RISPERDAL® CONSTA®

(risperidone) LONG-ACTING INJECTION

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)

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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 treatment of Bipolar I Disorder. (1.2)

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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. (5.15)

See Full Prescribing Information Section 2.8 for instructions for use.

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DOSAGE FORMS AND STRENGTHS

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

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CONTRAINDICATIONS

• Known hypersensitivity to the product (4)

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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)

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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)

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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)

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SIDE EFFECTS

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. (5.8)

Potential for cognitive and motor impairment has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. (5.9)

Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.10)

Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. (5.11)

Priapism: has been reported. Severe priapism may require surgical intervention. (5.12)

Thrombotic Thrombocytopenic Purpura (TTP): has been reported. (5.13)

Avoid inadvertent administration into a blood vessel. (5.15)

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. (5.18)

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) (5.18)

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ADVERSE REACTIONS

The most common adverse reactions in clinical trials in patients with schizophrenia (≥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 (≥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

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See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2014
1 INDICATIONS AND USAGE
1.1 Schizophrenia
RISPERDAL® CONSTA® (risperidone) is indicated for the treatment of schizophrenia [see Clinical Studies (14.1)].

2 DOSAGE AND ADMINISTRATION
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 dosages greater than 50 mg RISPERDAL® CONSTA®; however, a higher incidence of adverse effects was observed.

2.2 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)].

2.3 General Dosing Information

2.4 Dosage in Special Populations

2.5 Reinitiation of Treatment in Patients Previously Discontinued

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[*Sections or subsections omitted from the full prescribing information are not listed]
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 anticipated that responding patients be continued on the 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 low as 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Do not combine different dose strengths of RISPERDAL® CONSTA® in a single administration.

2.4 Dosage in Special Populations

Elderly

For elderly patients treated with RISPERDAL® CONSTA®, the recommended dosage is 25 mg IM every 2 weeks. Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL® CONSTA® and should be continued for 3 weeks 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)].

Renal or Hepatic Impairment

Patients with renal or hepatic impairment should be treated with titrated doses of oral RISPERDAL® prior to initiating treatment with RISPERDAL® CONSTA®. The recommended starting dose is 0.5 mg oral RISPERDAL® twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. A total daily dose of at least 2 mg oral RISPERDAL® is well tolerated. An injection of 25 mg RISPERDAL® CONSTA® can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower tolerance may be medically appropriate. Alternatively, a starting dose of RISPERDAL® CONSTA® of 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Patients with renal impairment may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have an increase in the free fraction of the risperidone, possibly resulting in an enhanced effect [see Clinical Pharmacology (12.3)]. Elderly patients and patients with a predisposition to hypertensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting or lying for several minutes before attempting to stand in the morning and slowly rising from a seated position). These patients should avoid sodium depletion or dehydration, and circumstances that accentuate hypotension (alcohol intake, high ambient temperature, etc.). Monitoring of orthostatic signs should be considered [see Warnings and Precautions (5.7)].

2.5 Reinitiation of Treatment in Patients Previously Discontinued

There are no data to specifically address reinitiation of treatment. When restarting patients who have had an interval off treatment with RISPERDAL® CONSTA®, supplementation with oral RISPERDAL® (or another antipsychotic medication) should be administered.

2.6 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients from other antipsychotics to RISPERDAL® CONSTA®, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of RISPERDAL® CONSTA® to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun [see Clinical Pharmacology (12.3)].

For patients who have never taken oral RISPERDAL®, it is recommended to start therapy with the lowest dose of 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.

2.7 Co-Administration of RISPERDAL® CONSTA® with Certain Other Medications

Co-administration of carbamazepine and other CYP 3A4 enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of the sum of risperidone and 9-hydroxyrisperidone combined, which could lead to decreased efficacy of RISPERDAL® CONSTA® treatment. The dose of risperidone needed to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers [see Drug Interactions (7.11)]. At the initiation of therapy with carbamazepine in the known CYP 3A4 hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL® CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of RISPERDAL® CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL® CONSTA® and discontinuing from carbamazepine or other CYP3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of RISPERDAL® CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg RISPERDAL® CONSTA®, it is recommended to continue treatment with the 25 mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. When RISPERDAL® CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied. [see Drug Interactions (7.11)]

2.8 Instructions for Use

Dose pack components include:

- RISPERDAL® CONSTA® requires close attention to the step-by-step 'Instructions for Use' to help avoid difficulties in the use of the kit.

RISPERDAL® CONSTA® must be reconstituted only in the diluent supplied in the dose pack, and must be administered with only the appropriate needle from the dose pack for subcutaneous or intramuscular injection. All components are required for administration. Do not substitute any components of the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone. It is recommended to administer immediately after reconstitution.

Remove the dose pack of RISPERDAL® CONSTA® from the refrigerator and allow it to come to room temperature for approximately 30 minutes prior to reconstitution.

1. Flip off the plastic colored cap from the vial. Do not remove the grey rubber stopper. Wipe the top of the grey rubber stopper with an alcohol wipe and allow to dry.
2. Peel back the blister pouch and remove the SmartSite® Needle-Free Vial Access Device by holding between the white luer cap and the skirt. Do not touch the spike tip of the access device at any time.

3. It is very important that the SmartSite® Needle-Free Vial Access Device be placed on the vial correctly or the diluent could leak upon transfer to the vial.

   Place the vial on a hard surface. Hold the base of the vial. Orient the SmartSite® Needle-Free Vial Access Device vertically over the vial so that the spike tip is at the center of the vial’s rubber stopper.

