



1125 Trenton-Habourton Road
Titusville, NJ 08560
(609) 730-2000
www.janssen.com

Contacts:

Media

Srikant Ramaswami:
Office: (908) 927-7978
Cell: (609) 647-8195
Email: Sramaswa@its.jnj.com

Investors

Louise Mehrotra: (732) 524-6491
Johnson & Johnson

Lesley Fishman: (732) 524-3922
Johnson & Johnson

New Data Demonstrate RISPERDAL[®] CONSTA[®] (Risperidone) Long-Acting Treatment May Improve Health Outcomes and Reduce Hospitalizations in Patients with Schizophrenia

SAN FRANCISCO, May 19, 2009 – Schizophrenia is one of the most disabling diseases,¹ and frequent relapses and rehospitalization as a result of the disease place enormous burdens on patients, caregivers and society.² According to two new studies, the use of RISPERDAL[®] CONSTA[®] (risperidone) Long-Acting Treatment (RLAT) may improve clinical and functional outcomes and reduce rates of rehospitalization among patients with schizophrenia. Results of the studies were presented this week at a major medical meeting.

In an analysis of two prospective, observational two-year studies conducted in the U.S. and three other countries, RISPERDAL[®] CONSTA[®] consistently and significantly improved clinical and functional outcomes for patients with schizophrenia. Data were collected at baseline and at three-month intervals up to 24 months, and included the Clinical Global Impression of Illness Severity (CGI-S), which measures clinical effectiveness outcomes, the Global Assessment of Functioning (GAF), and healthcare resource utilization. Patients were enrolled in the U.S. (N=532), Spain (N=1345), Australia (N=784) and Belgium (N=408).

Across countries, patients treated with RISPERDAL[®] CONSTA[®] experienced significant improvements in both outcome measurements compared with baseline scores (p<0.001). Patients completing the two-year studies experienced approximately a 1-point reduction in the CGI-S score and approximately a 15-point improvement in the GAF score.³

¹ World Health Organization. *The Global Burden of Disease: 2004 Update*. 2008.

² Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. *Curr Med Res Opin*. 2007 Oct;23(10):2305-12.

³ Crivera C, Kozma CM, Jacobs A, et al. Clinical and Functional Outcomes in Schizophrenia after Initiation of Risperidone Long-Acting Therapy: Results from U.S., Spain, Australia and Belgium. Poster presented at 162nd Annual American Psychiatric Association Meeting, 2009, San Francisco, USA.

“Helping patients to improve their functioning is a major goal of treatment for schizophrenia,” said Riad Dirani, Ph.D., Director of Outcomes Research, Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. “The findings of this analysis provide encouraging evidence of a functional improvement following treatment with long-acting therapy.”

A separate observational retrospective analysis presented at the meeting suggested that patients with schizophrenia in the Veterans Affairs (VA) system who also suffered from other medical or psychiatric illnesses had fewer and shorter-duration psychiatric hospitalizations after the initiation of RISPERDAL® CONSTA®.

This analysis identified all VA patients with schizophrenia who began RISPERDAL® CONSTA® between October 1, 2005 and September 30, 2006 and received at least four (total) injections (N=924). The analysis compared changes in health services use between 12 months prior to and 12 months after initiation of RISPERDAL® CONSTA®. Results showed that between the pre- and post- RISPERDAL® CONSTA® initiation periods, the mean number of psychiatric hospitalizations and length of stay significantly decreased for patients with three or more concurrent illnesses, while psychiatric-related outpatient visits increased.⁴

“The results of this analysis suggest that long-acting therapy may reduce the need for repeated hospitalizations and improve everyday psychiatric follow-up among patients with complex medical histories,” continued Dirani.

A limitation of these two studies is that they did not compare RISPERDAL® CONSTA® to placebo or other treatments.

The studies were presented and sponsored by Ortho-McNeil Janssen ScientificAffairs.

About Schizophrenia

According to the National Institute of Mental Health, an estimated one percent of the U.S. population suffers from schizophrenia – a brain disorder that impairs a person’s ability to think clearly, relate to others and distinguish between reality and imagination. It typically develops in adolescence or the early 20s, although symptoms may not become immediately obvious.

About RISPERDAL® CONSTA®

RISPERDAL® CONSTA® (risperidone) Long-Acting Treatment (RLAT) is a long-acting injectable atypical antipsychotic therapy used for the treatment of schizophrenia and the maintenance treatment of Bipolar I Disorder. It 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. RLAT 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.

About Janssen

Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., is based in Titusville, N.J. and is the only large pharmaceutical company in the U.S. dedicated solely to mental health. It

⁴ Ren XS, Crivera C, Sikirica M, et al. Initiation of Risperidone Long-Acting Therapy in Patients with Schizophrenia in the VA: Effects of Comorbid Conditions on Health Care Utilization. Poster presented at 162nd Annual American Psychiatric Association Meeting, 2009, San Francisco, USA.

currently has prescription medications for the treatment of schizophrenia, bipolar mania and the treatment of symptoms associated with autistic disorder. For more information about Janssen, visit <http://www.janssen.com/>.

IMPORTANT SAFETY INFORMATION FOR CONSUMERS ABOUT 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.

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.

Problems with the blood have been reported with RISPERDAL[®] CONSTA[®] and similar medications. Depending upon condition your doctor may choose to monitor your blood as you start therapy with RISPERDAL[®] CONSTA.

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.

Painful, long lasting erections have been reported with the use of RISPERDAL[®] CONSTA[®]. Call your doctor immediately if you think you are having this problem.

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 administering RISPERDAL[®] CONSTA[®] 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.

In a study of people taking RISPERDAL CONSTA, the most common side effects in the treatment of Bipolar I Disorder were weight gain (when used alone) and tremors (when used with other medications).

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 ($\geq 5\%$) 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 increase (5% in monotherapy trial) and tremor and parkinsonism ($\geq 10\%$ in adjunctive therapy trial).

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