2</sup> through March 2008.

ABILIFY is available by prescription only. ABILIFY should be taken once daily with or without food and is available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablet 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 target and starting dose is 15 mg/day in Bipolar I Disorder. In pediatric patients (aged 10-17) with Bipolar I Disorder, the recommended ABILIFY 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 oral ABILIFY 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 manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults
- ABILIFY is indicated for acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients 10 to 17 years of age
- ABILIFY is indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults
- ABILIFY Injection is indicated for the acute treatment of agitation associated with Bipolar I Disorder, manic or mixed in adults

**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.

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.

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

Physicians should advise patients to avoid alcohol while taking ABILIFY.

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

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose 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 (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 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%)

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.

**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 company whose mission is to extend and enhance human life.

To learn more about ABILIFY<sup>®</sup> (aripiprazole) and for *FULL PRESCRIBING INFORMATION*, including **Boxed WARNINGS** and *Medication Guide*, please visit [www.abilify.com](http://www.abilify.com).

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

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

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**References**

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<sup>1</sup> Data on file at Otsuka America Pharmaceutical, Inc.

<sup>2</sup> IMS Auditrac NGPS: ABILIFY total monthly retail prescriptions: Data accessed March 2008.