   For all assembly steps, hold the syringe only by the white collar located at the tip of the syringe. Holding the white collar will help to prevent the white collar from getting detached and ensure a good connection to the syringe. Be careful to not overtighten components when assembling. Over tightening connections may cause syringe component parts to loosen from the syringe body.

4. Hold the base of the vial and swab the syringe connection point (blue circle) of the SmartSite® Needle-Free Vial Access Device with an alcohol wipe and allow to dry prior to attaching the syringe to the SmartSite® Needle-Free Vial Access Device.

5. The prefilled syringe has a white tip consisting of 2 parts: a white collar and a smooth white cap. To open the syringe, hold the syringe by the white collar and snap off the smooth white cap (DO NOT TWIST OR CUT OFF THE WHITE CAP). Remove the white cap together with the rubber tip cap inside.

   With a straight downward push, press the spike tip of the SmartSite® Needle-Free Vial Access Device through the center of the vial’s rubber stopper until the device securely snaps onto the vial top.

6. While holding the white collar of the syringe, insert and press the syringe tip into the blue circle of the SmartSite® Needle-Free Vial Access Device and twist in a clockwise motion to secure the connection of the syringe to the SmartSite® Needle-Free Vial Access Device (avoid over-twisting). Hold the skirt of the SmartSite® Needle-Free Vial Access Device during attachment to prevent it from spinning.

   Keep the syringe and SmartSite® Needle-Free Vial Access Device aligned.

7. Inject the entire contents of the syringe containing the diluent into the vial.

8. Shake the vial VIGOROUSLY while holding the plunger rod down with the thumb for a minimum of 10 seconds to ensure a homogenous suspension. When properly mixed, the suspension appears uniform, thick, and milky in color. The microspheres will be visible in liquid, but no dry microspheres remain.

   DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.

9. Invert the vial completely and SLOWLY withdraw the entire content of the suspension from the vial into the syringe. Tear the section of the vial label at the perforation and apply the detached label to the syringe for identification purposes.

10. While holding the white collar of the syringe, unscrew the SmartSite® Needle-Free Vial Access Device. Discard both the vial and vial access device appropriately.

11. Select the appropriate needle provided with the kit:

   For GLUTEAL injection, select the 20G TW 2-inch needle (longer needle with yellow colored hub in blister with yellow print).

   For DELTOID injection, select the 21G UTW 1-inch needle (shorter needle with green colored hub in blister with green print).

12. Peel the blister pouch of the Needle-Pro® safety device open halfway. Grasp the transparent needle sheath using the plastic peel pouch. To prevent contamination, be careful not to touch the orange Needle-Pro® safety device’s luer connector. While holding the white collar of the syringe, attach the luer connection of the orange Needle-Pro® safety device to the syringe with an easy clockwise twisting motion.

13. While continuing to hold the white collar of the syringe, grasp the transparent needle sheath and seat the needle firmly on the orange Needle-Pro® safety device with a push and a clockwise twist. Seating the needle is an important step to secure the connection between the needle and the orange Needle-Pro® safety device.

14. RESUSPENSION OF RISPERDAL® CONSTA® WILL BE NECESSARY PRIOR TO ADMINISTRATION. AS SETTLING WILL OCCUR OVER TIME ONCE PRODUCT IS RECONSTITUTED. RESUSPEND THE MICROSHERES IN THE SYRINGE BY SHAKING VIGOROUSLY.

15. While holding the white collar of the syringe, pull the transparent needle sheath straight away from the needle. DO NOT TWIST the sheath as the luer connections may be loosened.

16. Tap the syringe gently to make any air bubbles rise to the top. Remove air in syringe by depressing the plunger rod, carefully and slowly, while holding the needle in an upright position. Inject the entire contents of the syringe intramuscularly (IM) into the selected gluteal or deltoid muscle of the patient immediately. Gluteal injection should be made into the upper outer quadrant of the gluteal area.

   DO NOT ADMINISTER INTRAVENOUSLY.

   WARNING: To avoid a needle stick injury with a contaminated needle:

   • Do not use free hand to press the Needle-Pro® safety device over the needle.

   • Do not intentionally disengage the Needle-Pro® safety device.

   • Do not attempt to straighten the needle or engage Needle-Pro® safety device if the needle is bent or damaged.

   • Do not mishandle the Needle-Pro® safety device as it may cause the needle to protrude from the Needle-Pro® safety device.

17. After the injection is complete, press the needle into the orange Needle-Pro® safety device using a one-handed technique. Perform a one-handed technique by GENTLY pressing the orange Needle-Pro® safety device against a flat surface. AS THE ORANGE NEEDLE-PRO® SAFETY DEVICE IS PRESSED, THE NEEDLE WILL FIRMLY ENGAGE INTO THE ORANGE NEEDLE-PRO® SAFETY DEVICE. Visually confirm that the needle is fully engaged into the orange Needle-Pro® safety device before discarding. Discard needle appropriately. Also discard the other (unused) needle provided in the dose pack.

   Stability after reconstitution: Once in suspension, the product may remain at room temperature (do not expose to temperatures above 77ºF (25ºC)). RISPERDAL® CONSTA® must be used within 6 hours of suspension, but should always be reconstituted prior to administration if not used immediately.

   Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

   Do Not Reuse: Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.
3 DOSE FORMS AND STRENGTHS
RISPERDAL® CONSTA® (risperidone) LONG-ACTING INJECTION

RISPERDAL® CONSTA® is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, and 50 mg risperidone. It is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL® CONSTA®, a SmartSite® Needle-Free Vial Access Device, and two Needle-Pro™ Safety needles for intramuscular injection (a 21 G TW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

4 CONTRAINDICATIONS
RISPERDAL® CONSTA® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

5.1 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. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral risperidone compared to patients treated with placebo. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis [See also Boxed Warning and Warnings and Precautions (5.1)]

5.3 Neuroleptic Malignant Syndrome (NMS)
A potentially fatal, delirium-seizure-psychosis complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes features of serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible is believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress or partially suppress extrapyramidal signs and symptoms of the syndrome and thereby mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® CONSTA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL® CONSTA®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® CONSTA® despite the presence of the syndrome.

5.5 Metabolic Changes
Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not complete.

In some cases, hyperglycemia has resolved when the atypical antipsychotic, including RISPERDAL®, was discontinued; however, some patients required continuation of atypical antipsychotic treatment despite discontinuation of RISPERDAL®.

Pooled data from 3 double-blind, placebo-controlled studies in subjects with schizophrenia and 4 double-blind, placebo-controlled monotherapy studies in subjects with bipolar mania with oral risperidone are presented in Table 1.

Table 1. Change in Random Glucose From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects With Schizophrenia or Bipolar Mania With Oral Risperidone

<table>
<thead>
<tr>
<th></th>
<th>Placebo 1-8 mg/day</th>
<th>&gt;8-16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>n=555</td>
<td>n=748</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Proportion of patients with shifts</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

In longer-term, controlled and uncontrolled studies in adult subjects, RISPERDAL® was associated with an increased change in glucose of +2.8 mg/dL at Week 24 (n=151) and +4.1 mg/dL at Week 48 (n=50).

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Pooled data from 7 placebo-controlled, 3- to 8-week, fixed- or flexible-dose studies in adult subjects with schizophrenia or bipolar mania are presented in Table 2.

Table 2. Change in Random Lipids From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects With Schizophrenia or Bipolar Mania With Oral Risperidone

<table>
<thead>
<tr>
<th></th>
<th>Placebo 1-8 mg/day</th>
<th>&gt;8-16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>n=559</td>
<td>n=742</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>n=183</td>
<td>n=307</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>n=183</td>
<td>n=307</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-17.4</td>
<td>-4.9</td>
</tr>
</tbody>
</table>

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with an increased change in triglycerides of +4.8 mg/dL at Week 24 (n=231) and +5.5 mg/dL at Week 48 (n=86); and (b) non-fasting triglycerides of +19.9 mg/dL at Week 24 (n=52).

Weight Gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Data from a placebo-controlled, 12-week, fixed-dose study in adult subjects with schizophrenia are presented in Table 3.
patients with advanced Alzheimer’s dementia, RISPERDAL® CONSTA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. [see also Boxed Warning and Warnings and Precautions (5.1)]

5.12 Priapism
Priapism has been reported during postmarketing surveillance [see Adverse Reactions (6.8)]. Severe priapism may require surgical intervention.

5.13 Thrombotic Thrombocytopenic Purpura (TTP)
A single case of TTP was reported in a 28-year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients).

5.14 Body Temperature Regulation
Disruption of body temperature regulation has been attributed to antipsychotic agents.

5.15 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. [see Dosage and Administration (2) and Adverse Reactions (6.7)]

5.16 Antiemetic Effect
Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or conditions such as intestinal obstruction, Reye’s syndrome, and brain tumor.

5.17 Suicide
There is an increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. [see Boxed Warning]; therefore, suicide due to an overdose is unlikely.

5.18 Use in Patients with Concomitant Illness
Clinical experience with RISPERDAL® CONSTA® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson’s Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL® CONSTA®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

5.19 Osteodystrophy and Tumors in Animals
RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 2-year carcinogenicity study conducted in mice and rats [see Nonclinical Toxicology (13.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.20 Monitoring: Laboratory Tests
Although patients with certain concomitant conditions that could affect metabolism or hemodynamic responses.

5.21 Anticholinergic Effects
RISPERDAL® CONSTA® may induce anticholinergic effects associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period with oral risperidone, probably reflecting its alpha-adrenergic antagonist properties. Syncope was reported in 0.8% (12/1459 patients) of patients treated with RISPERDAL® CONSTA® in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). RISPERDAL® CONSTA® should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment.

5.22 Exacerbation of Parkinson’s Disease
RISPERDAL® CONSTA® is used with particular caution in patients with Parkinson’s Disease or dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL® CONSTA®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

5.23 Geriatric Use
Clinical experience with RISPERDAL® CONSTA® in the non-psychiatric population is limited. The increased sensitivity to anticholinergic effects associated with RISPERDAL® CONSTA® may be greater in geriatric patients, and these patients should receive close monitoring for anticholinergic effects (e.g., extrapyramidal symptoms).

5.24 Use in Patients with History of Asthma, Allergy, or Pneumonia
RISPERDAL® CONSTA® and other antipsychotic drugs should be used cautiously in patients with a history of asthma, allergy, or pneumonia. [see Boxed Warning and Warnings and Precautions (5.1)]

5.25 Other Drugs
Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m2) treated with oral RISPERDAL®; an increase in the free fraction of risperidone is also seen in patients with severe hepatic impairment. Patients with renal or hepatic impairment should be monitored closely before treatment with RISPERDAL® CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, as such in patients with renal or hepatic impairment [see Dosage and Administration (2.4)].

