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)

INDICATIONS AND USAGE
• For the treatment of schizophrenia. (1.1)
• Upward dose adjustment of RISPERDAL® CONSTA® should not be made more frequently than every 3 weeks. (2)
• Known hypersensitivity to risperidone, paliperidone, or to any excipients in the vial kit. (3)

DOSE 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 buttsucks). Do not administer intravenously. (2)
• 25 mg intramuscular (IM) every 2 weeks. Patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks. (2)
• Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL® CONSTA®, and continued for 3 weeks (and then discontinued) to ensure adequate therapeutic plasma concentrations from RISPERDAL® CONSTA®. (2)
• Upward dose adjustment of RISPERDAL® CONSTA® should not be made more frequently than every 4 weeks. Clinical effects of each upward dose adjustment should not be anticipated earlier than 3 weeks after injection. (2)
• Avoid inadvertent administration into a blood vessel. (5.16)
• See Full Prescribing Information Section 2.8 for instructions for use.

DOSAGE FORMS AND STRENGTHS
Vial kits: 12.5 mg, 25 mg, 37.5 mg, and 50 mg (3)

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

WARNINGS AND PRECAUTIONS
• Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL® CONSTA® is not approved for use in patients with dementia-related psychosis. (5.2)
• Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring. (5.3)
• Tardive Dyskinesia: Discontinue treatment if clinically appropriate. (5.4)
• Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
• Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.5)
• Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
• Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.5)
• Hyperprolactinemia: Risperidone treatment may elevate prolactin levels. Long-standing hyperprolactinemia, when associated with hypogonadism, can lead to decreased bone density in men and women. (5.6)

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)

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

USE IN SPECIFIC POPULATIONS
• Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
• Renal or Hepatic Impairment: dose appropriate 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)
• Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)
• Elderly: dosing for otherwise healthy elderly patients is the same as for healthy nonelderly. Elderly may be more predisposed to orthostatic effects than nonelderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

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• Orthostatic hypotension: associated with dizziness, tachycardia, bradycardia, and syncope can occur, especially during initial dose titration or oral risperidone. Use caution in patients with cardiovascular disease, cerebrovascular disease, and conditions that could affect hemodynamic responses. (5.7)
• Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotics, including RISPERDAL® CONSTA®. Patients with history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood cell count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® CONSTA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
• Potential for cognitive and motor impairment: has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. (5.10)
• Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
• Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. (5.12)
• Priapism: has been reported. Severe priapism may require surgical intervention. (5.13)
• Thrombotic Thrombocytopenic Purpura (TTP): has been reported. (5.14)
• Avoid inadvertent administration into a blood vessel. (5.16)
• Increased sensitivity in patients with Parkinson’s disease or those with dementia-related psychosis 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)

DRUGS/FOODS THAT CAN AFFECT THE MEDICATION
• Orlistat use with RISPERDAL® may require increased dose of orlistat. (7.10)

PATIENT COUNSELING INFORMATION
See full prescribing information for complete boxed warning.
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FULL PRESCRIBING INFORMATION: CONTENTS*

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

2.1 Schizophrenia

The recommended dose for the treatment of schizophrenia is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for RISPERDAL CONSTA®, some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg RISPERDAL CONSTA® every 2 weeks. No additional benefit was observed with dosages greater than 50 mg RISPERDAL CONSTA®; however, a higher incidence of adverse effects was observed.

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

RISPERDAL CONSTA® is indicated for the treatment of schizophrenia [see Clinical Studies (14.1)].
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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 two 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. If 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 titration 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 hypotensive 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 on the edge of the bed 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 vital 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® for 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 establish tolerability with oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

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, which could lead to decreased efficacy of RISPERDAL CONSTA® treatment. The dose of risperidone needs 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 or other known CYP 3A4 hepatic enzyme inducers, patients should be closely monitored during the first 4-6 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 discontinued 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.

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

For deltoid or gluteal intramuscular injection only

IMPORTANT RESOURCES
For additional information, visit www.risperdalconsta.com or call Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736).

