Special Storage Requirements

- Must be stored in a refrigerator at 36°F to 46°F (2°C to 8°C). Protect from light. Do not freeze.

- Refrigeration is unavailable, Risperdal® Consta® can be stored at temperatures not exceeding 77°F (25°C) for no more than 7 days prior to administration.

- Do not expose unrefrigerated product to temperatures above 77°F (25°C).

Choice of Administration Sites Helps You Meet Patient Needs

- Delotoid Administration

- Greater flexibility to rotate administration sites

- Alternate option for patients who prefer gluteal injection

- Needle measures only 1 inch

- Less than traditional gluteal injections

- Patients may associate delotoid administration with traditional injections that areaccioculated to receive

Glutet Administration

- Alternate option for patients who prefer gluteal injection

- Available for patients who cannot tolerate delotio injection because of low muscle mass
FLEXIBILITY IN DOSING OPTIONS

12.5mg  25mg  37.5mg  50mg

BEFORE STARTING RISPERDAL® CONSTA®

- Rule out hypersensitivity if a patient has not taken risperidone in the past
- There is no need to transition to oral risperidone from another oral antipsychotic
- Patients can be offered the choice of intramuscular (IM) deltoid or gluteal injection*
  - As always, be sure to discuss with patients the choices they have with long-acting therapy. Use your clinical judgment to best address any concerns regarding proper dosing and administration

INITIATING THERAPY WITH RISPERDAL® CONSTA®

- The recommended starting dosage is 25 mg administered every 2 weeks by IM injection
- Some patients may benefit from a higher dosage of 37.5 mg to 50 mg every 2 weeks
- The maximum dosage is 50 mg every 2 weeks
- Do not make dosing adjustments more frequently than every 4 weeks

INJECTING RISPERDAL® CONSTA®

- Entire contents of vial must be injected at time of administration

SPECIAL CONSIDERATIONS

12.5-mg Dosing for Appropriate Patients
- When clinical factors warrant a dose adjustment, an initial dose of 12.5 mg may be appropriate in patients with
  - Hepatic or renal impairment
  - Drug interactions that increase risperidone plasma concentrations
  - Poor tolerability of psychotropic medications
- The efficacy of the 12.5-mg dose has not been investigated in clinical trials

PHARMACOKINETIC PROFILE FOR INITIATION OF RISPERDAL® CONSTA®

- Oral antipsychotic supplementation should be initiated or continued during the first 3 weeks of therapy
- A second injection should be administered after 2 weeks
  - Oral supplementation continues
- The main release of the drug starts from week 3 onward
  - Oral supplementation is no longer required
- Continue to administer RISPERDAL® CONSTA® once every 2 weeks

AFTER YOUR PATIENT HAS STARTED TREATMENT

- Oral antipsychotic supplementation should be initiated or continued during the first 3 weeks of therapy
- A second injection should be administered after 2 weeks
  - Oral supplementation continues
- The main release of the drug starts from week 3 onward
  - Oral supplementation is no longer required
- Continue to administer RISPERDAL® CONSTA® once every 2 weeks

The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, Parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities, and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increased (5% in monotherapy trial) and tremor and Parkinsonism (≥10% in adjunctive therapy trial).
FLEXIBILITY IN DOSING OPTIONS

12.5mg 25mg 37.5mg 50mg

BEFORE STARTING RISPERDAL® CONSTA®

- Rule out hypersensitivity if a patient has not taken risperidone in the past
- There is no need to transition to oral risperidone from another oral antipsychotic
- Patients can be offered the choice of intramuscular (IM) deltoid or gluteal injection*
  — As always, be sure to discuss with patients the choices they have with long-acting therapy. Use your clinical judgment to best address any concerns regarding proper dosing and administration

INITIATING THERAPY WITH RISPERDAL® CONSTA®

- The recommended starting dosage is 25 mg administered every 2 weeks by IM injection
- Some patients may benefit from a higher dosage of 37.5 mg to 50 mg every 2 weeks
- The maximum dosage is 50 mg every 2 weeks
- Do not make dosing adjustments more frequently than every 4 weeks

QUICK GUIDE TO STARTING RISPERDAL® CONSTA®

3 WEEKS ORAL ANTIPSYCHOTIC (APS)  RISPERDAL® CONSTA® Every 2 Weeks

- Begin or continue treatment with an oral antipsychotic (APS) for 3 weeks before starting RISPERDAL® CONSTA® for maintenance treatment

The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, Parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities, and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increased (5% in monotherapy trial) and tremor and Parkinsonism (≥10% in adjunctive therapy trial).