5.26 Use in Patients with Renal or Hepatic Impairment
RISPERDAL® CONSTA® produced increased plasma concentration of 9-hydroxyrisperidone in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m2) treated with oral RISPERDAL®; an increase in the free fraction of risperidone is also seen in patients with severe hepatic impairment. Patients with renal or hepatic impairment should be monitored closely before treatment with RISPERDAL® CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, as such in patients with renal or hepatic impairment [see Dosage and Administration (2.4)].

5.27 Use in Patients with Advanced Alzheimer’s Disease
RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks. RISPERDAL® CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity studies conducted in mice and rats [see Nonclinical Toxicology (13.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.28 Use in Patients with HIV Infection
Monitoring of orthostatic vital signs should be considered in all such patients, and conditions which could predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment.

5.29 Use in Patients with Pheochromocytoma
Disruption of body temperature regulation has been attributed to antipsychotic agents.

5.30 Use in Patients with Pneumonia
Severe priapism may require surgical intervention.

5.31 Use in Patients with Prior History of TTP
RISPERDAL® in a large, open premarketing experience (approximately 1300 patients).

5.32 Use in Patients with Renal or Hepatic Impairment
RISPERDAL® CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL® CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. (Cellular proliferation was not measured at the low dose or in females in either study.)

5.33 Use in Patients with Severe Renal or Hepatic Impairment
The effect dose for osteodystrophy and the tumor findings is 8 times the IM maximum recommended human dose (MRHD) (50 mg) on a mg/m2 basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the IM MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the IM MRHD on a mg/m2 basis). Plasma exposure (AUC) at the no-effect dose was one third the expected plasma exposure (AUC) at the IM MRHD.

5.34 Use in Patients with Severe Renal or Hepatic Impairment
Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone. Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study.

5.35 Use in Patients with Severe Renal or Hepatic Impairment
The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail in Section 13.1 (Carcinogenicity, Mutagenesis, Impairment of Fertility).

The relevance of these findings to human risk is unknown.
Disorder Type I or Type II and who experienced at least 4 episodes of mood disorder
placebo-controlled study were adult patients who met DSM-IV criteria for Bipolar
randomized into a 24-month double-blind, placebo-controlled period in which they
a 26-week stabilization period of open-label RISPERDAL ® CONSTA ® (n=501).

In addition to the studies in patients with schizophrenia, safety data are presented
in patients with bipolar disorder. The subjects in this multi-center, double-blind,
placebo-controlled study demonstrated a maintained response during this period were then
Subjects who demonstrated an initial response to oral risperidone in this period and those who
were stable on risperidone (oral or long-acting injection), were stable on other
antipsychotics or mood stabilizers, or were experiencing an acute episode. After a
3-week period of treatment with open-label oral risperidone (n=440), subjects who demonstrated an initial response to oral risperidone in this period and those who
were stable on risperidone (oral or long-acting injection) at study entry entered into a
26-week stabilization period of open-label RISPERDAL ® CONSTA ® (n=501). Subjects who demonstrated a maintained response during this period were then randomized into a 24-month double-blind, placebo-controlled period in which they received RISPERDAL ® CONSTA ® in addition to continuing their
treatment as usual, which consisted of various mood stabilizers (primarily lithium
valproate, and/or divalproex sodium, and/or lamotrigine). Patients who reached remission at the end of this 16-week open-label treatment phase (n=139) were then randomized into a 52-week double-blind, placebo-controlled phase in which they received RISPERDAL ® CONSTA ® (n=72) or placebo (n=67) as adjunctive treatment in addition to continuing their treatment as usual. Patients who did not reach remission at the end of the 16-week open-label treatment phase could choose to continue to receive RISPERDAL ® CONSTA ® as adjunctive therapy in an open-label manner, in addition to continuing their treatment as usual, for up to an additional
36 weeks as clinically indicated for a total period of up to 52 weeks; these patients
(n=70) were also included in the evaluation of safety.

Adverse events during exposure to study treatment were obtained by general
inquiry and recorded by clinical investigators using their own terminology.
Consequently, to provide a meaningful estimate of the proportion of individuals
experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are
adverse events that were considered to be reasonably associated with the use of
RISPERDAL ® CONSTA ® (adverse drug reactions) based on the comprehensive
assessment of the available adverse event information. A causal association for
RISPERDAL ® CONSTA ® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly
compared to rates in the clinical trials of another drug and may not reflect the rates
observed in clinical practice.

The majority of all adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled
Clinical Trials - Schizophrenia

Table 4 lists the adverse reactions reported in 2% or more of RISPERDAL ® CONSTA ®-
treated patients with schizophrenia in one 12-week double-blind, placebo-controlled
trial.

Table 4. Adverse Reactions in ≥ 2% of RISPERDAL ® CONSTA ®-Treated Patients
With Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System Organ Class</strong></td>
<td><strong>RISPERDAL ® CONSTA ®</strong></td>
</tr>
<tr>
<td></td>
<td>25 mg (N=59)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Toothache</td>
<td>1</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration</td>
<td></td>
</tr>
<tr>
<td>site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td>5</td>
</tr>
<tr>
<td>Weight increased</td>
<td>4</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
</tr>
<tr>
<td>Parkinsonism*</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia*</td>
<td>4</td>
</tr>
<tr>
<td>Sedation*</td>
<td>5</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>2</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
</tr>
</tbody>
</table>

Fatigue includes fatigue and asthenia. Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restless legs. Sedation includes sedation and somnolence.
6.2 Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Disorder

Table 5 lists the treatment-emergent adverse reactions reported in 2% or more of RISPERDAL® CONSTA®-treated patients in the 24-month double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with Bipolar I Disorder.

