



## **FDA Grants Approval for Use of RISPERDAL(R) CONSTA(R) as Both a Monotherapy and Adjunctive Therapy in the Maintenance Treatment of Bipolar I Disorder**

May 18, 2009

### **RISPERDAL CONSTA Is the First and Only Long-Acting Atypical Antipsychotic Therapy Available for Bipolar I Disorder**

CAMBRIDGE, Mass.--(BUSINESS WIRE)--May. 18, 2009-- Alkermes, Inc. (NASDAQ: ALKS) today announced that Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) has received approval from the U.S. Food and Drug Administration (FDA) for the use of RISPERDAL® CONSTA® (risperidone) Long-Acting Injection as both a monotherapy and adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder.

Bipolar disorder is a brain disorder that causes unusual shifts in a person's mood, energy and ability to function. It is often characterized by debilitating mood swings from extreme highs (mania) to extreme lows (depression). Type I bipolar disorder is characterized based on the occurrence of at least one manic episode, with or without the occurrence of a major depressive episode, and affects approximately one percent of the American adult population in any given year.

"Long-acting therapies are moving to the forefront of treatment for mental illness, and the approval of RISPERDAL CONSTA for bipolar disorder is exciting because it offers physicians assurance that the medication is being taken as prescribed," said Caleb Adler, M.D., principal investigator and associate professor of Clinical Psychiatry at the University of Cincinnati. "Further, the bi-weekly administration schedule encourages regular contact between patients and their treatment team."

The approval is based on two prospective, randomized, double-blind, placebo-controlled studies for the long-term treatment of bipolar I disorder. The first demonstrated that RISPERDAL CONSTA, when used as a monotherapy, was significantly better than placebo at delaying the time to relapse of any mood episode. The second study demonstrated that, for patients already taking lithium or valproate, the addition of RISPERDAL CONSTA significantly delayed the time to relapse compared to current treatments plus placebo.

"We are very pleased that RISPERDAL CONSTA will now be available to the many patients who suffer from bipolar I disorder and who need alternative therapies," stated Elliot Ehrich, M.D., chief medical officer of Alkermes. "We believe that the strong clinical data demonstrating safety and efficacy to treat this disorder, as well as years of clinical experience with RISPERDAL CONSTA in the prescribing community, will make this a valuable treatment for managing this serious, chronic disease."

RISPERDAL CONSTA was approved in 2003 as an atypical antipsychotic agent indicated for the treatment of schizophrenia and is now the first and only long-acting atypical antipsychotic therapy available for the treatment of schizophrenia and bipolar I disorder.

Visit <http://www.risperdalconsta.com> for full prescribing information.

#### **About RISPERDAL CONSTA**

RISPERDAL CONSTA is a long-acting injectable form of risperidone that was developed utilizing Alkermes' proprietary Medisorb® drug-delivery technology. Using this technology, risperidone is encapsulated in microspheres made of a biodegradable polymer, which are suspended in a water-based solution and administered to patients by intramuscular injection once every two weeks. RISPERDAL CONSTA is used for the treatment of schizophrenia and for bipolar I disorder. RISPERDAL CONSTA is manufactured by Alkermes, Inc. and marketed by Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. in the U.S. and Janssen-Cilag outside of the U.S.

The most common adverse reactions observed in all clinical trials with schizophrenia (≥5%) were headache, muscle stiffness and shaking, dizziness, restlessness, tiredness, constipation, indigestion, sedation, weight increase, pain in extremity and dry mouth.

The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increase (5% in monotherapy) and tremor and parkinsonism (>10% in adjunctive therapy trial).

#### **IMPORTANT SAFETY INFORMATION FOR RISPERDAL CONSTA**

**Elderly Patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL CONSTA (risperidone) is not approved for the treatment of patients with dementia-related psychosis.**

Neuroleptic Malignant Syndrome (NMS) is a rare and potentially fatal side effect reported with RISPERDAL CONSTA and similar medicines. Call your doctor immediately if the person being treated develops symptoms such as high fever; stiff muscles; shaking; confusion; sweating; changes in pulse, heart rate, or blood pressure; or muscle pain and weakness. Treatment should be stopped if the person being treated has NMS.

Tardive Dyskinesia (TD) is a serious, sometimes permanent side effect reported with RISPERDAL CONSTA and similar medications. TD includes uncontrollable movements of the face, tongue, and other parts of the body. The risk of developing TD and the chance that it will become permanent is thought to increase with the length of therapy and the overall dose taken by the patient. This condition can develop after a brief period of therapy at low doses, although this is much less common. There is no known treatment for TD, but it may go away partially or completely if therapy is stopped.

High blood sugar and diabetes have been reported with RISPERDAL CONSTA and similar medications. If the person being treated has diabetes or risk factors such as being overweight or a family history of diabetes, blood sugar testing should be performed at the beginning and throughout treatment with RISPERDAL CONSTA. Complications of diabetes can be serious and even life threatening. If signs of high blood sugar or diabetes

develop, such as being thirsty all the time, going to the bathroom a lot, or feeling weak or hungry, contact your doctor.

RISPERDAL CONSTA and similar medications can raise the blood levels of a hormone known as prolactin, causing a condition known as hyperprolactinemia. Blood levels of prolactin remain elevated with continued use. Some side effects seen with these medications include the absence of a menstrual period; breasts producing milk; the development of breasts by males; and the inability to achieve an erection. The connection between prolactin levels and side effects is unknown.

Some people taking RISPERDAL CONSTA may feel faint or lightheaded when they stand up or sit up too quickly. By standing up or sitting up slowly and following your healthcare professional's dosing instructions, this side effect can be reduced or it may go away over time.

