

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RISPERDAL CONSTA® safely and effectively. See full prescribing information for RISPERDAL CONSTA®.

RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION

Initial U.S. Approval: 2003

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL CONSTA® is not approved for use in patients with dementia-related psychosis. (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions (5.8)

02/2017

INDICATIONS AND USAGE

RISPERDAL CONSTA® is an atypical antipsychotic indicated:

- for the treatment of schizophrenia. (1.1)
- as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder. (1.2)

DOSAGE AND ADMINISTRATION

- For patients who have never taken oral RISPERDAL®, tolerability should be established with oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®. (2)
- Administer by deep intramuscular (IM) deltoid or gluteal injection. Each injection should be administered by a health care professional using the appropriate enclosed safety needle (1-inch for deltoid administration alternating injections between the two arms and 2-inch for gluteal administration alternating injections between the two buttocks). Do not administer intravenously. (2)
- 25 mg intramuscular (IM) every 2 weeks. Patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks. (2)
- Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL CONSTA®, and continued for 3 weeks (and then discontinued) to ensure adequate therapeutic plasma concentrations from RISPERDAL CONSTA®. (2)
- Upward dose adjustment of RISPERDAL CONSTA® should not be made more frequently than every 4 weeks. Clinical effects of each upward dose adjustment should not be anticipated earlier than 3 weeks after injection. (2)
- Avoid inadvertent administration into a blood vessel. (5.16)
- See Full Prescribing Information Section 2.8 for instructions for use.

DOSAGE FORMS AND STRENGTHS

Vial kits: 12.5 mg, 25 mg, 37.5 mg, and 50 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to risperidone, paliperidone, or to any excipients in RISPERDAL CONSTA®. (4)

WARNINGS AND PRECAUTIONS

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL CONSTA® is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.3)
- Tardive Dyskinesia: Discontinue treatment if clinically appropriate (5.4)
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
 - *Hyperglycemia and Diabetes Mellitus:* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.5)
 - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
 - *Weight Gain:* Significant weight gain has been reported. Monitor weight gain. (5.5)
- Hyperprolactinemia: Risperidone treatment may elevate prolactin levels. Long-standing hyperprolactinemia, when associated with

hypogonadism, can lead to decreased bone density in men and women. (5.6)

- Orthostatic hypotension: associated with dizziness, tachycardia, bradycardia, and syncope can occur, especially during initial dose titration with oral risperidone. Use caution in patients with cardiovascular disease, cerebrovascular disease, and conditions that could affect hemodynamic responses. (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotics, including RISPERDAL CONSTA®. Patients with history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood cell count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL CONSTA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- Potential for cognitive and motor impairment: has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. (5.10)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. (5.12)
- Priapism: has been reported. Severe priapism may require surgical intervention. (5.13)
- Thrombotic Thrombocytopenic Purpura (TTP): has been reported. (5.14)
- Avoid inadvertent administration into a blood vessel. (5.16)
- Suicide: There is increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. (5.17)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies: has been reported. Manifestations include mental status changes, motor impairment, extrapyramidal symptoms, and features consistent with Neuroleptic Malignant Syndrome. (5.19)
- Diseases or conditions that could affect metabolism or hemodynamic responses: Use with caution in patients with such medical conditions (e.g., recent myocardial infarction or unstable cardiac disease). (5.19)

ADVERSE REACTIONS

The most common adverse reactions in clinical trials in patients with schizophrenia ($\geq 5\%$) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increased (5% in monotherapy trial) and tremor and parkinsonism ($\geq 10\%$ in adjunctive therapy trial). (6)

The most common adverse reactions that were associated with discontinuation from clinical trials in patients with schizophrenia were agitation, depression, anxiety, and akathisia. Adverse reactions that were associated with discontinuation from bipolar disorder trials were hyperglycemia (one subject monotherapy trial) and hypokinesia and tardive dyskinesia (one subject each in adjunctive therapy trial). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Due to CNS effects, use caution when administering with other centrally-acting drugs. Avoid alcohol. (7.1)
- Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced. (7.2)
- Effects of levodopa and dopamine agonists may be antagonized. (7.3)
- Cimetidine and ranitidine increase the bioavailability of risperidone. (7.5)
- Clozapine may decrease clearance of risperidone. (7.6)
- Fluoxetine and paroxetine increase plasma concentrations of risperidone. (7.11)
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. (7.12)

USE IN SPECIFIC POPULATIONS

- Renal or Hepatic Impairment: dose appropriately with oral RISPERDAL® prior to initiating treatment with RISPERDAL

CONSTA®. A lower starting dose of RISPERDAL CONSTA® of 12.5 mg may be appropriate in some patients. (2.4)

- Nursing Mothers: should not breast feed. (8.3)
- Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)

- Elderly: dosing for otherwise healthy elderly patients is the same as for healthy nonelderly. Elderly may be more predisposed to orthostatic effects than nonelderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE

- 1.1 Schizophrenia
- 1.2 Bipolar Disorder

2 DOSAGE AND ADMINISTRATION

- 2.1 Schizophrenia
- 2.2 Bipolar Disorder
- 2.3 General Dosing Information
- 2.4 Dosage in Special Populations
- 2.5 Reinitiation of Treatment in Patients Previously Discontinued
- 2.6 Switching from Other Antipsychotics
- 2.7 Co-Administration of RISPERDAL CONSTA® with Certain Other Medications
- 2.8 Instructions for Use