Table 5. Adverse Reactions in ≥2% of Patients with Bipolar I Disorder Treated with RISPERDAL® CONSTA® as Monotherapy in a 24-Month Double-Blind, Placebo-Controlled Trial

<table>
<thead>
<tr>
<th>System/Or gan Class</th>
<th>Adverse Reaction</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL® CONSTA® (N=154)</td>
<td>Placebo (N=149)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>3 1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>3 1</td>
</tr>
</tbody>
</table>

Table 6 lists the treatment-emergent adverse reactions reported in 4% or more of patients in the 52-week double-blind, placebo-controlled treatment phase of a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar disorder.

Table 6. Adverse Reactions in ≥4% of Patients with Bipolar Disorder Treated with RISPERDAL® CONSTA® as Adjunctive Therapy in a 52-Week Double-Blind, Placebo-Controlled Trial

<table>
<thead>
<tr>
<th>System/Or gan Class</th>
<th>Adverse Reaction</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL® CONSTA® (N=72)</td>
<td>Placebo + Treatment as Usual (N=67)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Tremor</td>
<td>24 16</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td>15 6</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia</td>
<td>6 3</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>7 1</td>
</tr>
<tr>
<td></td>
<td>Disturbance in attention</td>
<td>4 0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Amenorrhea</td>
<td>4 1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>4 1</td>
</tr>
</tbody>
</table>
6.4 Discontinuations Due to Adverse Reactions

Schizophrenia
Approximately 11% (22/202) of RISPERDAL® CONSTA®-treated patients in the 12-week double-blind, placebo-controlled schizophrenia trial discontinued treatment due to an adverse event, compared with 13% (13/98) who received placebo. The adverse reactions associated with discontinuation in two or more RISPERDAL® CONSTA®-treated patients were: agitation (3%), depression (2%), anxiety (1%), and akathisia (1%).

Bipolar Disorder
In the 24-month double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 1 (0.6%) of 154 RISPERDAL® CONSTA®-treated patients discontinued due to an adverse reaction (hyperglycemia).

In the 52-week double-blind phase of the placebo-controlled trial in which RISPERDAL® CONSTA® was administered as adjunctive therapy to patients with bipolar disorder in addition to continuing their treatment as usual, approximately 4% (3/72) of RISPERDAL® CONSTA®-treated patients discontinued treatment due to an adverse event, compared with 1.5% (1/67) of placebo-treated patients. Adverse reactions associated with discontinuation in RISPERDAL® CONSTA®-treated patients were: hypokinesia (one patient) and tardive dyskinesia (one patient).

6.5 Dose Dependency of Adverse Reactions in Clinical Trials

Extrapyramidal Symptoms:
Two methods are used to measure extrapyramidal symptoms (EPS) in the 12-week double-blind, placebo-controlled trial comparing three doses of RISPERDAL® CONSTA® (25 mg, 50 mg, and 75 mg) with placebo in patients with schizophrenia, including: (1) the incidence of spontaneous reports of EPS symptoms; and (2) the change from baseline to endpoint on the total sum of the subscale scores for parkinsonism, dystonia, and dyskinesia of the Extrapyramidal Symptom Rating Scale (EPSRS).

As shown in Table 1, the overall incidence of EPS-related adverse reactions (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL® CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse reactions was higher in patients treated with 50 mg RISPERDAL® CONSTA®.

The median change from baseline to endpoint in total EPSRS score showed no worsening in patients treated with RISPERDAL® CONSTA® compared with patients treated with placebo: 0 (placebo group), -1 (25-mg group, significantly less than the placebo group), and 0 (50-mg group).

Dystonia
Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

6.6 Changes in ECG

The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® and 50 schizophrenic patients treated with placebo in the 12-week double-blind, placebo-controlled schizophrenia trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia’s and linear correction factors) during treatment with RISPERDAL® CONSTA®.

The electrocardiograms of 227 patients with Bipolar I Disorder were evaluated in the 24-month double-blind, placebo-controlled period. There were no clinically relevant differences in QTc intervals (using Fridericia’s and linear correction factors) during treatment with RISPERDAL® CONSTA® compared to placebo.

The electrocardiograms of 85 patients with bipolar disorder were evaluated in the 52-week double-blind, placebo-controlled trial. There were no statistically significant differences in QTc intervals (using Fridericia’s and linear correction factors) during treatment with RISPERDAL® CONSTA® 25 mg, 37.5 mg, or 50 mg when administered as adjunctive treatment in addition to continuing treatment as usual compared to placebo.

6.7 Pain Assessment and Local Injection Site Reactions

The mean intensity of injection pain reported by patients with schizophrenia using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® experienced redness, swelling, or induration at the injection site.

In a separate study to observe local-site tolerability in which RISPERDAL® CONSTA® was administered into the deltoid muscle every 2 weeks over a period of 8 weeks, no patient discontinued treatment due to local injection site pain or reaction. Clinician ratings indicated that only mild redness, swelling, or induration at the injection site was observed in subjects treated with 37.5 mg or 50 mg RISPERDAL® CONSTA® at 2 hours after deltoid injection. All ratings returned to baseline at the pre-injection assessment of the next injection 2 weeks later. No moderate or severe reactions were observed in any subject.

