U.S. Food and Drug Administration Approves ABILIFY® (aripiprazole) for Adolescent Patients with Schizophrenia

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Otsuka-sponsored Study Supported Efficacy, Safety and Tolerability of ABILIFY in Pediatric Patients Ages 13-17 with Schizophrenia

TOKYO & PRINCETON, N.J.--(BUSINESS WIRE)--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 the atypical antipsychotic ABILIFY® (aripiprazole) for the treatment of schizophrenia in adolescents aged 13-17 years. In adolescents, ABILIFY treats positive and negative symptoms of schizophrenia. The FDA first approved ABILIFY for the treatment of schizophrenia in adults on November 15, 2002.

"Until now, FDA-approved treatment options for adolescent patients with schizophrenia were limited," said Robert Findling, M.D., Director of Child and Adolescent Psychiatry, University Hospitals Case Medical Center, Cleveland, Ohio. "The approval of this new indication for ABILIFY provides an additional effective treatment option for these patients."

This approval is based on results from a six-week, randomized, double-blind, placebo-controlled study that demonstrated significant improvement with ABILIFY compared to placebo on the primary efficacy endpoint, Positive and Negative Syndrome Scale (PANSS) Total Score.1

"We are extremely pleased that ABILIFY, the first available dopamine partial agonist, is approved for the treatment of pediatric patients (13 to 17 years of age) suffering from schizophrenia," said Tatsuo Higuchi, President and Representative Director, Otsuka Pharmaceutical Co., Ltd. "ABILIFY® (aripiprazole) offers an effective new option to help treat this serious mental illness."

"Schizophrenia is one of the most complex of all mental health disorders," said Elliott Sigal, M.D., Ph.D., Executive Vice President, Chief Scientific Officer and President, Research and Development, Bristol-Myers Squibb. "We remain committed to providing innovative therapies, such as ABILIFY, to help patients, including adolescents, living with schizophrenia."

Clinical Trial Design and Findings

The findings are from a six-week, double-blind, randomized, placebo-controlled, multi-center study that evaluated the efficacy and safety of ABILIFY in pediatric patients, 13-17 years old, with a primary diagnosis of schizophrenia.1 The study, sponsored by Otsuka Pharmaceutical Co., Ltd. and its U.S. subsidiary, Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, N.J.), was conducted at 101 centers in 13 countries and enrolled 302 ethnically diverse pediatric patients. All patients were experiencing an acute episode of schizophrenia and required hospitalization at the time of enrollment.1 After a minimum three-day wash-out period without any antipsychotic treatment, pediatric patients were randomly assigned to receive one of two fixed doses of ABILIFY [10 mg/day (n=100) or 30 mg/day (n=102)] or placebo (n=100).1 ABILIFY was started at 2 mg/day and titrated to the target dose.1

The primary efficacy endpoint was the mean change from baseline to endpoint (Week 6) in a standard measure called the PANSS Total Score,1 which can range from 30 (no symptoms) to 210 points (most severe symptoms).2 Safety evaluations included incidence of adverse events, discontinuation rate due to adverse events and laboratory measures.1

Approximately 85 percent of patients completed the six-week study (84 percent of ABILIFY 10 mg, 82 percent of ABILIFY 30 mg and 90 percent of placebo-treated patients).1 Both doses of ABILIFY demonstrated significant improvement when compared to placebo in mean change from baseline to endpoint (Week 6) in PANSS Total Score.1

In this study of pediatric patients with schizophrenia, common adverse events (greater than or equal to 5 percent and at least twice the rate of placebo) associated with ABILIFY were extrapyramidal disorder, somnolence and tremor. These common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (ABILIFY 10 mg: 13 percent; ABILIFY 30 mg: 21.6 percent; placebo: 5 percent), somnolence (ABILIFY 10 mg: 11 percent; ABILIFY® (aripiprazole) 30 mg: 21.6 percent; placebo: 6 percent) and tremor (ABILIFY 10 mg: 2 percent; ABILIFY 30 mg: 11.8 percent; placebo: 2 percent). The discontinuation rate due to an adverse event was 5 percent for ABILIFY and 2 percent for placebo.

In this six-week study, weight gain greater than or equal to 7 percent increase from baseline was seen in 5 percent of pediatric patients treated with ABILIFY and 1 percent of placebo-treated patients. The mean change from baseline in weight was 0.13 kilograms (kg) for ABILIFY and -0.83 kg for placebo.
About ABILIFY

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. ABILIFY is also indicated for the treatment of schizophrenia in adults and adolescents (13-17 years old). ABILIFY Injection is indicated for the treatment of adults with agitation associated with schizophrenia or Bipolar I Disorder, manic or mixed.

Initially approved in November 2002, over 12.5 million prescriptions have been written for ABILIFY in the U.S.3 through June 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™ 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 oral target dose is 15 mg to 30 mg/day in Bipolar I Disorder and 10 mg to 15 mg/day in schizophrenia. In adolescent patients with schizophrenia, the recommended ABILIFY oral target dose is 10 mg/day (with a starting dose of 2 mg/day which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 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 ABILIFY® (aripiprazole) 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 schizophrenia in adults

-- ABILIFY is indicated for the treatment of schizophrenia in adolescents 13 to 17 years of age

-- ABILIFY is indicated for acute and maintenance treatment of bipolar disorder with or without psychotic features

ABILIFY Injection is indicated for the treatment of adults with agitation associated with schizophrenia or bipolar disorder, manic or mixed.

IMPORTANT SAFETY INFORMATION:

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

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. 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 and bipolar 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 events** (greater than or equal to 5 percent incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- **Adult patients with schizophrenia:** akathisia (8 percent vs 4 percent)
- **Pediatric patients (13 to 17 years) with schizophrenia:** extrapyramidal disorder (17 percent vs 5 percent), somnolence (16 percent vs 6 percent), and tremor (7 percent vs 2 percent)
- **Adult patients with bipolar mania:** constipation (13 percent vs 6 percent), akathisia (15 percent vs 3 percent), sedation (8 percent vs 3 percent), tremor (7 percent vs 3 percent), restlessness (6 percent vs 3 percent), and extrapyramidal disorder (5 percent vs 2 percent)
- **Adult patients with agitation associated with schizophrenia or bipolar mania:** nausea (9 percent vs 3 percent)

Please see FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, 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® (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 17 countries and regions worldwide. Otsuka and its consolidated subsidiaries earned US$7.2 billion in annual revenues in fiscal 2006.

Bristol-Myers Squibb is a global pharmaceutical and related health care products company whose mission is to extend and enhance human life.

*For more information and FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, 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)*

**REFERENCES:**

1. Data on file at Otsuka America Pharmaceutical, Inc.

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