Important Information

RISPERDAL CONSTA® requires close attention to these step-by-step Instructions for Use to help ensure successful administration.

Use components provided
The components in this dose pack are specifically designed for use with RISPERDAL CONSTA®. RISPERDAL CONSTA® must be reconstituted only in the diluent supplied in the dose pack.

Do not substitute ANY components of the dose pack.

Do not store suspension after reconstitution
Administer dose as soon as possible after reconstitution to avoid settling.

Proper dosing
The entire contents of the vial must be administered to ensure intended dose of RISPERDAL CONSTA® is delivered.

SINGLE-USE DEVICE

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.

Dose pack contents

West-Medimop Vial Adapter®
Luer opening
Spike tip
Skirt

Prefilled Syringe
Plunger rod
Diluent
White collar

Vial
Colored cap
Microspheres

Terumo SurGuard® 3 Injection Needles
Deltoid 2-inch
Gluteal 2-inch
Transparent needle protector
Needle safety device

RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION
Step 1  Assemble components

Take out dose pack  Connect vial adapter to vial

---

**Step 1:**

**Assemble components**

**Take out dose pack**

- **Wait 30 minutes**
  
  Remove dose pack from the refrigerator and allow to sit at room temperature for at least 30 minutes before reconstituting.
  
  **Do not** warm any other way.

**Connect vial adapter to vial**

- **Remove cap from vial**
  
  Flip off colored cap from vial.
  
  Wipe top of the grey stopper with an alcohol swab. Allow to air dry.
  
  **Do not** remove grey rubber stopper.

- **Prepare vial adapter**
  
  Hold sterile blister as shown.
  
  Peel back and remove paper backing.
  
  **Do not** remove vial adapter from blister.
  
  **Do not** touch spike tip at any time. This will result in contamination.

- **Connect vial adapter to vial**
  
  Place vial on a hard surface and hold by the base. Center vial adapter over the grey rubber stopper. Push vial adapter straight down onto vial top until it snaps securely into place.
  
  **Do not** place vial adapter on at an angle or diluent may leak upon transfer to the vial.

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**Connect prefilled syringe to vial adapter**

- **Remove sterile blister**
  
  Remove vial adapter from sterile blister only when you are ready to remove the white cap from the prefilled syringe.

  Keep vial vertical to prevent leakage. Hold base of vial and pull up on the sterile blister to remove.
  
  **Do not** shake.
  
  **Do not** touch exposed luer opening on vial adapter. This will result in contamination.

- **Use proper grip**
  
  Hold by white collar at the tip of the syringe.
  
  **Do not** hold syringe by the glass barrel during assembly.

- **Remove cap**
  
  Holding the white collar, snap off the white cap.
  
  **Do not** twist or cut off the white cap.
  
  **Do not** touch syringe tip. This will result in contamination.

  **SNAP!**

  When the cap is removed, the syringe will look like this.

  The broken-off cap can be discarded.

- **Connect syringe to vial adapter**
  
  Hold vial adapter by skirt to keep stationary.
  
  **Hold syringe by white collar** then insert tip into the luer opening of the vial adapter.
  
  **Do not** hold the glass syringe barrel. This may cause the white collar to loosen or detach.
  
  Attach the syringe to the vial adapter with a firm clockwise, twisting motion until it feels snug.
  
  **Do not** over-tighten. Over-tightening may cause the syringe tip to break.
**Step 2** Reconstitute microspheres

**Inject diluent**
Inject entire amount of diluent from syringe into the vial.

*Vial contents will now be under pressure. Keep holding the plunger rod down with thumb.*

**Suspend microspheres in diluent**
Continuing to hold down the plunger rod, shake vigorously for at least 10 seconds, as shown.

*Check the suspension. When properly mixed, the suspension appears uniform, thick and milky in color. Microspheres will be visible in the liquid. Immediately proceed to the next step so suspension does not settle.*

**Transfer suspension to syringe**
Invert vial completely. Slowly pull plunger rod down to withdraw entire contents from the vial into the syringe.

