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NURSE PRACTITIONERS' PRESCRIBING REFERENCE®

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PRESCRIBING ALERT®

Dear Healthcare Professional,

At *NPPR*, we strive to bring you important drug information in a concise and timely fashion. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT announcing the approval of a new indication for RISPERDAL® CONSTA® (risperidone) LONG-ACTING INJECTION from Ortho-McNeil-Janssen Pharmaceuticals, Inc. RISPERDAL® CONSTA® is approved as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.

This approval was based on two prospective, randomized, double-blind, controlled studies for the long-term treatment of Bipolar I Disorder. In one 52-week study, RISPERDAL® CONSTA® significantly delayed time to relapse when used as adjunctive therapy to lithium or valproate compared with placebo plus lithium or valproate.[1,a] In a second long-term study, RISPERDAL® CONSTA® significantly delayed time to relapse when used as monotherapy compared with placebo.[1,b]

[a] Demonstrated in a 52-week, multicenter, randomized, double-blind, placebo-controlled study in 124 patients with Bipolar I Disorder. Doses of 25, 37.5, or 50 mg were given by intramuscular injection every 2 weeks, in addition to their individually defined adjunctive treatment which consisted of mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. All other antipsychotics were discontinued after the first 3 weeks of the initial injection. Patients who were judged to be stable for the last 4 weeks were randomized in the double-blind phase. The primary endpoint was time to relapse to any new mood episode.[1]

[b] Demonstrated in up to 104 weeks in a multicenter, randomized, double-blind, placebo-controlled study in 303 patients with Bipolar I Disorder. Doses of 25, 37.5, or 50 mg were given by intramuscular injection every 2 weeks. Patients who were judged to be stable for the last 8 weeks were randomized in the double-blind phase. The primary endpoint was time to relapse to any new mood episode.[1]

The most common adverse reactions in the double-blind, placebo-controlled periods of the bipolar disorder trials were weight increase (5% in the monotherapy trial) and tremor and Parkinsonism (≥10% in the adjunctive treatment trial).[1]

IMPORTANT SAFETY INFORMATION

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.

(Important Safety Information continued on back)

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 D_2 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: RISPERDAL® CONSTA® should be injected into the deltoid or gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel.

Suicide: The possibility of suicide attempt is inherent in mental illness. 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).

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 bipolar disorder were weight increased (5% in monotherapy trial) and tremor and Parkinsonism (≥10% in adjunctive therapy trial).

More information about RISPERDAL® CONSTA® is available in the current edition of *NPPR*.

For your reference, please see enclosed full Prescribing Information, including Boxed Warning, for RISPERDAL® CONSTA®.

Sincerely,

Grace L. McBride

Grace L. McBride
Editorial Director,
NPPR Custom Programs

REFERENCES

1. RISPERDAL® CONSTA® [Prescribing Information]. Ortho-McNeil-Janssen Pharmaceuticals, Inc, Titusville, NJ.
2. Data on file, RIS-BIP-302 (B). Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, NJ.
3. Data on file, RIS-BIM-3003. Johnson & Johnson Pharmaceutical Research and Development, Titusville, NJ.

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PRESCRIBING ALERT

RISPERDAL® CONSTA®

(risperidone) Long-Acting Injection

Company: Ortho-McNeil-Janssen Pharmaceuticals, Inc. ℞

Pharmacological Class: Benzisoxazole

Active Ingredient: Risperidone 12.5 mg, 25 mg, 37.5 mg, 50 mg; per vial; suspension for long-acting intramuscular injection after reconstitution.

Indications*: Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.

Adults*: Risperidone-naive: rule out risperidone hypersensitivity before using injection. Give by deep deltoid or gluteal intramuscular injection. Give with oral risperidone (or other antipsychotic) for 3 weeks, then stop oral form. ≥18 yrs: 25 mg intramuscular every 2 weeks; may adjust dose every 4 weeks. Max 50 mg every 2 weeks. For intramuscular injection only.

Children: <18 yrs: not recommended

New indication, flexibility in administration sites

How supplied: Injection (single-use vial)—1 dose (pack w. diluent, supplies); also available as a hospital unit dose blister pack of 100
Vial/kit: 12.5 mg, 25 mg, 37.5 mg, 60 mg

** See Prescribing Information for additional indications and dosing.*

Please see Important Safety Information, including Boxed Warning, for RISPERDAL® CONSTA® on the reverse side and enclosed full Prescribing Information.

☑ **Approved for the maintenance treatment of Bipolar I Disorder either as monotherapy or adjunctive therapy to lithium or valproate[1]**

- Proven efficacy with guaranteed medication coverage when administered every 2 weeks[1]
- Flexibility in administration sites, with deltoid and gluteal options to meet patient needs[1,a]

[a] Deltoid administration is only appropriate for patients with adequate muscle mass.

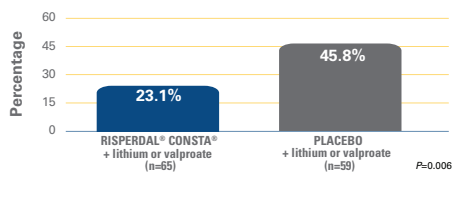
☑ **In a 52-week trial of patients with Bipolar I Disorder, RISPERDAL® CONSTA® significantly delayed time to relapse when used as adjunctive therapy to lithium or valproate[1,2] (*P*=0.01)**

- 23.1% of patients relapsed on RISPERDAL® CONSTA® when used as adjunctive therapy to lithium or valproate (n=65)[2]
- 45.8% of patients relapsed on placebo when used as adjunctive therapy to lithium or valproate (n=59)[2]

☑ **In a long-term monotherapy trial of patients with Bipolar I Disorder, RISPERDAL® CONSTA® significantly delayed time to relapse when used as monotherapy[1,3,c,d] (*P*<0.001)**

- 30% of patients relapsed on RISPERDAL® CONSTA® (n=140)[3]
- 56% of patients relapsed on placebo (n=135)[3]

PERCENTAGE OF PATIENTS WHO RELAPSED[b]



[b] Demonstrated in a 52-week, multicenter, randomized, double-blind, placebo-controlled study in 124 patients with Bipolar I Disorder. Doses of 25, 37.5, or 50 mg were given by intramuscular injection every 2 weeks, in addition to their individually defined adjunctive treatment which consisted of mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. All other antipsychotics were discontinued after the first 3 weeks of the initial injection. Patients who were judged to be stable for the last 4 weeks were randomized in the double-blind phase. The primary endpoint was time to relapse to any new mood episode.[1]

Source: Data on file, RIS-BIM-3003.[3]

[c] Demonstrated in up to 104 weeks in a multicenter, randomized, double-blind, placebo-controlled study in 303 patients with Bipolar I Disorder. Doses of 25, 37.5, or 50 mg were given by intramuscular injection every 2 weeks. Patients who were judged to be stable for the last 8 weeks were randomized in the double-blind phase. The primary endpoint was time to relapse to any new mood episode.[1]

[d] Patients were enrolled until they experienced a relapse or completed 104 weeks. The trial was terminated when a predetermined number of relapses (114) were observed. At study completion, the median duration of exposure was 280.5 days (9.2 months) for RISPERDAL® CONSTA® and 151 days (5 months) for placebo.[3]

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REFERENCES

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