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**ABILIFY® (aripiprazole) RECEIVES EXPANDED INDICATIONS FOR MAINTENANCE TREATMENT IN BOTH PEDIATRIC PATIENTS (AGED 10-17) WITH MANIC AND MIXED EPISODES OF BIPOLAR I DISORDER AND ADOLESCENTS (AGED 13-17) WITH SCHIZOPHRENIA**

***-- ABILIFY is Also Granted an Indication for Add-On Treatment to Lithium or Valproate in the Treatment of Pediatric Patients (Aged 10-17) With Bipolar I Disorder --***

TOKYO, JAPAN and PRINCETON, NJ, May 8, 2008 – Otsuka Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Company (NYSE: BMY) announced that ABILIFY® (aripiprazole) received expanded indications in Bipolar I Disorder and Schizophrenia. ABILIFY is now indicated for maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients (aged 10-17) and maintenance treatment of Schizophrenia in adolescents (aged 13-17). In addition, ABILIFY is also granted an indication for 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 pediatric patients (aged 10-17).

ABILIFY was recently approved for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients (aged 10-17), in February 2008, and for the acute treatment of Schizophrenia in adolescents (aged 13-17) in October 2007. The FDA first approved ABILIFY for the treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults in September 2004, and for the treatment of Schizophrenia in adults in November 2002.

The safety and effectiveness of ABILIFY in pediatric patients with Bipolar Mania were established in a four-week, placebo-controlled clinical trial in 197 pediatric patients (aged

10-17). The safety and effectiveness of ABILIFY® (aripiprazole) in adolescents with Schizophrenia were established in a six-week, placebo-controlled clinical trial in 202 pediatric patients (aged 13-17). Although maintenance efficacy in these patient populations has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of ABILIFY pharmacokinetic parameters in adults and pediatric patients.

There is no body of evidence available to answer the question of how long the adolescent patient treated with ABILIFY should be maintained. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Periodic reassessment should be conducted to determine the need for maintenance treatment.

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated. However, such efficacy and lack of pharmacokinetic interaction between ABILIFY and lithium or valproate can be extrapolated from adult data along with comparisons of ABILIFY pharmacokinetic parameters in adult and pediatric patients.

“We are extremely pleased to receive expanded indications on the use of ABILIFY in these patient populations,” said Taro Iwamoto, Ph.D., Chief Executive Officer, President and Chief Operating Officer, Otsuka Pharmaceutical Development and Commercialization, Inc.

“Expanding the clinical uses of an important therapy such as ABILIFY gives caregivers and pediatric patients with Bipolar I Disorder or Schizophrenia a new treatment option in their fight against serious disease,” said Elliott Sigal, M.D., Ph.D., Executive Vice President, Chief Scientific Officer and President, Research and Development, Bristol-Myers Squibb.

### **About ABILIFY**

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

(aged 10-17). ABILIFY<sup>®</sup> (aripiprazole) is also indicated for acute and maintenance treatment of Schizophrenia in adults and in adolescents (aged 13-17).

ABILIFY<sup>®</sup> (aripiprazole) Injection is indicated for the acute treatment of agitation associated with Schizophrenia or Bipolar 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>1</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<sup>®</sup> (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 and 10 mg to 15 mg/day in Schizophrenia. 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 two days and to the target dose of 10 mg/day after two additional days). In adolescents with Schizophrenia, the recommended ABILIFY target dose is 10 mg/day (with a starting dose of 2 mg/day which was titrated to 5 mg after two days and to the target dose of 10 mg after two additional days). The 30 mg/day dose was not shown to be more efficacious than the 10 mg/day dose. In adult patients with agitation associated with Bipolar Mania or Schizophrenia, 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 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® (aripiprazole)**

### **INDICATIONS:**

- ABILIFY is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depression Disorder in adults
- 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 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 and pediatrics 10 to 17 years of age
- ABILIFY is indicated for acute and maintenance treatment of Schizophrenia in adults and in adolescents 13 to 17 years of age
- ABILIFY Injection is indicated for the acute treatment of agitation associated with Schizophrenia or Bipolar 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 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 of the need of 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 events** (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® (aripiprazole). 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 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 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 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® (aripiprazole) vs placebo, respectively]:

- Adult patients with Major Depression 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%)
- 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%)
- 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.

#### **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. 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® (aripiprazole) and for *FULL PRESCRIBING INFORMATION*, including **Boxed WARNINGS** and *Medication Guide*, please 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> IMS Auditrac NGPS: ABILIFY total monthly retail prescriptions: Data accessed March 2008.