**Remove vial adapter**
Hold white collar on the syringe and unscrew from vial adapter.
Tear section of the vial label at the perforation. Apply detached label to the syringe for identification purposes.
Discard both vial and vial adapter appropriately.

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**Step 3** Attach needle

**Select appropriate needle**
Choose needle based on injection location (gluteal or deltoid).

**Attach needle**
Peel blister pouch open part way and use to grasp the base of the needle, as shown.

*Holding the white collar on the syringe, attach syringe to needle luer connection with a firm clockwise twisting motion until snug. Do not touch needle luer opening. This will result in contamination.*

**Resuspend microspheres**
Fully remove the blister pouch.
Just before injection, shake syringe vigorously again, as some settling will have occurred.
Step 4 Inject dose

Remove transparent needle protector
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.
Do not twist transparent needle protector, as the luer connection may loosen.

Remove air bubbles
Hold needle upright and tap gently to make any air bubbles rise to the top. Slowly and carefully press plunger rod upward to remove air.

Inject
Immediately inject entire contents of syringe intramuscularly (IM) into the gluteal or deltoid muscle of the patient.
Gluteal injection should be made into the upper-outer quadrant of the gluteal area.
Do not administer intravenously.

Secure needle in safety device
Using one hand, place needle safety device at a 45-degree angle on a hard, flat surface. Press down with a firm, quick motion until needle is fully engaged in safety device.
Avoid needle stick injury:
Do not use two hands.
Do not intentionally disengage or mishandle the needle safety device.
Do not attempt to straighten the needle or engage the safety device if the needle is bent or damaged.

Properly dispose of needles
Check to confirm needle safety device is fully engaged. Discard in an approved sharps container. Also discard the unused needle provided in the dose pack.

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The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly 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 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 glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including RISPERDAL®, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing at the beginning of atypical antipsychotic treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including RISPERDAL®, was discontinued; however, some patients required continuation of anti-diabetic 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.
3.2 Weight Gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1-8 mg/day</th>
<th>&gt;8-16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>0.6</td>
<td>6.9</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>-4.5</td>
</tr>
</tbody>
</table>

5.5 Falls
Somanolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL CONSTA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis
Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including RISPERDAL CONSTA®. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and a history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood 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. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue RISPERDAL CONSTA® and have their WBC followed until recovery.

5.10 Potential for Cognitive and Motor Impairment
Somanolence was reported by 5% of patients treated with RISPERDAL CONSTA® in multiple-dose trials. Since risperidone 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.

5.11 Seizures
During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL CONSTA®. Therefore, RISPERDAL CONSTA® should be used cautiously in patients with a history of seizures.

5.12 Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drugs use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer’s dementia. RISPERDAL® 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)]

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

5.14 Thrombotic Thrombocytopenic Purpura (TTP)
A single case of TTP was reported in a 26 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

5.15 Body Temperature Regulation
Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® or RISPERDAL CONSTA® use. Caution is advised when prescribing RISPERDAL CONSTA® for patients who will be exposed to temperature extremes.

5.16 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)]

5.17 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 of conditions such as intestinal obstruction, Reye’s syndrome, and brain tumor.

5.8 Falls
Somatic, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL CONSTA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

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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 of conditions such as intestinal obstruction, Reye’s syndrome, and brain tumor.
6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.2)]
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis [see Warnings and Precautions (5.2)]
- Neuroleptic malignant syndrome [see Warnings and Precautions (5.3)]
- Tardive dyskinesia [see Warnings and Precautions (5.4)]
- Metabolic changes [see Warnings and Precautions (5.5)]
- Hyperprolactinemia [see Warnings and Precautions (5.6)]
- Orthostatic hypotension [see Warnings and Precautions (5.7)]
- Falls [see Warnings and Precautions (5.8)]
- Leukopenia/Neutropenia and Agranulocytosis [see Warnings and Precautions (5.9)]
- Potential for cognitive and motor impairment [see Warnings and Precautions (5.10)]
- Seizures [see Warnings and Precautions (5.11)]
- Dysphagia [see Warnings and Precautions (5.12)]
- Priapism [see Warnings and Precautions (5.13)]
- Thrombotic Thrombocytopenic Purpura (TTP) [see Warnings and Precautions (5.14)]
- Disruption of body temperature regulation [see Warnings and Precautions (5.15)]
- Avoidance of inadvertent injection into a blood vessel [see Warnings and Precautions (5.16)]