AFTER YOUR PATIENT HAS STARTED TREATMENT

- Oral antipsychotic supplementation should be initiated or continued during the first 3 weeks of therapy
- A second injection should be administered after 2 weeks
  — Oral supplementation continues
- The main release of the drug starts from week 3 onward
  — Oral supplementation is no longer required
- Continue to administer RISPERDAL® CONSTA® once every 2 weeks

PHARMACOKINETIC PROFILE FOR INITIATION OF RISPERDAL® CONSTA®

Pharmacokinetic simulation. Correlation to clinical effect has not been established.

SPECIAL CONSIDERATIONS

12.5-mg Dosing for Appropriate Patients
- When clinical factors warrant a dose adjustment, an initial dose of 12.5 mg may be appropriate in patients with
  — Hepatic or renal impairment
  — Drug interactions that increase risperidone plasma concentrations
  — Poor tolerability of psychotropic medications
- The efficacy of the 12.5-mg dose has not been investigated in clinical trials

Administration
- Entire contents of vial must be injected at time of administration
**Administration:** Care should be taken to avoid inadvertent injection into a blood vessel.

**Possible benefits of Deltoid Administration:**
- Greater flexibility to rotate administration sites
- Less fear
- Less embarrassment
- Greater flexibility to rotate administration sites

**WARNING:** Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. A meta-analysis of 17 placebo-controlled trials (including placebo-controlled trials of atypical antipsychotics) of patients with dementia-related psychosis compared to placebo showed a risk of death for patients treated with atypical antipsychotics that was approximately 2.5 times the risk of death for placebo-treated patients. Dementia-related psychosis is a syndrome with symptoms that can include agitation, hallucinations, delusions, disorientation, disinhibition, irritability, mood lability, and wandering. The cause of death was varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, cerebrovascular disease or conditions that would predispose patients to hypotension) or respiratory (e.g., aspiration). None of the deaths has been attributed to the antipsychotic drug as opposed to some characteristic(s) of the patient.

**IMPORTANT SAFETY INFORMATION FOR RISPERDAL® CONSTA® (risperidone) long-acting injection**

**RISPERDAL® CONSTA® (risperidone) long-acting injection is indicated for the treatment of:**

- Schizophrenia and as monotherapy or as adjunctive therapy to lithium or valproate for the
  treatment of:
  - Bipolar I Disorder

**Commonly Observed Adverse Reactions for RISPERDAL® CONSTA®**

- Dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce
  hyperglycemia should also undergo fasting blood glucose testing. All patients treated with
  atypical antipsychotics should be monitored for symptoms of hyperglycemia. Monitor glucose
  levels and the elevation persists during chronic administration. Risperidone is associated with
  prolactin levels and the elevation persists during chronic administration. Risperidone is associated with
  increased mortality. The extent to which the findings of increased mortality in observational
  studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the
  patients is not clear. RISPERDAL® CONSTA® is not approved for the treatment of patients with
demencia-related psychotics.

**Hyperprolactinemia:** Prolactin levels and the elevation persists during chronic administration. Risperidone is associated with

**Hyperglycemia and Diabetes Mellitus:** Hyperglycemia and diabetes mellitus, some cases extreme

- Somnolence was reported in multiple trials in subjects treated with RISPERDAL® CONSTA®. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during

**Thrombotic Thrombocytopenic Purpura (TTP):** Has been reported.

**Diabetes Mellitus:**

Hyperprolactinemia: Risperidone can raise prolactin levels and the elevation persists during chronic administration.

**Somnolence:**

**Atypical Antipsychotics:** Anti-psychotic agents that may influence prolactin (PRL) levels are used in the treatment of side effects and other conditions. The risk of developing TD and the severity of the clinical syndrome is highly variable, but it is generally believed to be minimized by treatment with atypical antipsychotic drugs. The risk of developing TD and the severity of the clinical syndrome is highly variable, but it is generally believed to be minimized by treatment with atypical antipsychotic drugs. The risk of developing TD and the severity of the clinical syndrome is highly variable, but it is generally believed to be minimized by treatment with atypical antipsychotic drugs. **Schizophrenia** and as monotherapy or as adjunctive therapy to lithium or valproate for the

**TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the severity of clinical syndrome is highly variable, but it is generally believed to be minimized by treatment with atypical antipsychotic drugs.**

**Please see accompanying full Prescribing Information for RISPERDAL® CONSTA® with caution**

**PI:** Includes product description, mechanism of action, warnings, precautions, contraindications, and warnings.

**Please see accompanying full Prescribing Information for RISPERDAL® CONSTA®**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. A meta-analysis of 17 placebo-controlled trials (including placebo-controlled trials of atypical antipsychotics) of patients with dementia-related psychosis compared to placebo showed a risk of death for patients treated with atypical antipsychotics that was approximately 2.5 times the risk of death for placebo-treated patients. Dementia-related psychosis is a syndrome with symptoms that can include agitation, hallucinations, delusions, disorientation, disinhibition, irritability, mood lability, and wandering. The cause of death was varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, cerebrovascular disease or conditions that would predispose patients to hypotension) or respiratory (e.g., aspiration). None of the deaths has been attributed to the antipsychotic drug as opposed to some characteristic(s) of the patient.**

