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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RISPERDAL® (risperidone) tablets, RISPERDAL® (risperidone) oral solution, RISPERDAL® M-TAB® (risperidone) orally disintegrating tablets

Initial U.S. Approval: 1993

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® is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Boxed Warning	08/2008
Warnings and Precautions (5.1)	08/2008
Warnings and Precautions, Leucopenia, Neutropenia, and Agranulocytosis (5.8)	09/2009

----------INDICATIONS AND USAGE----------

RISPERDAL® is an atypical antipsychotic agent indicated for:

- Treatment of schizophrenia in adults and adolescents aged 13-17 years (1.1)
- Alone, or in combination with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults, and alone in children and adolescents aged 10-17 years (1.2)
- Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years (1.3)

----------DOSAGE AND ADMINISTRATION----------

	Initial Dose	Titration	Target Dose	Effective Dose Range
Schizophrenia- adults (2.1)	2 mg /day	1-2 mg daily	4-8 mg daily	4-16 mg /day
Schizophrenia – adolescents (2.1)	0.5mg /day	0.5- 1 mg daily	3mg /day	1-6 mg /day
Bipolar mania – adults (2.2)	2-3 mg /day	1mg daily	1-6mg /day	1-6 mg /day
Bipolar mania in children/ adolescents (2.2)	0.5 mg /day	0.5-1mg daily	2.5mg /day	0.5-6 mg /day
Irritability associated with autistic disorder (2.3)	0.25 mg /day (<20 kg) 0.5 mg /day (≥20 kg)	0.25-0.5 mg at ≥ 2 weeks	0.5 mg /day (<20 kg) 1 mg /day (≥20 kg)	0.5-3 mg /day

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)
- Oral solution: 1 mg/mL (3)
- Orally disintegrating tablets: 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to the product (4)

----------WARNINGS AND PRECAUTIONS----------

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL® is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome (5.3)
- Tardive dyskinesia (5.4)
- Hyperglycemia and diabetes mellitus (5.5)
- Hyperprolactinemia (5.6)
- Orthostatic hypotension (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotics, including RISPERDAL®. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.8)
- Potential for cognitive and motor impairment (5.9)
- Seizures (5.10)
- Dysphagia (5.11)
- Priapism (5.12)
- Disruption of body temperature regulation (5.13)
- Antiemetic Effect (5.14)
- Suicide (5.15)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies (5.16)
- Diseases or conditions that could affect metabolism or hemodynamic responses (5.16)

----------ADVERSE REACTIONS----------

The most common adverse reactions in clinical trials (≥10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia. (6)

The most common adverse reactions that were associated with discontinuation from clinical trials were somnolence, nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia. (6)

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

----------DRUG INTERACTIONS----------

- Due to CNS effects, use caution when administering with other centrally-acting drugs. Avoid alcohol. (7.1)
- Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced. (7.2)
- Effects of levodopa and dopamine agonists may be antagonized. (7.3)
- Cimetidine and ranitidine increase the bioavailability of risperidone. (7.5)
- Clozapine may decrease clearance of risperidone. (7.6)
- Fluoxetine and paroxetine increase plasma concentrations of risperidone. (7.10)
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. (7.11)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: should not breast feed. (8.3)
- Pediatric Use: safety and effectiveness not established for schizophrenia less than 13 years of age, for bipolar mania less than 10 years of age, and for autistic disorder less than 5 years of age. (8.4)
- Elderly or debilitated; severe renal or hepatic impairment; predisposition to hypotension or for whom hypotension poses a risk: Lower initial dose (0.5 mg twice daily), followed by increases in dose in increments of no more than 0.5 mg twice daily. Increases to dosages above 1.5 mg twice daily should occur at intervals of at least 1 week. (8.5, 2.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: MM/YYYY

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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Adults

RISPERDAL® (risperidone) is indicated for the acute and maintenance treatment of schizophrenia *[see Clinical Studies (14.1)]*.

Adolescents

RISPERDAL® is indicated for the treatment of schizophrenia in adolescents aged 13–17 years *[see Clinical Studies (14.1)]*.

1.2 Bipolar Mania

Monotherapy - Adults and Pediatrics

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults and in children and adolescents aged 10-17 years *[see Clinical Studies (14.2)]*.

Combination Therapy – Adults

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder *[see Clinical Studies (14.3)]*.