- Antiemetic effect [see Warnings and Precautions (5.17)]
- Increased sensitivity in patients with Parkinson’s disease or those with dementia with Lewy bodies [see Warnings and Precautions (5.18)]
- Dementia phase could cause neurocognitive dysfunction and/or neurodegeneration that could affect metabolism or hemodynamic responses [see Warnings and Precautions (5.18)]
- Osteodystrophy and tumors in animals [see Warnings and Precautions (5.19)]

The most common adverse reactions in clinical trials in patients with schizophrenia (≥ 5%): headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth.

In addition, RISPERDAL® was 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.

Material risk is unknown.

The relevance of these findings to human risk is unknown.
RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION

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>System/Organ Class</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL CONSTA®</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>25 mg (N=99)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Toothache</td>
</tr>
<tr>
<td></td>
<td>Salivary hypersecretion</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
</tr>
<tr>
<td></td>
<td>Weight decreased</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism*</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Akathisia*</td>
</tr>
<tr>
<td></td>
<td>Sedation*</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Syncpe</td>
</tr>
<tr>
<td></td>
<td>Hypoesthesia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Sinus congestion</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
</tr>
</tbody>
</table>

* Fatigue includes fatigue and asthenia. Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restlessness. 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/Organ Class</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL CONSTA®</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>(N=154)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</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/Organ Class</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL CONSTA® + Treatment as Usual+</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>(N=72)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Gait abnormal</td>
</tr>
<tr>
<td></td>
<td>Infections and infestations</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Increased appetite</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism®</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia®</td>
</tr>
<tr>
<td></td>
<td>Sedation®</td>
</tr>
<tr>
<td></td>
<td>Disturbance in attention</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Amenorrhea</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
</tr>
</tbody>
</table>

* Patients received double-blind RISPERDAL CONSTA® or placebo in addition to continuing their treatment as usual, which included mood stabilizers, antidepressants, and/or anxiolytics.

® Parkinsonism includes muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia. Dyskinesia includes muscle twitching and dyskinesia.

® Sedation includes sedation and somnolence.

6.3 Other Adverse Reactions Observed During the Clinical Trial Evaluation of Risperidone

The following additional adverse reactions occurred in < 2% of the RISPERDAL CONSTA®-treated patients in the above schizophrenia double-blind, placebo-controlled trial dataset, in < 2% of the RISPERDAL CONSTA®-treated patients in the above double-blind, placebo-controlled period of the monotherapy bipolar disorder trial dataset, or in < 4% of the RISPERDAL CONSTA®-treated patients in the above double-blind, placebo-controlled period of the adjunctive treatment bipolar disorder trial dataset. The following also includes additional adverse reactions reported at any frequency in RISPERDAL CONSTA®-treated patients who participated in the open-label phases of the above bipolar disorder studies and in other studies, including double-blind, active controlled and open-label studies in schizophrenia and bipolar disorder.
Risperdal® (risperidone) Long-Acting Injection