**Deltoid Administration:** Care should be taken to avoid inadvertent injection into a blood vessel.

**For intramuscular injection only. Care should be taken to avoid inadvertent injection into a blood vessel.**

**Use RISPERDAL® CONSTA® with caution in patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia.**

**Use RISPERDAL® CONSTA® with caution in patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia.**

**Use RISPERDAL® CONSTA® with caution in patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia.**

**If refrigeration is unavailable, RISPERDAL® CONSTA® can be stored at room temperature. Do not freeze.**
Needles shown are not actual size. Please ensure the correct needle is used for each blood vessel.

• Please see accompanying full Prescribing Information

IMPORTANT SAFETY INFORMATION FOR RISPERDAL® CONSTA® (risperidone)—continued

RISPERDAL® CONSTA® (risperidone) long-acting injection is indicated for the treatment of schizophrenia and as an adjunct to or as monotherapy in the maintenance treatment of Bipolar I Disorder.

IMPORTANT SAFETY INFORMATION FOR RISPERDAL® CONSTA® (risperidone)—continued

RISPERDAL® CONSTA® long-acting injection is indicated for the treatment of schizophrenia and as an adjunct to or as monotherapy in the maintenance treatment of Bipolar I Disorder.

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) for a total of 997 elderly patients with dementia-related psychosis who were randomly assigned to a drug or placebo show that the risk of death for drug recipients was approximately 1.5 to 2.1 times that of placebo recipients. In one 9-week trial of elderly patients with dementia-related psychosis, risperidone recipients were 2.4 times more likely to die than placebo recipients. The relative risk of mortality in drug recipients compared to placebo recipients is thought to be greatest for elderly inhabnates with the most severe cognitive impairment and those with the most intractable psychotic symptoms.

Important: All patients treated with antipsychotic drugs for elderly patients with dementia-related psychosis should be observed closely for clinical worsening and the emergence of new symptoms, especially behavioral changes, including agitation. Such changes may be precursors of behavioral abnormalities, including delusions, hallucinations, or other neuropsychiatric conditions that are not correctly diagnosed or adequately treated, which suggests that dementia patients treated with antipsychotics should be monitored closely. Safety and effectiveness of RISPERDAL® CONSTA® in such patients have not been established. If behavioral deterioration or marked behavioral changes occur in a patient taking antipsychotics, it should be noted whether the symptoms may be related to the use of antipsychotics. The risk of death was seen in both drug-treated patients and placebo-treated patients, but drug-treated patients were at a significantly higher risk.

Because elderly patients with dementia-related psychosis are at greater risk for accidents and because of the higher mortality rate in this group, the overall risk benefit ratio for the use of antipsychotics in elderly patients with dementia-related psychosis is unknown. RISPERDAL® CONSTA® should only be used in patients for whom this may be of concern.

Prolonged use of antipsychotic drugs results in a greater risk of death, with the greatest risk in elderly patients. The overall risk-benefit ratio for the use of antipsychotics in elderly patients with dementia-related psychosis is unknown.

Agranulocytosis, pancytopenia, and thrombocytopenia have been reported with antipsychotics, including RISPERDAL® CONSTA®. Patients with a history of agranulocytosis or sepsis should be monitored for signs of infection or sepsis; patients should be monitored closely for the development of fever, chills, sore throat, white blood cell count, or other signs of infection or sepsis; patients should have regular white blood cell counts, total blood cell counts, and platelet counts and have no history of agranulocytosis or sepsis with RISPERDAL® CONSTA®. Patients with a history of agranulocytosis or sepsis should be monitored closely for signs of infection or sepsis; patients should be monitored closely for the development of fever, chills, sore throat, white blood cell count, or other signs of infection or sepsis; patients should have regular white blood cell counts, total blood cell counts, and platelet counts and have no history of agranulocytosis or sepsis with RISPERDAL® CONSTA®.

The overall risk-benefit ratio for the use of antipsychotics in elderly patients with dementia-related psychosis is unknown. RISPERDAL® CONSTA® should only be used in patients for whom this may be of concern.

The risk-benefit ratio for the use of antipsychotics in elderly patients with dementia-related psychosis is unknown. RISPERDAL® CONSTA® should only be used in patients for whom this may be of concern.
Administration: Care should be taken to avoid inadvertent injection into a blood vessel.