6.8 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of risperidone because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrial fibrillation, blood cholesterol increased, blood triglycerides increased, diabetes mellitus, diabetic ketoacidosis in patients with impaired glucose metabolism, drug withdrawal syndrome neonatal, dysgeusia, hypoglycemia, hyperthyroidism, ileus, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice, mania, pancreatitis, priapism, QT prolongation, sleep apnea syndrome, thrombocytopenia, urinary retention, and water intoxication. In addition, the following adverse reactions have been observed during postapproval use of RISPERDAL® CONSTA®: drug reactions and Stevens-Johnson syndrome, cerebrovascular accidents, and diabetes mellitus aggravated.

Retinal artery occlusion after injection of RISPERDAL® CONSTA® has been reported during postmarketing surveillance. This has been reported in the presence of abnormal arteriogenous anastomosis.

Serious injection site reactions including abscess, cellulitis, cyst, hematoma, nodule, and ulcer have been reported with RISPERDAL® CONSTA® during postmarketing surveillance. Isolated cases required surgical intervention.

Very rarely, cases of anaphylactic reaction after injection with RISPERDAL® CONSTA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone.

DRUG INTERACTIONS

The interactions of RISPERDAL® CONSTA® with coadministration of other drugs have not been systematically evaluated. The drug interaction data provided in this section is based on studies with oral RISPERDAL®.

7.1 Centrally-Acting Drugs and Alcohol

Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® CONSTA® is administered in combination with other centrally-acting drugs or alcohol.

7.2 Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, RISPERDAL® CONSTA® may enhance the hypotensive effects of other therapeutic agents with this potential.

7.3 Levodopa and Dopamine Agonists

RISPERDAL® CONSTA® may antagonize the effects of levodopa and dopamine agonists.

7.4 Amtriptyline

Amtriptyline may not affect the pharmacokinetics of risperidone or of 9-hydroxyrisperidone and 9-hydroxyrisperidone combined following concomitant administration with oral RISPERDAL®.

7.5 Cimetidine and Ranitidine

Cimetidine and ranitidine increased the bioavailability of oral risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and 9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%.

7.6 Clozapine

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

7.7 Lithium

Repeated doses of oral RISPERDAL® (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (Cmax) of lithium (n=13).

7.8 Valproate

Repeated doses of oral RISPERDAL® (4 mg once daily) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (Cmax) after concomitant administration of oral RISPERDAL®.

7.9 Digoxin

Oral RISPERDAL® (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

7.10 Topiramate

Oral RISPERDAL® administered at doses from 1-6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone Cmax and a 33% decrease in risperidone AUC0-12 hour at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral RISPERDAL® on the pharmacokinetics of topiramate.

7.11 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see Clinical Pharmacology 12.2). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (CYP2D6*1) patients does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.
Risperdal® Consta® (risperidone) Long-Acting Injection

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. Fluoxetine and Paroxetine

Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily), CYP 2D6 inhibitors, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the plasma concentration of risperidone should be re-evaluated. The dose of Risperdal® Consta® should be decreased in patients receiving the recommended dose of 25 mg Risperdal® Consta®. It is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the Risperdal® Consta® dose to 12.5 mg or necessitates interruption of Risperdal® Consta® treatment. When Risperdal® Consta® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. [see also DOSAGE AND ADMINISTRATION (2.5)]. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Erythromycin

There were no significant interactions between oral Risperdal® and erythromycin.

7.12 Carbamazepine and Other CYP 3A4 Enzyme Inducers

Carbamazepine co-administration with oral Risperdal® decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known CYP 3A4 enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of Risperdal® Consta® treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of Risperdal® Consta® may need to be adjusted. A dose increase, or additional oral Risperdal®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of Risperdal® Consta® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of Risperdal® Consta® and discontinuing from carbamazepine or other CYP 3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the Risperdal® Consta® dose to 12.5 mg or necessitates interruption of Risperdal® Consta® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. [see also DOSAGE AND ADMINISTRATION (2.5)].

7.13 Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, Risperdal® Consta® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral Risperdal® did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m² basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m² basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 10 times the oral MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects of oral risperidone were evident by a decrease in body weight gain of live pups and an increase in the number of dead pups at birth (Day 0) and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increased in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were crossed-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m² basis.

No studies were conducted with Risperdal® Consta®. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agensis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to oral Risperdal® therapy is unknown.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs (including Risperdal®) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypotonia, hypotonia, tremor, discontinuation, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Risperdal® Consta® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of Risperdal® Consta® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with Risperdal® Consta® and for at least 12 weeks after the last injection.

8.4 Pediatric Use

Risperdal® Consta® has not been studied in children younger than 18 years old. However, juvenile animal toxicology studies have been conducted with oral risperidone.

Jugendige children were treated for 40 weeks with oral risperidone doses of 0.31, 1.25, or 5 mg/kg/day. Decreased sexual maturation was observed at a no-effect dose of 0.31 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus paliperidone (9-hydroxy-risperidone) which were similar to those in children and adolescents receiving the maximum recommended human dose (MRHD) of 6 mg/day. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12 week drug-free recovery period.

In a study in which juvenile rats were treated with oral risperidone from days 12 to 50 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.62 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus paliperidone about half those observed in humans at the MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest testable dose (1.25 mg/kg/day). This dose produced plasma levels (AUC) of risperidone plus paliperidone which were about two thirds of those observed in humans at the MRHD.

The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated in children and adolescents.

