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**SIX-WEEK INVESTIGATIONAL STUDY IN ADULTS WITH MAJOR DEPRESSIVE DISORDER EVALUATES THE EFFECTIVENESS OF ADJUNCTIVE ARIPIPRAZOLE THERAPY WITH ANTIDEPRESSANTS**

*- Results Presented at 160<sup>th</sup> Annual Meeting of the American Psychiatric Association -*

(SAN DIEGO, MAY 21, 2007) – In adults with major depressive disorder, adding aripiprazole to antidepressant therapy (ADT) resulted in significant improvement in the primary endpoint, the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score. In this six-week, randomized, placebo-controlled study presented here at the 160th Annual Meeting of the American Psychiatric Association, the Bristol-Myers Squibb Company (NYSE: BMY) and Otsuka Pharmaceutical Co., Ltd. atypical antipsychotic aripiprazole was added to antidepressants in patients who did not have an adequate response to ADT alone.<sup>1</sup> (Berman, 2007, APA Poster) These findings are from one of two completed studies evaluating adjunctive aripiprazole with ADT.

“Investigational studies are important because many patients with major depressive disorder do not achieve adequate symptom response,” said study investigator Arif Khan, M.D., Medical Director, Northwest Clinical Research Center, Bellevue, Wash., and Adjunct Professor, Psychiatry, Duke University, Durham, N.C. “The findings from this study contribute more information about the potential use of add-on medications to antidepressant therapy in patients who inadequately respond to antidepressants alone.”

## **Study Design and Findings**

This double-blind, randomized, placebo-controlled, multi-center, six-week study enrolled adults diagnosed with major depressive disorder who had an inadequate response to one or more ADTs. After a seven to 28-day screening phase, adults in this study underwent an eight-week prospective treatment phase with one ADT plus single-blind placebo to confirm their inadequate response to ADT. The ADTs included escitalopram, fluoxetine, paroxetine controlled release, sertraline or venlafaxine extended release, dosed per label guidelines. A total of 362 adults with inadequate response then entered the six-week randomized treatment phase during which they continued their ADT plus double-blind adjunctive placebo or adjunctive aripiprazole (2-20 mg/day).

The primary efficacy endpoint was the mean change from baseline – the end of the prospective treatment phase – to the end of the randomized treatment phase in a standard measure called the MADRS Total Score, which can range from 0 (no symptoms) to 60 points (most severe symptoms). A reduction in MADRS Total Score represents improvement in depressive symptoms. Some of the secondary endpoints included Sheehan Disability Scale (SDS), MADRS-measured remission and response rates and Clinical Global Impression-Severity of Illness (CGI-S) score.

For the primary endpoint, the study showed that adults taking adjunctive aripiprazole had a greater reduction in MADRS Total Score from baseline compared to placebo (-8.8 vs. -5.8 points, p-value less than 0.001).

The discontinuation rate due to an adverse event for adults taking add-on aripiprazole was 3.3 percent and 2.3 percent for placebo. The most common adverse events in the add-on aripiprazole and add-on placebo groups, respectively, (greater than or equal to 5 percent and at least twice the incidence of placebo) were akathisia (23.1 percent vs. 4.5 percent), insomnia (7.7 percent vs. 2.3 percent), restlessness (14.3 percent vs. 3.4 percent), upper respiratory tract infection (8.2 percent vs. 4 percent), and blurred vision (6.6 percent vs. 1.7 percent).

## **About Major Depressive Disorder**

Major depressive disorder (MDD) is characterized by one or more major depressive episodes, (i.e., at least two weeks of depressed mood or loss of interest accompanied by at least four additional symptoms of depression.)<sup>2 (DSM IV)</sup> It affects 6.7 percent of American adults

(approximately 15 million individuals) in a given year<sup>3</sup> (Kessler, 2005, p. 620, Table 1) and is the most common mental health disorder after anxiety.<sup>4</sup> (Merck Manual, 1995-2005, p. 1, ¶2)

### **About Aripiprazole**

Aripiprazole is indicated for the treatment of schizophrenia including maintaining stability in adults 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, and for maintaining efficacy in adults with Bipolar I Disorder with a recent manic or mixed episode who had been stabilized and then maintained for at least six (6) weeks. Physicians who elect to use aripiprazole for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual. Aripiprazole Injection is indicated for the treatment of agitation in adults with schizophrenia or bipolar disorder, manic or mixed.