Possible benefits of:

• Greater flexibility to rotate administration sites
• Less embarrassment
• Less fear
• Needle measures only 1 inch

Less stigma than traditional gluteal injections

Patients may associate deltoid administration with traditional gluteal injections that are being accessioned to receive treatment.

Glutathione: Alternative option for patients who prefer gluteal injection

• Available for patients who cannot tolerate deltoid injections because of low muscle mass

IMPORTANT SAFETY INFORMATION FOR RISPERDAL® CONSTA®—continued

Dysphagia: Mild dysphagia (≥1% in adjunctive therapy trial) and dysphagia (≥1% in placebo-controlled trial) have been reported in patients treated with RISPERDAL® CONSTA®. Patients with a history of clinically significant low normal esophageal motility (e.g., achalasia) and those who have had a history of esophageal disease or who are at risk for esophageal disease should be considered for an alternative route of administration. Patients with swallowing difficulties should be observed closely for signs or symptoms of aspiration pneumonia.

Cerebrovascular Disease: Close supervision of high-risk patients should accompany drug therapy. Patients with a history of cerebrovascular disease or conditions that would predispose patients to increased intracranial pressure (e.g., uncontrolled hypertension and uncontrolled diabetes mellitus) should be considered for an alternative route of administration.

Clozapine: Patients should be monitored for symptoms of hyperglycemia, which may include increased thirst, increased urination, increased fatigue, increased weight, or other changes in bodily functions. Initial monitoring should be conducted at regular intervals for the first 2 years and periodically thereafter. Further monitoring should be conducted if hyperglycemia develops or if patients develop other symptoms associated with hyperglycemia.

RISPERDAL® CONSTA® is contraindicated in patients with a known hypersensitivity to risperidone or any of the excipients in the formulation. It is also contraindicated in patients who have had a history of significant hypotension or syncope associated with treatment with antipsychotics. In a limited number of patients, RISPERDAL® CONSTA® has been associated with postural hypotension and orthostatic symptoms. Patients who have a history of cardiovascular disease, those at risk for cardiovascular disease, or those with an impaired cardiovascular function should be monitored closely for symptoms of orthostatic hypotension. If orthostatic symptoms (e.g., lightheadedness, dizziness, fainting) occur, RISPERDAL® CONSTA® should be used with caution in patients with these conditions.

Thromboembolic Events: The risk of thromboembolic events may be increased in patients treated with atypical antipsychotics. These events may include deep vein thrombosis, pulmonary embolism, and cerebrovascular events. Patients with a history of thromboembolic events or cerebrovascular disease or with a history of cerebrovascular disease or conditions that would predispose patients to increased intracranial pressure (e.g., uncontrolled hypertension and uncontrolled diabetes mellitus) should be considered for an alternative route of administration.

Please see the prescribing information for RISPERDAL® CONSTA® for other important safety information.
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® (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

RISPERDAL® CONSTA® is an atypical antipsychotic indicated:
• for the treatment of schizophrenia. (1.1)
• as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder. (1.2)

Dosage and Administration

• For patients who have never taken oral RISPERDAL®, tolerability should be established with oral RISPERDAL® prior to initiating treatment with RISPERDAL® CONSTA®. (2)
• Administer by deep intramuscular (IM) deltoid or gluteal injection. Each injection should be administered by a health care professional using the appropriate enclosed safety needle (1-inch for deltoid administration alternating injections between the two arms and 2-inch for gluteal administration alternating infections 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.

DOSE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

• Known hypersensitivity to the product (4)

WARNINGS AND PRECAUTIONS

• Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL® CONSTA® is not approved for use in patients with dementia-related psychosis (5.2)
• Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.3)
• Tardive Dyskinesia: Discontinue treatment if clinically appropriate (5.4)
• Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
  • Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.5)
  • Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
  • Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.5)
• Hyperprolactinemia: Risperidone treatment may elevate prolactin levels. Long-standing hyperprolactinemia, when associated with hypogonadism, can lead to decreased bone density in men and women. (5.6)
• Orthostatic hypotension: associated with dizziness, tachycardia, bradycardia, and syncope can occur, especially during initial dose titration with oral risperidone. Use caution in patients with cardiovascular disease, cerebrovascular disease, and conditions that could affect hemodynamic responses. (5.7)

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

• Renal or Hepatic Impairment: dose appropriately with oral RISPERDAL® prior to initiating treatment with RISPERDAL® CONSTA®. A lower starting dose of RISPERDAL® CONSTA® of 12.5 mg may be appropriate in some patients. (2.4)
• Nursing Mothers: should not breast feed. (8.3)
• Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)
• Elderly: dosing for otherwise healthy elderly patients is the same as for healthy nonelderly. Elderly may be more predisposed to orthostatic effects than nonelderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

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)].

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

2 DOSAGE AND ADMINISTRATION
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
For patients who have never taken oral Risperdal®, it is recommended to
establish tolerability with oral Risperdal® prior to initiating treatment with
Risperdal® Consta®.