8.5 Geriatric Use

In an open-label study, 57 clinically stable, elderly patients (≥ 65 years old) with schizophrenia or schizoaffective disorder received Risperdal® Consta® every 2 weeks for up to 12 months. In general, no differences in the tolerability of Risperdal® Consta® were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern [see WARNINGS AND PRECAUTIONS (5.7)].

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with oral placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase in mortality in elderly patients with dementia-related psychosis was seen with the use of oral risperidone regardless of concomitant use with furosemide. Risperdal® Consta® is not approved for the treatment of patients with dementia-related psychosis. [see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Risperdal® Consta® (risperidone) is not a controlled substance.

9.2 Abuse

Risperdal® Consta® has not been systematically studied in animals or humans for its potential for abuse. Because Risperdal® Consta® is to be administered by health care professionals, the potential for misuse or abuse by patients is low.
RISPERDAL® CONSTA® (risperidone) LONG-ACTING INJECTION

9.3 Dependence
RISPERDAL® CONSTA® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE
10.1 Human Experience
No cases of overdose were reported in premarketing studies with RISPERDAL® CONSTA®. Because RISPERDAL® CONSTA® is to be administered by health care professionals, the potential for overdose by patients is low.

In premarketing experience with oral RISPERDAL®, there were eight reports of acute RISPERDAL® overdose, with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug’s known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to oral RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de points has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

Postmarketing experience with oral RISPERDAL® includes reports of acute overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to oral RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de points has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

10.2 Management of Overdose
In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If arrhythmia therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolongation and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If a theoretical hazard of QT prolongation is associated with the administration of RISPERDAL® and other QT prolonging agents, it is reasonable to expect that the alpha-blocking properties of bretrenal might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to risperidone. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION
Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl]7,6,8,9-tetrahydro-2-methyl-4H-pyrind[1,2-alpyrimidin-4-one. Its molecular formula is C23H27FN4O2 and its molecular weight is 410.49. The structural formula is:

![Chemical Structure]

Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® CONSTA® (risperidone) Long-Acting Injection is a combination of extended-release microspheres for injection and diluent for parenteral use.

The extended-release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 poly lactide-co-glycolide (PLGA) at a concentration of 381 mg risperidone per gram of microspheres. The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes: polyoctadeca 20, sodium carbomethyl cellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.

RISPERDAL® CONSTA® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action of RISPERDAL® CONSTA®, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5HT2) receptor antagonism.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT2), dopamine Type 2 (D2), cl and α2 adrenergic, and H1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10-6 M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

12.2 Pharmacodynamics
The clinical effect from RISPERDAL® CONSTA® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (see Clinical Pharmacology [12.3]). Antagonism at receptors other than D2 and 5HT2 (see Clinical Pharmacology [12.1]) may explain some of the other effects of RISPERDAL® CONSTA®.

12.3 Pharmacokinetics
Absorption
After a single intramuscular (gluteal) injection of RISPERDAL® CONSTA®, there is a small initial release of the drug (<1% of the dose), followed by a lag of 3 weeks. The main release of the drug starts from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the intramuscular (IM) injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with RISPERDAL® CONSTA® to maintain therapeutic levels until the main release of risperidone from the injection site has begun (see Dosage and Administration [2]). Following single doses of RISPERDAL® CONSTA®, the pharmacokinetics of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone were linear in the dosing range of 12.5 mg to 50 mg.

The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of RISPERDAL® CONSTA® results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Following multiple doses of 25 mg and 50 mg RISPERDAL® CONSTA®, plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone were linear.

Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

Distribution
Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α1-acid glycoprotein. The protein plasma binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High plasma concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 mg/mL and of 9-hydroxyrisperidone at 50 mg/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions
Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are “poor metabolizers”) and is inhibited by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

The interactions of RISPERDAL® CONSTA® with coadministration of other drugs have not been systematically evaluated in human subjects. Drug interactions are based primarily on experience with oral RISPERDAL®. Risperidone is subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone (see Drug Interactions [7.11]). This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of RISPERDAL® in patients receiving quinidine have not been evaluated, but observations in a modest number (n = 70) of poor metabolizers
given oral RISPERDAL® do not suggest important differences between poor and extensive metabolizers. Second, co-administration of carbamazepine and other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with oral RISPERDAL® cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone [see Drug Interactions (7.12)]. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely [see Drug Interactions (7.11)].

Excretion
Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces. The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL® CONSTA® administration is 2 to 6 days, and is associated with a monoeXponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL® CONSTA®. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

Renal Impairment
In patients with moderate to severe renal disease treated with oral RISPERDAL®, clearance was 40% less and for oral risperidone and its active metabolite decreased by 60% compared with young healthy subjects. Although patients with renal impairment were not studied with RISPERDAL® CONSTA®, it is recommended that patients with renal impairment be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL® CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with renal impairment [see Dosage and Administration (2.4)].

Hepatic Impairment
While the pharmacokinetics of oral RISPERDAL® in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of albumin. Although patients with hepatic impairment were not studied with RISPERDAL® CONSTA®, it is recommended that patients with hepatic impairment be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL® CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with hepatic impairment [see Dosage and Administration (2.4)].

Elderly
In an open-label trial, steady-state concentrations of risperidone plus 9-hydroxyrisperidone in otherwise healthy elderly patients (≥ 65 years old) treated with RISPERDAL® CONSTA® for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. Dosing recommendations are the same for otherwise healthy elderly patients and nonelderly patients [see Dosage and Administration (2)].