Initially approved in November 2002, over 10 million prescriptions have been written for aripiprazole in the U.S.<sup>5</sup>

Aripiprazole is available by prescription only. Aripiprazole is available in tablets, orally disintegrating tablets, oral solution, and injection for intramuscular use.

Patients should talk to their healthcare professional for more information about aripiprazole.

### **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). Aripiprazole is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).**

- **Neuroleptic malignant syndrome (NMS)**—As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with aripiprazole. 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

- **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 aripiprazole
- **Hyperglycemia and diabetes mellitus**—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including 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 aripiprazole

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. Prescriptions for aripiprazole should be written for the smallest quantity consistent with good patient management to reduce the risk of overdose.

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

Physicians should advise patients to avoid alcohol while taking aripiprazole.

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

**Commonly observed adverse events** (greater than or equal to 5% incidence and at a rate at least twice the rate of placebo for aripiprazole vs placebo, respectively):

#### **Aripiprazole Oral**

In 3-week bipolar mania trials the following were reported: akathisia (15% vs 3%), constipation (13% vs 6%), sedation (8% vs 3%), tremor (7% vs 3%), restlessness (6% vs 3%), and extrapyramidal disorder (5% vs 2%).

In 4- to 6-week schizophrenia trials the following was reported: akathisia (8% vs 4%).

A similar adverse event profile was observed in a 26-week trial in schizophrenia except for a higher incidence of tremor (aripiprazole 8% vs placebo 2%).

#### **Aripiprazole Injection**

In short-term (24 hour) trials in patients with agitation associated with schizophrenia or bipolar mania the following was reported: nausea (9% vs 3%).

### **Treatment-emergent adverse events reported with:**

#### **Aripiprazole Oral**

In short-term trials of patients with schizophrenia (up to 6 weeks) or bipolar disorder (up to 3 weeks), the following were reported at an incidence greater than or equal to 10% and greater than placebo, respectively: headache (30% vs 25%), anxiety (20% vs 17%), insomnia (19% vs 14%), nausea (16% vs 12%), vomiting (12% vs 6%), dizziness (11% vs 8%), constipation (11% vs 7%), dyspepsia (10% vs 8%), and akathisia (10% vs 4%).

#### **Aripiprazole Injection**

In short-term (24 hour) trials, the following were reported at an incidence greater than or equal to 5% and greater than placebo, respectively: headache (12% vs 7%), nausea (9% vs 3%), dizziness (8% vs 5%), and somnolence (7% vs 4%).

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

Bristol-Myers Squibb 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, original products, focusing its core businesses on pharmaceutical products for the treatment of disease and consumer products for the maintenance of everyday health. The Otsuka Pharmaceutical Group comprises 87 companies and employs approximately 27,000 people in 17 countries and regions worldwide. Otsuka and its consolidated subsidiaries earned US \$6.8 billion in consolidated annual revenues in fiscal 2005.

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

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)

### Forward Looking Statement

*This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995, regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. There can be no guarantee that a registrational submission will be made to the FDA based on the data described in this press release or if such registrational submission is made, that it would receive FDA approval. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2006 and in our Quarterly Reports on Form 10-Q. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.*

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### References

- <sup>1</sup> Berman RM, Marcus RN, Swanink R, Carson Jr WH, McQuade RD, Khan A. Efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study (study cn138-139). Poster presentation at: annual meeting of the American Psychiatric Association, San Diego, California, Monday, May 21, 2007, 3:00 p.m. – 5:00 p.m. PST – Poster Session 3.
- <sup>2</sup> Diagnostic and Statistical Manual of Mental Disorders. Fourth ed-TR. Psychiatry Online Web site. Available at: <http://www.psychiatryonline.com/content.aspx?aID=2016>. Accessed April 9, 2007.
- <sup>3</sup> Kessler RC, Chiu WT, Demler OD, Walters EE. Prevalence, severity, and comorbidity of 12-month *DSM-IV* disorders in the national comorbidity survey replication. *Arch Gen Psychiatry*. 2005;62:617-627.
- <sup>4</sup> *Merck Manual of Medical Information – Second Home Edition*. Whitehouse Station, NJ: Merck Research Laboratories; Copyright © 1995-2005 Merck & Co.
- <sup>5</sup> IMS Auditrac NGPS: Abilify total monthly retail prescriptions: Data accessed 11/2006.