Blood and Lymphatic System Disorders: anemia, neutropenia
Cardiac Disorders: tachycardia, atrioventricular block first degree, palpitations, sinus bradycardia, bundle branch block left, bradycardia, sinus tachycardia, bundle branch block right
Ear and Labyrinth Disorders: ear pain, vertigo
Endocrine Disorders: hyperprolactinemia
Eye Disorders: conjunctivitis, visual acuity reduced
Gastrointestinal Disorders: diarrhea, vomiting, abdominal pain upper, abdominal pain, stomach discomfort, gastritis
General Disorders and Administration Site Conditions: injection site pain, chest discomfort, chest pain, influenza like illness, sluggishness, malaise, induration, injection site induration, injection site swelling, injection site reaction, face edema
Immune System Disorders: hypersensitivity
Infections and Infestations: nasopharyngitis, influenza, bronchitis, urinary tract infection, rhinitis, respiratory tract infection, ear infection, pneumonia, lower respiratory tract infection, pharyngitis, sinusitis, viral infection, infection, localized infection, cystitis, gastroenteritis, subcutaneous abscess
Injury and Poisoning: fall, procedural pain
Investigations: blood prolactin increased, alanine aminotransferase increased, electrocardiogram abnormal, gamma-glutamyl transferase increased, blood glucose increased, hepatic enzyme increased, aspartate aminotransferase increased, electrocardiogram QT prolonged, glucose urine present
Metabolism and Nutritional Disorders: anorexia, hyperglycemia
Musculoskeletal, Connective Tissue, and Bone Disorders: polydipsia
Nervous System Disorders: peripheral neuropathy, decreased temperature, decreased blood pressure, transaminases increased, white blood cell count increased, hemoglobin decreased, pancreatitis, peripheral coldness

Psychiatric Disorders: blunted affect, confusional state, middle insomnia, listlessness, anorgasmo
Renal and Urinary Disorders: enuresis, dysuria, pollakiuria
Reproductive System and Breast Disorders: vaginal discharge, retrograde ejaculation, ejaculation disorder, ejaculation failure, breast enlargement
Respiratory, Thoracic, and Mediastinal Disorders: epistaxis, wheezing, pneumonia aspiration, dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory disorder, hyperventilation, nasal edema
Skin and Subcutaneous Tissue Disorders: erythema, skin discoloration, skin lesion, skin disorder, rash erythematous, rash papular, hyperkeratosis, dandruff, seborrheic dermatitis, rash generalized, rash maculopapular
Vascular Disorders: flushing

6.4 Discontinuations Due to Adverse Reactions

Scleroderma
Approximately 11% (22/202) of Risperdal®-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®-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® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, (0.6%) of 154 Risperdal®-treated patients discontinued due to an adverse reaction (hyperglycemia).
In the 52-week double-blind phase of the placebo-controlled trial in which Risperdal® was administered as adjunctive therapy to patients with bipolar disorder in addition to continuing with their treatment as usual, approximately 4% (3/72) of Risperdal®-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®-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 were used to measure extrapyramidal symptoms (EPS) in the 12-week double-blind, placebo-controlled trial comparing three doses of Risperdal® (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 score (sum of the subscale scores for parkinsonism, dyskinesia, and dysynesia) of the Extrapyramidal Symptom Rating Scale (ESRS).

As shown in Table 1, the overall incidence of EPS-related adverse reactions (akathisia, dyskinesia, and tremor) in patients treated with 25 mg Risperdal® 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®. The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with Risperdal® 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® and 98 schizophrenic patients treated with placebo in the 12-week double-blind, placebo-controlled 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®.

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® 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 changes 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; RISPERDAL CONSTA® 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 predose 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 or establish a causal relationship to drug exposure.

Chronic administration of clozapine with risperidone may decrease the plasma clearance of risperidone. Therefore, additional oral RISPERDAL® and carbamazepine or other CYP 3A4 enzyme inducers, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 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® to 12.5 mg or necessitate 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 dosage of RISPERDAL CONSTA® may need to be increased. 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 enzyme 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 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)]
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antipsychotics, including RISPERDAL CONSTA® during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see Clinical Considerations). Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including RISPERDAL CONSTA®, during pregnancy (see Clinical Considerations). Juvenile animal studies conducted with oral risperidone have been determined not to have an adverse effect on the breastfed child from RISPERDAL CONSTA® or from the mother’s clinical need for RISPERDAL CONSTA® and any potential adverse effects on the breastfed child from RISPERDAL CONSTA® or from the mother’s underlying condition.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including RISPERDAL CONSTA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medicaid database of 928 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk major of birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

Oral administration of risperidone to pregnant mice caused cleft palate at 10 mg/kg/day which is 3 times the MRHD of 16 mg/day based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6 times the MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6 and 1.2 times the MRHD based on mg/m² body surface area; postnatal development and growth of the offspring were also delayed. Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 5 mg/kg/day which are 0.1 to 3 times the MRHD of 16 mg/day based on mg/m² body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths increased at 2.5 mg/kg or 1.5 times the MRHD based on mg/m² body surface area.