Race and Gender Effects
No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether or not corrected for body weight) or race.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis - Oral
Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to male and female rats, and for 52 weeks to male and female mice. The doses are equivalent to 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the mating and fertility study in which males only were treated. In a subchronic study in Beagle dogs in which oral risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses of 0.6 to 10 times the oral MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm values partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

No mating and fertility studies were conducted with RISPERDAL® CONSTA®.

14 CLINICAL STUDIES
14.1 Schizophrenia
The effectiveness of RISPERDAL® CONSTA® in the treatment of schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of other oral formulations of RISPERDAL®. Data from the long-term effectiveness of RISPERDAL® CONSTA® in the treatment of schizophrenia was established in a 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

Efficacy data were obtained from 400 patients with schizophrenia who were randomized to receive injections of 25 mg, 50 mg, or 75 mg RISPERDAL® CONSTA® or placebo every 2 weeks. During a 1-week run-in period, patients were discontinued from other antipsychotics and were titrated to a dose of 4 mg oral RISPERDAL®. Patients who received RISPERDAL® CONSTA® were given doses of oral RISPERDAL® (2 mg for patients in the 25-mg group, 4 mg for patients in the 50-mg group, and 6 mg for patients in the 75-mg group) for the 3 weeks after the first injection. The primary efficacy variable in this trial was change from baseline to endpoin in the total PANSS score. The mean total PANSS score at baseline for schizophrenia patients in this study was 81.5.

Total PANSS scores showed significant improvement in the change from baseline to endpoint in schizophrenic patients treated with each dose of RISPERDAL® CONSTA® (25 mg, 50 mg, or 75 mg) compared with patients treated with placebo. While there were no statistically significant differences between the treatment effects for the three dose groups, the effect size for the 75 mg dose group was actually numerically less than that observed for the 50 mg dose group.

Subgroup analyses did not indicate any differences in treatment outcome as a function of age, race, or gender.
14.2 Bipolar Disorder - Monotherapy
The effectiveness of RISPERDAL® CONSTA® for the maintenance treatment of Bipolar I Disorder was established in a multicenter, double-blind, placebo-controlled study of adult patients who met DSM-IV criteria for Bipolar Disorder Type I, who were stable on medications or experiencing an acute manic or mixed episode. A total of 501 patients were treated during a 26-week open-label period with RISPERDAL® CONSTA® at a starting dose of 25 mg and titrated, if deemed clinically desirable, to 37.5 mg or 50 mg; in patients not tolerating the 25 mg dose, the dose could be reduced to 12.5 mg. Time to relapse was delayed in patients receiving RISPERDAL® CONSTA® monotherapy as compared to placebo. The majority of relapses were due to manic rather than depressive symptoms. Based on their bipolar disorder history, subjects entering this study had had, on average, more manic episodes than depressive episodes.

14.3 Bipolar Disorder - Adjunctive Therapy
The effectiveness of RISPERDAL® CONSTA® as an adjunct to treatment with lithium or valproate for the maintenance treatment of Bipolar Disorder was established in a multi-center, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV criteria for Bipolar Disorder Type I and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12 months, including at least 2 episodes in the 6 months prior to the start of the study. A total of 240 patients were treated during a 18-week open-label period with RISPERDAL® CONSTA® at a starting dose of 25 mg, and titrated, if deemed clinically desirable, to 37.5 mg or 50 mg, as adjunctive therapy in addition to continuing their treatment as usual for their bipolar disorder, which consisted of mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. All oral antipsychotics were discontinued after the first three weeks of the initial RISPERDAL® CONSTA® injection. In the open-label phase, 124 (51.7%) were judged to be stable and were randomized to double-blind treatment with either the same dose of RISPERDAL® CONSTA® or placebo and monitored for relapse. The primary endpoint was time to relapse to any mood episode (depression, mania, hypomania, or mixed).

Time to relapse was delayed in patients receiving RISPERDAL® CONSTA® monotherapy as compared to placebo. The majority of relapses were due to manic rather than depressive symptoms. Based on their bipolar disorder history, subjects entering this study had had, on average, more manic episodes than depressive episodes.

16 HOW SUPPLIED/STORAGE AND HANDLING
RISPERDAL® CONSTA® (risperidone) is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone. It is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL® CONSTA®, a SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety needles for intramuscular injection (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

17 PATIENT COUNSELING INFORMATION
Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL® CONSTA®.

17.1 Orthostatic Hypotension
Patients should be advised of the risk of orthostatic hypotension and instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position) [see Warnings and Precautions (5.7)].

17.2 Interference with Cognitive and Motor Performance
Because RISPERDAL® CONSTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL® CONSTA® does not affect them adversely [see Warnings and Precautions (5.9)].

17.3 Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® [see Use in Specific Populations (8.1)].

17.4 Nursing
Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® [see Use in Specific Populations (8.3)].

17.5 Concomitant Medication
Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions [see Drug Interactions (7)].

17.6 Alcohol
Patients should be advised to avoid alcohol during treatment with RISPERDAL® CONSTA® [see Drug Interactions (7.1)].

Product of Ireland
Risperidone active ingredient is manufactured by: Janssen Pharmaceutical Wallingstown, Little Island, County Cork, Ireland
Microspheres are manufactured by: Alkermes, Inc.
Wilmington, Ohio

Diluent is manufactured by: Vetter Pharma Fertigung GmbH & Co. KG
Ravensburg or Langenargen, Germany or Cilag AG
Schaffhausen, Switzerland
RISPERDAL® CONSTA® is manufactured for: Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
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RISPERDAL® CONSTA® (risperidone) LONG-ACTING INJECTION

Janssen