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

2.3 General Dosing Information
2.4 Dosage in Special Populations

2.5 Reinitiation of Treatment in Patients Previously Discontinued

2.6 Switching from Other Antipsychotics

2.7 Co-Administration of Risperdal® Consta® with Certain Other
Medications

2.8 Instructions for Use

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related
Psychosis

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients
with Dementia-Related Psychosis

5.3 Neuroleptic Malignant Syndrome (NMS)

5.4 Tardive Dyskinesia

5.5 Metabolic Changes

5.6 Hyperprolactinemia

5.7 Orthostatic Hypotension

5.8 Leukopenia, Neutropenia, and Agranulocytosis

5.9 Potential for Cognitive and Motor Impairment

5.10 Seizures

5.11 Dysphagia

5.12 Priapism

5.13 Thrombotic Thrombocytopenic Purpura (TTP)

5.14 Body Temperature Regulation

5.15 Administration

5.16 Antiemetic Effect

5.17 Suicide

5.18 Use in Patients with Concomitant Illness

5.19 Osteodystrophy and Tumors in Animals

5.20 Monitoring: Laboratory Tests

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

6.2 Commonly-Observed Adverse Reactions in Double-Blind,
Placebo-Controlled Clinical Trials - Bipolar Disorder

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

6.4 Discontinuations Due to Adverse Reactions

6.5 Dose Dependency of Adverse Reactions in Clinical Trials

17 PATIENT COUNSELING INFORMATION
17.1 Orthostatic Hypotension

17.2 Interference with Cognitive and Motor Performance

17.3 Pregnancy

17.4 Nursing

17.5 Concomitant Medication

17.6 Alcohol

[*SeCTIONS OR SUBSECTIONS OMITTED FROM THE FULL PRESCRIBING INFORMATION ARE NOT LISTED*]
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 the 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.

2.2 Bipolar Disorder

The recommended dose for monotherapy or adjunctive therapy to lithium or valproate is 25 mg IM every 2 weeks. In patients who have a history of poor tolerability to psychotrophic 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 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. The total daily dose of oral RISPERDAL® is well tolerated. No adjustment of 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 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 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® (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)].
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 syringe assembly steps, hold the syringe only by the white collar and a smooth white cap. To open the syringe, pull the white collar together with the rubber tip cap inside. For all syringe 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.

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.

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.

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 needle from 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. RE_SUSPEND THE MICROSPHERES 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-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 resuspended 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.
There is no known treatment for established cases of tardive dyskinesia, although brief treatment periods at low doses 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 it. However, the syndrome can develop, although much less commonly, after relatively long-term antipsychotic treatment. Therefore, cumulative dose of antipsychotic drugs administered to the patient increase.

3.2 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 dementia-related psychosis. [See also Boxed Warning and Precautions (5.1)].

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal, multisystemic, 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 are 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 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 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 this 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 antipsychotic use and hyperglycemia-related adverse events is not complete and is not fully 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 treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia including polyuria, polydipsia, 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 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 risperdone 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 Risperdone

<table>
<thead>
<tr>
<th>Glucose Level</th>
<th>Baseline</th>
<th>1-8 mg/day</th>
<th>&gt;8-16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Mean change (mg/dL)</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Serum Glucose, &gt;140 mg/dL to ≥200 mg/dL</td>
<td>3/725</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Serum Glucose, &lt;140 mg/dL to &lt;200 mg/dL</td>
<td>3/702</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Serum Glucose, &lt;200 mg/dL to ≥240 mg/dL</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

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

Dyslipidemia

Unfavorable 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 Risperdone

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Baseline</th>
<th>1-8 mg/day</th>
<th>&gt;8-16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>727</td>
<td>727</td>
<td></td>
</tr>
<tr>
<td>Mean change (mg/dL)</td>
<td>6.3%</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, &lt;200 mg/dL to ≥240 mg/dL</td>
<td>22/516</td>
<td>25/516</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, &lt;200 mg/dL to &lt;200 mg/dL</td>
<td>10/231</td>
<td>10/231</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, &lt;200 mg/dL to ≥500 mg/dL</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with an increase in triglycerides of +6.3 mg/dL at Week 24 (n=231) and +5.5 mg/dL at Week 48 (n=86); and (b) non-fast ing 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.