In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in offspring of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats; regardless of whether or not the offspring were cross-fostered. Risperidone also appeared to impair maternal behavior in that offspring body weight gain and survival (from Day 1 to 4 of lactation) were reduced in offspring born to control but reared by drug-treated dams. All of these effects occurred at 5 mg/kg which is 3 times the MRHD based on mg/m² and the only dose tested in the study.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3% and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone (see Clinical Considerations). Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of RISPERDAL CONSTA® [see Clinical Pharmacology (12.3)]. The clinical significance of RISPERDAL CONSTA® administered before pregnancy or anytime during pregnancy is not known.

Oral administration of risperidone to pregnant mice caused cleft palate at doses 3 to 4 times the maximum recommended human dose (MRHD) with maternal toxicity observed at 4-times the MRHD based on mg/m² body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the MRHD based on mg/m² body surface area. Increased stillbirths and decreased birth weight occurred after oral risperidone administration to pregnant rats at 1.5-times the MRHD based on mg/m² body surface area. Learning was impaired in offspring of rats when the dams were dosed at 0.6-times the MRHD and offspring mortality increased at doses 0.1 to 3 times the MRHD based on mg/m² body surface area.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of risperidone (D2 receptor antagonism), treatment with RISPERDAL CONSTA® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see Warnings and Precautions (5.6)].

8.4 Pediatric Use

Safety and effectiveness of RISPERDAL CONSTA® in pediatric patients have not been established. However, juvenile animal toxicology studies have been conducted with oral risperidone.

Juvenile Animal Studies

Juvenile dogs were treated with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans) at doses of 0.31, 1.25, or 5 mg/kg/day, which are 1.2, 3.4 and 13.5 times the MRHD of 6 mg/day for children, based on mg/m² body surface area. Bone length and density were decreased with a no-effect dose of 0.31 mg/kg/day; this dose produced plasma AUC of risperidone plus its active metabolite paliperidone (9-hydroxy-risperidone) that were similar to those in children and adolescents receiving the MRHD of 6 mg/day. In addition, sexual maturation was delayed 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. Juvenile rats, treated with oral risperidone from days 12 to 50 of age (equivalent to the period of infancy through adolescence in humans) showed impaired learning and memory performance (reversible only in females), with a no-effect dose of 0.63 mg/kg/day which is 0.5 times the MRHD of 6 mg/day for children, based on
RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION

mg/m² body surface area. This dose produced plasma AUC of risperidone plus paliperidone about half the exposure observed in humans at the MRHD. No other consistent changes on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the MRHD of 6 mg/day for children.

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 pathogenic mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of 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)].

9.2 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.

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® overdosage, 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 and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 360 mg, was associated with a seizure.

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 included respiratory distress, exacerbation of psychotic symptoms, and increased blood pressure.

10.2 Management of Overdosage

In case of acute overdosage, 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 antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium 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

RISPERDAL CONSTA® contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-[6-[2-benzisoxazol-3-yl]-1-piperidinyl(methyl)]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-yl]-1H-indazole][21H]-inden-1-one. Its molecular formula is C₂₃H₂₄F₄N₂O₂ and its molecular weight is 410.49. The structural formula is:

![Structural formula of risperidone](image)

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 polyoctyl-co-glycolide (PLG) 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 citric acid anhydrous, disodium hydrogen phosphate dihydrate, polysorbate 20, sodium carboxymethyl cellulose, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent by gentle mixing.

RISPERDAL CONSTA® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 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 risperidone in schizophrenia is unclear. The drug’s therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major active metabolite, 9-hydroxyrisperidone (paliperidone) [see Clinical Pharmacology (12.3)]. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of risperidone [see Clinical Pharmacology (12.1)].