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- 5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Tardive Dyskinesia
- 5.5 Metabolic Changes
- 5.6 Hyperprolactinemia
- 5.7 Orthostatic Hypotension
- 5.8 Falls
- 5.9 Leukopenia, Neutropenia, and Agranulocytosis
- 5.10 Potential for Cognitive and Motor Impairment
- 5.11 Seizures
- 5.12 Dysphagia
- 5.13 Priapism
- 5.14 Thrombotic Thrombocytopenic Purpura (TTP)
- 5.15 Body Temperature Regulation
- 5.16 Administration
- 5.17 Antiemetic Effect
- 5.18 Suicide
- 5.19 Use in Patients with Concomitant Illness
- 5.20 Osteodystrophy and Tumors in Animals
- 5.21 Monitoring: Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia
- 6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Bipolar Disorder
- 6.3 Other Adverse Reactions Observed During the Clinical Trial Evaluation of Risperidone
- 6.4 Discontinuations Due to Adverse Reactions
- 6.5 Dose Dependency of Adverse Reactions in Clinical Trials

- 6.6 Changes in ECG
- 6.7 Pain Assessment and Local Injection Site Reactions
- 6.8 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Centrally-Acting Drugs and Alcohol
- 7.2 Drugs with Hypotensive Effects
- 7.3 Levodopa and Dopamine Agonists
- 7.4 Amitriptyline
- 7.5 Cimetidine and Ranitidine
- 7.6 Clozapine
- 7.7 Lithium
- 7.8 Valproate
- 7.9 Digoxin
- 7.10 Topiramate
- 7.11 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes
- 7.12 Carbamazepine and Other CYP 3A4 Enzyme Inducers
- 7.13 Drugs Metabolized by CYP 2D6

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

- 10.1 Human Experience
- 10.2 Management of Overdosage

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Schizophrenia
- 14.2 Bipolar Disorder - Monotherapy
- 14.3 Bipolar Disorder - Adjunctive Therapy

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Orthostatic Hypotension
- 17.2 Interference with Cognitive and Motor Performance
- 17.3 Pregnancy
- 17.4 Nursing
- 17.5 Concomitant Medication
- 17.6 Alcohol

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING 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 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. [see Warnings and Precautions (5.1)]

1 INDICATIONS AND USAGE

1.1 Schizophrenia

RISPERDAL CONSTA[®] (risperidone) is indicated for the treatment of schizophrenia [see Clinical Studies (14.1)].

1.2 Bipolar Disorder

RISPERDAL CONSTA[®] is indicated as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder [see Clinical Studies (14.2, 14.3)].

2 DOSAGE AND ADMINISTRATION

For patients who have never taken oral RISPERDAL[®], it is recommended to establish tolerability with oral RISPERDAL[®] prior to initiating treatment with RISPERDAL CONSTA[®].

RISPERDAL CONSTA[®] should be administered every 2 weeks by deep intramuscular (IM) deltoid or gluteal injection. Each injection should be administered by a health care professional using the appropriate enclosed safety needle [see Dosage and Administration (2.8)]. For deltoid administration, use the 1-inch needle alternating injections between the two arms. For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. Do not administer intravenously.

2.1 Schizophrenia

The recommended dose for the treatment of schizophrenia is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for RISPERDAL CONSTA[®], some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The

maximum dose should not exceed 50 mg RISPERDAL CONSTA[®] every 2 weeks. No additional benefit was observed with dosages greater than 50 mg RISPERDAL CONSTA[®]; however, a higher incidence of adverse effects was observed.

The efficacy of RISPERDAL CONSTA[®] in the treatment of schizophrenia has not been evaluated in controlled clinical trials for longer than 12 weeks. Although controlled studies have not been conducted to answer the question of how long patients with schizophrenia should be treated with RISPERDAL CONSTA[®], oral risperidone has been shown to be effective in delaying time to relapse in longer-term use. It is recommended that responding patients be continued on treatment with RISPERDAL CONSTA[®] at the lowest dose needed. The physician who elects to use RISPERDAL CONSTA[®] for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.2 Bipolar Disorder

The recommended dose for monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder is 25 mg IM every 2 weeks. Some patients may benefit from a higher dose of 37.5 mg or 50 mg. Dosages above 50 mg have not been studied in this population. The physician who elects to use RISPERDAL CONSTA[®] for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.3 General Dosing Information

A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with hepatic or renal impairment, for certain drug interactions that increase risperidone plasma concentrations [*see Drug Interactions (7.11)*] or in patients who have a history of poor tolerability to psychotropic medications. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Oral RISPERDAL[®] (or another antipsychotic medication) should be given with the first injection of RISPERDAL CONSTA[®] and continued for 3 weeks (and then discontinued) to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site [*see Clinical Pharmacology (12.3)*].

Upward dose adjustment should not be made more frequently than every 4 weeks. The clinical effects of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

In patients with clinical factors such as hepatic or renal impairment or certain drug interactions that increase risperidone plasma concentrations [*see Drug Interactions (7.11)*], dose reduction as

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