RISPERDAL CONSTA may affect your alertness or driving ability; therefore, do not drive or operate machinery before talking to your healthcare professional.

RISPERDAL CONSTA should be used cautiously in people with a seizure disorder, who have had seizures in the past, or who have conditions that increase their risk for seizures.

Extrapyramidal Symptoms (EPS) are usually persistent movement disorders or muscle disturbances, such as restlessness, tremors, and muscle stiffness. If you observe any of these symptoms, talk to your healthcare professional.

Inform your healthcare professional if you become pregnant or intend to become pregnant during therapy with RISPERDAL CONSTA. Caution should be exercised when RISPERDAL CONSTA is administered to a nursing woman.

RISPERDAL CONSTA may make you more sensitive to heat. You may have trouble cooling off, or be more likely to become dehydrated, so take care when exercising or when doing things that make you warm.

Some medications interact with RISPERDAL CONSTA. Please inform your healthcare professional of any medications or supplements that you are taking. Avoid alcohol while on RISPERDAL CONSTA.

In a study of people taking RISPERDAL CONSTA, the most common side effects in the treatment of schizophrenia were headache, tremors, dizziness, restlessness, tiredness, constipation, indigestion, sleepiness, weight gain, pain in the limbs, and dry mouth.

If you have any questions about RISPERDAL CONSTA or your therapy, talk with your doctor.

## **IMPORTANT SAFETY INFORMATION FOR PROFESSIONALS ABOUT RISPERDAL CONSTA**

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

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL CONSTA (risperidone) is not approved for the treatment of patients with dementia-related psychosis.**

**Cerebrovascular Adverse Events (CAEs):** CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. RISPERDAL CONSTA is not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including RISPERDAL CONSTA. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). 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):** TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose. Elderly patients appeared to be at increased risk for TD. Prescribing should be consistent with the need to minimize the risk of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

**Hyperglycemia and Diabetes:** Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including RISPERDAL CONSTA. Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D2 receptors, RISPERDAL CONSTA elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

**Orthostatic Hypotension:** RISPERDAL CONSTA may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. RISPERDAL CONSTA should be used with caution in patients with known cardiovascular disease, and conditions that would predispose patients to hypotension.

**Leukopenia, Neutropenia and Agranulocytosis** have been reported with antipsychotics, including risperidone. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a decline in WBC and in the absence of other causative factors, discontinuation of Risperdal Consta should be considered.

**Potential for Cognitive and Motor Impairment:** RISPERDAL CONSTA has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that RISPERDAL CONSTA does not affect them adversely.

**Seizures:** RISPERDAL CONSTA should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold.

**Dysphagia:** Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia.

**Priapism** has been reported. Severe priapism may require surgical intervention.

**Thrombotic Thrombocytopenic Purpura (TTP)** has been reported.

**Administration:** Care should be taken to avoid inadvertent injection into a blood vessel.

**Suicide:** The possibility of suicide attempt is inherent in psychotic illnesses. Close supervision of high-risk patients should accompany drug therapy.

Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies has been reported. Manifestations and features are consistent with NMS.

Use Risperdal Consta with caution in patients with conditions and medical conditions that could affect metabolism or hemodynamic responses. (e.g. Recent Myocardial infarction or unstable cardiac disease)

**Extrapyramidal Symptoms (EPS):** The overall incidence of EPS-related adverse events in patients treated with 25 mg and 50 mg of RISPERDAL® CONSTA® and placebo, respectively, were akathisia\* (4%, 11%, 6%), Parkinsonism† (8%, 15%, 9%) and tremor (0%, 3%, 0%).

\* Akathisia and restlessness

† Extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia

**Weight Gain:** In a 12-week trial, the percentage of patients experiencing weight gain (>7% of baseline body weight) was 6% placebo versus 9% RISPERDAL CONSTA.

**Maintenance Treatment:** Patients should be periodically reassessed to determine the need for continued treatment.

**Commonly Observed Adverse Reactions for RISPERDAL CONSTA:** The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, Parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities, and dry mouth.

The most common adverse reactions in clinical trials in patients with bipolar disorder trials were weight increased (5% in monotherapy trial) and tremor and parkinsonism (> 10% in adjunctive therapy trial).

## About Alkermes

Alkermes, Inc. is a fully integrated biotechnology company committed to developing innovative medicines to improve patients' lives. Alkermes developed, manufactures and commercializes VIVITROL® for alcohol dependence and manufactures RISPERDAL® CONSTA® for schizophrenia. Alkermes' robust pipeline includes extended-release injectable, pulmonary and oral products for the treatment of prevalent, chronic diseases, such as central nervous system disorders, addiction and diabetes. Headquartered in Cambridge, Massachusetts, Alkermes has research facilities in Massachusetts and a commercial manufacturing facility in Ohio.

Certain statements set forth above may constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and the company's business is subject to significant risk and uncertainties and there can be no assurance that its actual results will not differ materially from its expectations. These risks and uncertainties include, among others, the degree to which clinical study results in bipolar I disorder will be predictive of results in commercial use; whether Alkermes can continue to manufacture RISPERDAL CONSTA on a commercial scale, economically or in sufficient quantities to supply the market; and whether RISPERDAL CONSTA will continue to be commercialized successfully by its partner, Janssen. For further information with respect to factors that could cause the company's actual results to differ materially from expectations, reference is made to the reports the company filed with the Securities and Exchange Commission under the Securities Exchange Act of 1934, as amended. The forward-looking statements made in this release are made only as of the date hereof and the company disclaims any intention or responsibility for updating predictions or financial expectations contained in this release.

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