12.2 Pharmacodynamics

Risperidone is a monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT₂) dopamine Type 2 (D₂), c1 and c2 adrenergic, and H₁ histaminergic receptors. Risperidone showed low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT₃, 5HT₄, and 5HT₆ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D₂ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10² M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

12.3 Pharmacokinetics

Absorption

After a single intramuscular (glutal) injection of RISPERDAL CONSTA®, there is a small initial release of the drug (< 1% of the dose), followed by a lag time 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 in plasma; therefore, administration is continued 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 plasma protein 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 therapeutic 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 ng/mL and of 9-hydroxyrisperidone at 50 ng/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 to inhibition 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 could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone [see Drug Interactions (7.1)]. It would also be possible for risperidone to interfere with metabolism of other drugs by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely [see Drug Interactions (7.1)].

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 94%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL CONSTA® administration is 3 to 6 days, and is associated with a monoeponential 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.

RISPERDAL® was eliminated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with intramuscular (IM) injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m² basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreatic adenomas, and mammary gland adenocarcinomas. The table below summarizes the multiples of the human dose on mg/m² (mg/kg) basis at which these tumors occurred.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Species</th>
<th>Sex</th>
<th>Lowest Effect Level</th>
<th>Highest No-Effect Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenomas</td>
<td>mouse</td>
<td>Female</td>
<td>0.75 (9.4)</td>
<td>0.2 (2.4)</td>
</tr>
<tr>
<td>Endocrine pancreas adenomas</td>
<td>rat</td>
<td>Male</td>
<td>1.5 (9.4)</td>
<td>0.4 (2.4)</td>
</tr>
<tr>
<td>Mammary gland adenocarcinomas</td>
<td>mouse</td>
<td>Female</td>
<td>0.2 (2.4)</td>
<td>none</td>
</tr>
<tr>
<td>Mammary gland neoplasm, Total</td>
<td>rat</td>
<td>Male</td>
<td>1.5 (9.4)</td>
<td>0.4 (2.4)</td>
</tr>
</tbody>
</table>

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear [see Warnings and Precautions (3.6)].

Carcinogenesis - Intramuscular
Risperidone was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with intramuscular (IM) injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m² basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m² basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 1 times the IM MRHD on a mg/m² basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m² basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD.
Dopamine D2 receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 10-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with risperidone every 2 weeks IM. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown [see Warnings and Precautions (5.6)].

**Impairment of Fertility**

Oral risperidone (0.16 to 5 mg/kg) impaired mating, but not fertility, in rat reproductive studies at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD of 16 mg/day) based on mg/m2 body surface area. The effect appeared to be in females, since impaired mating behavior was not noted in the male fertility study. 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 0.6 to 10 times the oral MRHD on mg/m2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

**14 CLINICAL STUDIES**

**14.1 Schizophrenia**

The effectiveness of RISPERDAL CONSTA® in the treatment of schizophrenia 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 16-week open-label period with RISPERDAL CONSTA® (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 for at least the last 4 weeks and were randomized to double-blind treatment with either the same dose of RISPERDAL CONSTA® or placebo in addition to continuing their treatment as usual and monitored for relapse during a 52-week period. The primary endpoint was time to relapse to any new 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, on average, more manic episodes than depressive episodes.

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, on average, more manic episodes than depressive episodes.

**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.
PATIENT COUNSELING INFORMATION

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

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)].

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 (5.10)].

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)].

Alcohol

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

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with RISPERDAL CONSTA®. Advise patients that RISPERDAL CONSTA® may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to RISPERDAL CONSTA® during pregnancy [see Use in Specific Populations (8.1)].

Lactation

Advise breastfeeding women using RISPERDAL CONSTA® to monitor infants for somnolence, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs [see Use in Specific Populations (8.2)].

Infertility

Advise females of reproductive potential that RISPERDAL CONSTA® may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible [see Use in Specific Populations (8.3)].

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
Langenargen, Germany

or
Cilag AG
Schaffhausen, Switzerland

RISPERDAL CONSTA® is manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
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