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**NEW INVESTIGATIONAL DATA USING INTRAMUSCULAR ADMINISTRATION OF  
ARIPIPRAZOLE IN PATIENTS WITH ACUTE BIPOLAR MANIA AND  
SCHIZOPHRENIA**

(ATLANTA, May 25, 2005) – In two double-blind, randomized, multicenter studies reported this week at the 158<sup>th</sup> Annual Meeting of the American Psychiatric Association, data were presented on the investigational use of intramuscular (IM) aripiprazole in patients with either acute bipolar mania or schizophrenia. The primary efficacy measure for both studies was mean change from baseline to two hours post-initial IM injection, in the Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score: poor impulse control, tension, hostility, uncooperativeness and excitement.

In these studies, the first injection was followed by inpatient evaluation for 24 hours. If needed, a second injection was given at least two hours post-initial injection and a third injection, if needed, at least two hours post-second injection. For the placebo group, the third injection contained aripiprazole IM 10 mg.

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### **Detailed Study Information:**

#### ***Intramuscular Aripiprazole or Lorazepam versus Placebo for Agitation in Acute Mania***

This double-blind, randomized, multicenter study compared two investigational doses of IM aripiprazole (10 mg and 15 mg), and IM lorazepam (2 mg) with placebo. Mean changes from baseline in PEC scores two hours after the initial IM injection were aripiprazole 10 mg (n=75), -8.7; aripiprazole 15 mg (n=75), -8.7; lorazepam 2 mg (n=68), -9.6; placebo (n=73), -5.8 (for all active drugs p-value was less than 0.001 versus placebo).

In this study, the most commonly reported adverse events for either dose of aripiprazole occurring in frequency greater than five percent were nausea, vomiting, headache, somnolence, sedation, dizziness and insomnia.

“Patients experiencing acute agitation in bipolar disorder can be highly distressed and require treatment that works quickly,” said Gary Sachs, MD, Associate Professor of Psychiatry, Harvard Medical School, Director of the Bipolar Clinic and Research Program, Massachusetts General Hospital. “These data provide important information about the potential use of intramuscular medicine in this patient population.”

#### ***Intramuscular Aripiprazole or Haloperidol versus Placebo in Acute Schizophrenia: A Pivotal Phase III Study***

In the second double-blind, multicenter investigational trial, acutely agitated patients with schizophrenia and schizoaffective disorder were randomized to IM aripiprazole (10 mg), IM haloperidol (6.5 mg) or IM placebo in a 2:2:1 fashion. Mean changes from baseline in PEC scores two hours post-initial IM injection were aripiprazole (n=173), -7.3; haloperidol (n=184), -7.8; and placebo (n=88), -4.8 (p-value less than 0.001 for both drugs versus placebo).

The most commonly reported adverse events for aripiprazole in this study, occurring in frequency greater than or equal to five percent were headache, dizziness, nausea and insomnia.

### **About Aripiprazole**

Aripiprazole is indicated for the treatment of schizophrenia including maintaining stability in patients who had been symptomatically stable on other antipsychotic medications for periods of

three months or longer and observed for relapse during a period of up to 26 weeks. Aripiprazole is also indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder. Most recently, in March 2005, aripiprazole was FDA-approved for maintaining efficacy in patients with Bipolar I Disorder with a recent manic or mixed episode who had been stabilized and then maintained for at least six weeks. Physicians who elect to use aripiprazole for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. Since its initial approval in 2002, over 3.7 million prescriptions have been written in the United States.<sup>i</sup>

Aripiprazole is available by prescription only. In addition to administration as a once-daily tablet, aripiprazole was recently FDA-approved in a 1 mg/mL oral solution. Aripiprazole Oral Solution is an important new treatment option for adult patients who are unable to or have difficulty swallowing tablets, and provides flexibility in addressing individual patient needs. Patients should talk to their healthcare provider for more information. To learn more about aripiprazole and for full product information, please visit [www.bms.com](http://www.bms.com).

#### **IMPORTANT SAFETY INFORMATION:**

##### **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

**Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.**

As with all antipsychotic medications, including aripiprazole, a rare condition referred to as **neuroleptic malignant syndrome (NMS)** has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia (TD)**.

**Cerebrovascular adverse events** (e.g., 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 aripiprazole, including a significant dose response relationship in a fixed-dose trial. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

**Hyperglycemia**, including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients should be appropriately tested before and monitored during treatment.

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, aripiprazole should be used with caution in patients with a history of **seizures** or with conditions that lower the seizure threshold.

Like other antipsychotics, aripiprazole may have the potential to **impair judgment, thinking or motor skills**. Patients should not drive or operate hazardous machinery until they are certain aripiprazole 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.

As antipsychotics have been associated with **esophageal dysmotility and aspiration**, aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

As the possibility of a **suicide** attempt is inherent in psychotic illness and bipolar disorder, close supervision of high-risk patients should accompany drug therapy.

Physicians should determine if a patient is **pregnant** or intends to become pregnant while taking aripiprazole. Patients should be advised not to drink alcohol, or breast-feed while taking aripiprazole.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

**Commonly observed adverse events** reported with aripiprazole in 3-week bipolar mania trials at a greater than or equal to 5% incidence for aripiprazole and at a rate at least twice the rate of placebo include, respectively, akathisia (15% versus 4%), constipation (13% versus 6%), and accidental injury (6% versus 3%).

**Treatment-emergent adverse events** reported with aripiprazole in short-term trials at an incidence greater than or equal to 10% and greater than placebo, respectively, include headache (31% versus 26%), agitation (25% versus 24%), anxiety (20% versus 17%), insomnia (20% versus

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15%), nausea (16% versus 12%), dyspepsia (15% versus 13%), somnolence (12% versus 8%), akathisia (12% versus 5%), lightheadedness (11% versus 8%), vomiting (11% versus 6%), and constipation (11% versus 7%).

The adverse events reported in a 26-week, double-blind schizophrenia trial comparing aripiprazole and placebo were generally consistent with those reported in the short-term, placebo-controlled schizophrenia trials, except for a higher incidence of tremor: 9% for aripiprazole versus 1% for placebo.

Physicians who elect to use aripiprazole for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Aripiprazole is taken once daily with or without food.

### **About Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.**

Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd. are collaborative partners in the development and commercialization of aripiprazole in the United States and major European countries.

Aripiprazole was discovered by Otsuka Pharmaceutical Co., Ltd. Founded in 1964, Otsuka Pharmaceutical Co., Ltd. is a healthcare company with the mission statement: "Otsuka - people creating new products for better health worldwide." Otsuka researches, develops, manufactures and markets innovative products, focusing its core businesses on pharmaceutical products for the treatment of disease and consumer products for the maintenance of everyday health. Otsuka leads a corporate group comprised of 73 companies and approximately 23,000 people around the world. With 39 consolidated subsidiaries employing approximately 17,000 people, Otsuka earned US \$4.4 billion in consolidated annual revenues in fiscal 2003.

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

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<sup>1</sup> IMS Weekly NPA Plus, Verispan longitudinal database as of February 11, 2005.