Table 3. Change in Random Weight From Seven Placebo-Controlled, 12-Week, Fixed-Dose Studies in Adult Subjects With Schizophrenia

<table>
<thead>
<tr>
<th>Weight Change (kg)</th>
<th>Baseline</th>
<th>1-8 mg/day</th>
<th>&gt;8-16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>727</td>
<td>727</td>
<td></td>
</tr>
<tr>
<td>Mean change (kg)</td>
<td>1.6</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, &lt;500 mg/dL to ≥500 mg/dL</td>
<td>22/516</td>
<td>25/516</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, &lt;200 mg/dL to ≥200 mg/dL</td>
<td>10/231</td>
<td>10/231</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, &lt;200 mg/dL to &lt;200 mg/dL</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with an increase in weight of +1.6 kg at Week 24 (n=231) and +5.5 kg at Week 48 (n=86); and (b) non-fast ing triglycerides of +19.9 mg/dL at Week 24 (n=52).
5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) are of neural-crest or mesenchymal origin. The class of potential neural crest-related neoplasia, referred to as “neural crest carcinomas,” is characterized by morphologic similarities to neural crest cells and is currently being investigated as a potential mechanism for the occurrence of tumors in the central nervous system.

5.7 Orthostatic Hypotension

RISPERDAL® CONSTA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period with oral risperidone, probably reflecting its alpha-adrenergic antagonistic 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.

Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL® and antihypertensive medication.

5.8 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 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.

5.9 Potential for Cognitive and Motor Impairment

Somnolence 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.

5.10 Seizures

During premarketing testing, seizures occurred in 0.3% (5/1489) patients of patients treated with RISPERDAL® CONSTA®. Therefore, RISPERDAL® CONSTA® should be used cautiously in patients with a history of seizures.

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in 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 Thoracic-Thromboembolic 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). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

5.14 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.

5.15 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 Antimetic 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 bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. RISPERDAL® CONSTA® is to be administered by a health care professional [see Dosage and Administration (2)]; 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.

Caution is advisable when using RISPERDAL® CONSTA® in patients with diseases or conditions that could affect metabolism or hematodynamic responses. RISPERDAL® CONSTA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product’s premarket testing.

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. 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 or hepatic impairment [see Dosage and Administration (2.4)].

5.19 Osteodystrophy and Tumors in Animals

RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and in renal tumor-bearing males in the 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 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.)

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.

Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone. Adrenomedullary pheochromocytomas and 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.

5.20 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.
RISPERDAL® CONSTA® (risperidone) LONG-ACTING INJECTION

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 Precautions (5.1)]
- 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)]
- Leukopenia/Neutropenia and Agranulocytosis [see Warnings and Precautions (5.8)]
- Potential for cognitive and motor impairment [see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]
- Dysphagia [see Warnings and Precautions (5.11)]
- Pruritus [see Warnings and Precautions (5.12)]
- Thrombotic Thrombocytopenic Purpura (TTP) [see Warnings and Precautions (5.13)]
- Disruption of body temperature regulation [see Warnings and Precautions (5.14)]
- Avoidance of inadvertent injection into a blood vessel [see Warnings and Precautions (5.15)]
- Antidiabetic effect [see Warnings and Precautions (5.16)]
- Suicide [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)]
- Diseases or conditions that could affect metabolism or hemodynamic responses [see Interactions (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%) were: headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions in the double-blind, placebo-controlled periods of the bipolar disorder trials were weight increased (5% in the monotherapy trial) and tremor and parkinsonism (≥ 10% in the adjunctive treatment trial).

The most common adverse reactions that were associated with discontinuation from the 12-week double-blind, placebo-controlled trial in patients with schizophrenia (causing discontinuation in ≥ 1% of patients) were agitation, depression, and anxiety, and akathisia. Adverse reactions that were associated with discontinuation from the double-blind, placebo-controlled periods of the bipolar disorder trials were hyperglycemia (one patient in the monotherapy trial) and hypokinesia and tardive dyskinesia (one patient each in the adjunctive treatment trial).

The data described in this section are derived from a clinical trial database consisting of 2392 patients exposed to one or more doses of RISPERDAL® CONSTA® for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received RISPERDAL® CONSTA® while participating in a 12-week double-blind, placebo-controlled trial, two hundred two (202) of the 332 schizophrenia patients who received 25 mg or 50 mg RISPERDAL® CONSTA®. The conditions and duration of treatment with RISPERDAL® CONSTA® in the other clinical trials varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

In addition to the studies in patients with schizophrenia, safety data are presented from a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder. The subjects in this multi-center, double-blind, placebo-controlled study were adult patients who met DSM-IV criteria for Bipolar Disorder Type I and who were stable on risperidone (oral or long-acting injection), were stable on other antipsychotics or mood stabilizers, and/or antidepressants, and/or anxiolytics. 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>System Organ Class</th>
<th>Adverse Reaction</th>
<th>25 mg (n=59)</th>
<th>50 mg (n=103)</th>
<th>Placebo (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>0</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Toothache</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Salivary hypersecretion</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue*</td>
<td>3</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Weight decreased</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>15</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism*</td>
<td>8</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>7</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Akathisia*</td>
<td>4</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Sedation*</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypoesthesia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sinus congestion</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
<td>2</td>
<td>0</td>
<td>0</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% 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 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>Adverse Reaction</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL® CONSTA®</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N=154)</td>
<td>(N=149)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>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/Organ Class</th>
<th>Adverse Reaction</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RISPERDAL® CONSTA®</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N=72)</td>
<td>(N=67)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait abnormal</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Parkinsonismb</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Sedationc</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

