U.S. Food and Drug Administration Approves ABILIFY® (aripiprazole) for the Treatment of Irritability Associated with Autistic Disorder in Pediatric Patients (Ages 6 to 17 Years)

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PRINCETON, N.J. & TOKYO--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and Otsuka Pharmaceutical Co., Ltd. announced today that the U.S. Food and Drug Administration (FDA) has approved the supplemental New Drug Application (sNDA) for ABILIFY® (aripiprazole) for the treatment of irritability associated with autistic disorder in pediatric patients ages 6 to 17 years, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

While there is no approved treatment for the core symptoms of autistic disorder, irritability can be an associated behavior of autistic disorder and is manifested as aggression towards others, deliberate self-injurious behaviors, temper tantrums, aggression and quickly changing moods. Behavioral problems such as irritability can be a source of impairment or distress to an individual with autistic disorder.

Pharmacological treatment for pediatric patients with irritability associated with autistic disorder is indicated as part of a total treatment program that includes psychological, educational, and social interventions. The decision to initiate pharmacological treatment in children with irritability associated with autistic disorder should be made between healthcare providers and caregivers only after a thorough diagnostic evaluation and discussion of both the benefits and risks associated with pharmacological treatment. If treatment is initiated, American Psychiatric Association (APA) consensus guidelines recommend routine assessment and monitoring of patients’ weight, waist circumference, blood pressure, fasting plasma-glucose level and fasting lipid profile for the development of metabolic adverse effects.¹

The approval of ABILIFY® for this indication is based on data from two eight-week, randomized, double-blind, placebo-controlled, multicenter, Phase III studies in which ABILIFY, compared to placebo, significantly improved scores on the Irritability subscale of the caregiver-rated Aberrant Behavior Checklist (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of irritability in autistic disorder, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Participating patients had a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of autistic disorder, confirmed by the Autism Diagnostic Interview-Revised, and exhibited behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems.

The efficacy of ABILIFY® (aripiprazole) for the maintenance treatment of irritability associated with autistic disorder has not been evaluated. While there is no body of evidence available to answer the questions of how long the patient treated with ABILIFY should be maintained, patients should be periodically reassessed to determine the continued need for maintenance treatment.

Study Design
Study CN138-178 was a flexible-dose study involving 98 patients at approximately 20 U.S. sites. Study CN138-179 was a fixed-dose study involving 218 patients at 37 U.S. sites. Both studies enrolled patients 6 to 17 years of age; over 75% of these subjects were under 13 years of age. In addition to having a DSM-IV diagnosis of autistic disorder, confirmed by Autism Diagnostic Interview-Revised, participants exhibited symptoms of irritability that were at least moderate in severity based on a Clinical Global Impression of Severity score ≥ 4 and an Aberrant Behavior Checklist Irritability (ABC-I) Subscale score ≥ 18. In both studies, the primary efficacy endpoint was the mean change from baseline to Week 8 in the ABC-I Subscale score, which is an 15-item, caregiver-rated subscale that measures symptoms of irritability in cognitively impaired children. Safety measures in both studies included incidence of adverse events, laboratory measures, electrocardiograms and changes in body weight.

These studies were not designed or intended to evaluate ABILIFY® for the treatment of the core symptoms of autistic disorder, which are abnormalities in social interaction and communication and the presence of restricted, repetitive, and stereotyped patterns of behaviors, activities, or interests.

Data Results
Patients in the flexible-dose study (CN138-178) were randomized in a 1:1 ratio to receive either ABILIFY 2 mg/day to 15 mg/day or placebo. Patients receiving ABILIFY initiated treatment on a dose of 2 mg/day and then were flexibly titrated to clinical response, with all dose increases occurring at the time of weekly study visits with no dose increases permitted after Week 6. The mean daily dose at the end of the 8-week treatment was 8.6 mg/day with the majority of patients taking either
Increased Mortality in Elderly Patients with Dementia-Related Psychosis

ABILIFY® (aripiprazole) demonstrated significantly greater improvement compared to placebo on the primary study endpoint, the adjusted mean change from baseline to Week 8 on the ABC-I Subscale score (p<0.001). ABILIFY also demonstrated a statistically significant greater improvement compared to placebo on the adjusted mean CGI-I scores at Week 8 (p<0.001).