### 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.

### 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

### 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
- posture abnormal, myalgia, back pain, buttock pain, muscular weakness, neck pain, musculoskeletal chest pain

### Nervous system disorders
- coordination abnormal, dystonia, tardive dyskinesia, drooling, paresthesia, dizziness postural, convulsion, akinesia, hypokinesia, dysarthria

### Psychiatric disorders
- insomnia, agitation, anxiety, sleep disorder, depression, initial insomnia, libido decreased, nervousness

### Renal and urinary disorders
- urinary incontinence

### Reproductive system and breast disorders
- galactorrhea, oligomenorrhea, erectile dysfunction, sexual dysfunction, ejaculation disorder, gynaecomastia, breast discomfort, menstruation irregular, menstruation delayed, menstrual disorder, ejaculation delayed

### Respiratory, thoracic and mediastinal disorders
- nasal congestion, pharyngolaryngeal pain, dyspnea, rhinorrhea

### Skin and subcutaneous tissue disorders
- rash, eczema, pruritus generalized, pruritus

### Vascular disorders
- hypotension, orthostatic hypotension

### Additional Adverse Reactions Reported with Oral RISPERDAL®

The following is a list of additional adverse reactions that have been reported during the clinical trial evaluation of oral RISPERDAL®, regardless of frequency of occurrence:

### Blood and Lymphatic Disorders
- granulocytopenia

### Cardiovascular Disorders
- atrioventricular block

### Ear and Labyrinth Disorders
- tinnitus

### Eye Disorders
- ocular hyperemia, eye discharge, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, lacrimation increased, photophobia, glaucoma

### Gastrointestinal Disorders
- abdominal pain upper, dysphagia, fecaloma, abdominal discomfort, fecal incontinence, lip swelling, chelitis, apathy

### General Disorders
- thirst, feeling abnormal, gait disturbance, pitting edema, edema, chills, discomfort, generalized edema, drug withdrawal syndrome, peripheral coldness

### Immune System Disorders
- drug hypersensitivity

### Infections and Infestations
- tonsillitis, eye infection, cellulitis, otitis media, onychomycosis, acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

### Investigations
- body temperature increased, heart rate increased, eosinophil count increased, white blood cell count decreased, hemoglobin decreased, blood creatine phosphokinase increased, hematocrit decreased, body temperature decreased, blood pressure decreased, transaminases increased

### Metabolism and Nutrition Disorders
- polydipsia

### Musculoskeletal, Connective Tissue, and Bone Disorders
- joint swelling, joint stiffness, rhabdomyalgia, torticolis

### Nervous System Disorders
- hypopituitarism, balance disorder, dysarthria, unresponsive to stimuli, depressed level of consciousness, movement disorder, hypokinesia, parkinsonian rest tremor, transient ischemic attack, cerebrovascular accident, masked facies, speech disorder, loss of consciousness, muscle contractions involuntary, akinesia, cerebral ischemia, cerebrovascular disorder, neuroleptic malignant syndrome, diabetic coma, head titubation

### Psychiatric Disorders
- blunted affect, confusional state, middle insomnia, listlessness, anorgasmia

### Renal and Urinary Disorders
- enuresis, dysuria, pollakiuria

### Reproductive System and Breast Disorders
- joint swelling, joint stiffness, rhadomyolysis, torticolis

### 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

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 with 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 were 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 in the total subscore of the subscale scores for parkinsonism, dystonia, and dyskinesia of the Extrapyramidal Symptom Rating Scale (ESRS).

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 mean change from baseline to endpoint in total ESRS 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 98 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 = unbearable pain) 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 after the pre-dose 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 they occur spontaneously with the use of many drugs. They appear approximately certain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopexia, anaphylactic reaction, angioedema, atrial fibrillation, blood cholesterol increased, blood triglycerides increased, diabetes mellitus, diabetic ketosis in patients with impaired glucose metabolism, drug withdrawal syndrome neonatal, dysgeusia, hypoglycemia, hypothermia, 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 postmarketing use of RISPERDAL® CONSTA®: cerebrovascular disorders, including abnormal artherovascular anastomosis.