Patients in the fixed-dose study (CN138-179) were randomized in a 1:1:1:1 ratio to receive one of three doses of ABILIFY (5 mg/day, 10 mg/day or 15 mg/day) or placebo. Patients receiving ABILIFY initiated treatment at a dose of 2 mg/day for one week. The dose of ABILIFY was increased to 5 mg/day for one week, and then increased by 5 mg/day at weekly intervals until the assigned dose was achieved. Completion rates in the fixed-dose study were similar across the three ABILIFY dose groups (ABILIFY 5 mg/day: 83.0%; ABILIFY 10 mg/day: 83.1%; ABILIFY 15 mg/day: 87.0%; placebo: 73.1%).

Each dose of ABILIFY demonstrated significantly greater improvement compared to placebo on the primary study endpoint: the adjusted mean change from baseline to Week 8 on the ABC-I Subscale score (ABILIFY 5 mg: p<0.05; ABILIFY 10 mg: p<0.01; ABILIFY 15 mg: p=0.001; placebo). Differences between dose groups were not evaluated.

The weight gain observed at Week 8 in a pooled analysis of the two studies was 1.6 kg for ABILIFY versus 0.4 kg for placebo. Clinically significant weight gain (≥7% change from baseline) was seen in 26% of ABILIFY-treated patients and 7% of placebo-treated patients. There were no clinically significant differences in lipids compared with placebo.

Commonly observed adverse events (≥5% and more than twice placebo) across both studies were sedation (ABILIFY 21%; placebo: 4%), fatigue (ABILIFY: 17%; placebo: 2%), vomiting (ABILIFY: 14%; placebo: 7%), somnolence (ABILIFY: 10%; placebo: 6%), tremor (ABILIFY: 10%; placebo: 0%), hypersecretion (ABILIFY: 14%; placebo: 3%), pyrexia (ABILIFY: 9%; placebo: 1%), and diarrhea (ABILIFY: 9%; placebo: 0%). The most common reasons for discontinuation (≥1% of ABILIFY-treated patients) were sedation, drooling, tremor, vomiting and extrapyramidal disorder.

There were no clinically significant differences in ECG (including QTc) compared with placebo. There was a statistically significant decrease in mean prolactin levels in patients treated with ABILIFY® (aripiprazole) compared to placebo.

About the Aberrant Behavior Checklist Irritability (ABC-I) Subscale

The Aberrant Behavior Checklist (ABC) is a caregiver-rated assessment tool that has five subscales: Irritability, Social Withdrawal/Lethargy, Stereotypic Behavior, Hyperactivity/Non-compliance and Inappropriate Speech. The ABC-Irritability (ABC-I) Subscale, which was the primary outcome measure in both trials, contains 15 items that measure symptoms of irritability, including aggression towards others, deliberate self-injuriousness, temper tantrums and quickly changing moods.

About Autistic Disorder

Autistic disorder is a neurodevelopmental disorder that is characterized by impairment in verbal and non-verbal communication skills, impairment in social interactions and the presence of restricted activities and/or repetitive patterns of behavior or interests, with an estimated prevalence of 10 to 20 cases per 10,000. The ABILIFY studies were not designed or intended to evaluate ABILIFY for the treatment of the core symptoms of autistic disorder.

Moderate or severe behavioral problems such as irritability, aggressiveness and self-injurious behavior also may be associated with autistic disorder. These behavioral problems can be a source of impairment or distress to an individual with autistic disorder.

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

INDICATIONS

ABILIFY is indicated for:

- Treatment of irritability associated with Autistic Disorder in pediatric patients (aged 6 to 17 years), including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods
- Use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults
- 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
- 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
- Acute and maintenance treatment of Schizophrenia in adults and in adolescents 13 to 17 years of age

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. 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 during treatment should undergo fasting blood glucose testing. 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** (≥5% incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- 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 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%)
- 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.

Please see FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, and Medication Guide for ABILIFY® (aripiprazole) at [www.abilify.com](http://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. 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 committed to discovering, developing and delivering innovative medicines that help patients prevail over serious diseases.

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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