Serious injection site reactions including abscess, cellulitis, cyst, hematoma, necrosis, 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 Amitriptyline

Amitriptyline did not affect the pharmacokinetics of risperidone or of 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 h 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 non-psychotropic 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) 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 levels of risperidone should be re-evaluated in the dose of Risperdal® Consta®. When initiation of fluoxetine or paroxetine is selected, 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. [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 continued on the 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 (0.03-10 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 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 peripostnatal 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 5 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 were noted in adult females by a dose of 0.3 mg/kg/day in a decrease 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 increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to alter behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to controls but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m² basis.

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, hypothermia, hypotonia, tremor, metabolicacidosis, 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.

Juvenile dogs were treated for 4 weeks with oral risperidone doses of 0.1, 0.25, or 0.5 mg/kg/day. No effects of drug treatment were seen at the no-effect dose of 0.31 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus its active metabolite 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 0.65 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 initiated at lower doses (0.125 mg/day) and titrated upward, if needed, until the appropriate dose is reached. This slow titration schedule will 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 (8.7)].

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 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 (8.1)].

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.
9.3 Dependence
Risperdal® Konsta® 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® Konsta®. Because Risperdal® Konsta® 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. Only 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 36 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, 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 antiarrhythmic therapy is administered, disopyramide, procainamide, or quinidine can be given. If QT prolongation effects that may be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretiam 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]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-benzisoxazole-4-one. Its molecular formula is C27H33FNO5 and its molecular weight is 410.49. The structural formula is:

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

Risperdal® Konsta® (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 polylactide-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 polysorbate 20, sodium carboxymethyl 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® Konsta® 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 dermot administration and a 20 G TW 2-inch needle with needle protection device for glutal administration).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action of Risperdal® Konsta®, 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) cfl 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 295 nM) for the serotonin 5HT3, 5HT4, 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 >10-5 M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

12.2 Pharmacodynamics
The clinical effect from Risperdal® Konsta® 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® Konsta®.

12.3 Pharmacokinetics
Absorption
After a single intramuscular (glutal) injection of Risperdal® Konsta®, 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 a few weeks following the intramuscular (IM) injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with Risperdal® Konsta® to maintain therapeutic levels until the main release of risperidone from the injection site has begun [see Dosage and Administration (11)]. Following single doses of Risperdal® Konsta®, 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® Konsta® 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® Konsta®, plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone were linear. Deltoid and glutal 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 displace each other from plasma binding sites. High 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 2C6. 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® Konsta® with coadministration of other drugs have not been systematically evaluated in human subjects. Drug interactions are based primarily on experience with oral Risperdal®. Risperdal® 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., phenytin, 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 half-life of risperidone plus 9-hydroxyrisperidone is about 6 hours and is associated with a monoexponential decline in plasma concentrations. A 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 L/h and 5 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 levels of 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 alpha 1-acid glycoprotein. 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 (2.4)].

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. The administered doses are equivalent to 1.9, 7.7, 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 male rats, since impaired mating behavior was not noted in the mating and fertility study in which males only were treated. With oral administration, 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 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 oral RISPERDAL®. Formulation and delivery characteristics of oral and long-acting injectable formulations of risperidone were also shown to be comparable [see Drug Interactions (7.2)].

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. These doses provide therapeutic plasma levels until the full release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets. Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated, multi-item inventory, composed of five subscales to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/ excitement, and anxiety/depression.

The primary efficacy variable in this trial was change from baseline to endpoint in the total PANSS score. The mean total PANSS score at baseline for schizophrenic 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® (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). In the open-label phase, 303 (60%) patients 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 mania 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® (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%) patients 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 adjunctive therapy with RISPERDAL® CONSTA® as compared to placebo. The relapse types were about half depressive and half manic or mixed 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).

12.5-mg vial/kit (NDC 50458-309-11): 41 mg (equivalent to 12.5 mg of risperidone) of a white to off-white powder provided in a vial with a violet flip-off cap (NDC 50458-309-01).

25-mg vial/kit (NDC 50458-306-11): 78 mg (equivalent to 25 mg of risperidone) of a white to off-white powder provided in a vial with a pink flip-off cap (NDC 50458-306-01).

37.5-mg vial/kit (NDC 50458-307-11): 116 mg (equivalent to 37.5 mg of risperidone) of a white to off-white powder provided in a vial with a green flip-off cap (NDC 50458-307-01).

50-mg vial/kit (NDC 50458-308-11): 152 mg (equivalent to 50 mg of risperidone) of a white to off-white powder provided in a vial with a blue flip-off cap (NDC 50458-308-01).

Storage and Handling
The entire dose pack should be stored in the refrigerator (36°- 46°F; 2°- 8°C) and protected from light.

If refrigeration is unavailable, RISPERDAL® CONSTA® can be stored at temperatures not exceeding 77°F (25°C) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 77°F (25°C).

Keep out of reach of children.