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1.3 Irritability Associated with Autistic Disorder

Pediatrics

RISPERDAL® is indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5–16 years, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

Usual Initial Dose

RISPERDAL® can be administered once or twice daily. Initial dosing is generally 2 mg/day. Dose increases should then occur at intervals not less than 24 hours, in increments of 1-2 mg/day, as tolerated, to a recommended dose of 4-8 mg/day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4-16 mg/day *[see Clinical Studies (14.1)]*. However, doses above 6 mg/day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. In a single study supporting once-daily dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While it is unknown how long a patient with schizophrenia should remain on RISPERDAL®, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years *[*see *Clinical Studies (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Adolescents

The dosage of RISPERDAL® should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg/day, no additional benefit was seen above 3 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

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There are no controlled data to support the longer term use of RISPERDAL® beyond 8 weeks in adolescents with schizophrenia. The physician who elects to use RISPERDAL® for extended periods in adolescents with schizophrenia should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that after an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or treating patients with concomitant antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. The period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

2.2 Bipolar Mania

Usual Dose

Adults

RISPERDAL® should be administered on a once-daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day *[see Clinical Studies (14.2, 14.3)]*. RISPERDAL® doses higher than 6 mg per day were not studied.

Pediatrics

The dosage of RISPERDAL® should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg/day, no additional benefit was seen above 2.5 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

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Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with RISPERDAL®. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of RISPERDAL® in such longer-term treatment (i.e., beyond 3 weeks). The physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.3 Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)

The safety and effectiveness of RISPERDAL® in pediatric patients with autistic disorder less than 5 years of age have not been established.

The dosage of RISPERDAL® should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL® can be administered once daily, or half the total daily dose can be administered twice daily.

Dosing should be initiated at 0.25 mg per day for patients < 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weigh less than 15 kg.

In clinical trials, 90% of patients who showed a response (based on at least 25% improvement on ABC-I, *[see Clinical Studies (14.4)]*) received doses of RISPERDAL® between 0.5 mg and 2.5 mg per day. The maximum daily dose of RISPERDAL® in one of the pivotal trials, when the therapeutic effect reached plateau, was 1 mg in patients < 20 kg, 2.5 mg in patients ≥ 20 kg, or 3 mg in patients > 45 kg. No dosing data is available for children who weighed less than 15 kg.

Once sufficient clinical response has been achieved and maintained, consideration should be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. The

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physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Patients experiencing persistent somnolence may benefit from a once-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

2.4 Dosage in Special Populations

The recommended initial dose is 0.5 mg twice daily in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg twice daily. Increases to dosages above 1.5 mg twice daily should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect *[see Clinical Pharmacology (12.3)]*. Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored *[see Warnings and Precautions (5.2, 5.7, 5.16)]*. If a once-daily dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-daily regimen for 2-3 days at the target dose. Subsequent switches to a once-daily dosing regimen can be done thereafter.

2.5 Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with RISPERDAL® would be expected to cause decreases in the plasma concentrations of the sum of risperidone and 9-hydroxyrisperidone combined, which could lead to decreased efficacy of RISPERDAL® treatment. The dose of RISPERDAL® needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers *[see Drug Interactions (7.11)]*.

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of RISPERDAL® needs to be titrated accordingly when fluoxetine or paroxetine is co-administered *[see Drug Interactions (7.10)]*.

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2.6 Administration of RISPERDAL® Oral Solution

RISPERDAL® Oral Solution can be administered directly from the calibrated pipette, or can be mixed with a beverage prior to administration. RISPERDAL® Oral Solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea.

2.7 Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resistant pouch containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tablet through the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

3 DOSAGE FORMS AND STRENGTHS

RISPERDAL® Tablets are available in the following strengths and colors: 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green). All are capsule shaped, and imprinted with “JANSSEN” on one side and either “Ris 0.25”, “Ris 0.5”, “R1”, “R2”, “R3”, or “R4” on the other side according to their respective strengths.

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RISPERDAL® Oral Solution is available in a 1 mg/mL strength.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in the following strengths, colors, and shapes: 0.5 mg (light coral, round), 1 mg (light coral, square), 2 mg (coral, square), 3 mg (coral, round), and 4 mg (coral, round). All are biconvex and etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

4 CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone. Therefore, RISPERDAL® is contraindicated in patients with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

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

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of 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 risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[See also Boxed Warnings and Warnings and Precautions (5.1)]*

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom 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 creatinine 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 both 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

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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) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® 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.

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

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics 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 should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, RISPERDAL® elevates prolactin levels and the elevation persists during chronic administration. RISPERDAL® 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.

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Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Non-Clinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.7 Orthostatic Hypotension

RISPERDAL® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment *[see Dosage and Administration (2.1, 2.4)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in 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. Clinically significant hypotension has been observed with concomitant use of 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®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

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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/mm^3) should discontinue RISPERDAL® and have their WBC followed until recovery.

5.9 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® 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 RISPERDAL® therapy does not affect them adversely.

5.10 Seizures

During premarketing testing in adult patients with schizophrenia, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® 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® 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

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

5.13 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® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

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5.14 Antiemetic Effect

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

5.15 Suicide

The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

5.16 Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, 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 in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® 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 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients *[*see *Dosage and Administration (2.4)]*.

5.17 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*

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- 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)]*
- Hyperglycemia and diabetes mellitus *[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)]*
- Priapism *[see Warnings and Precautions (5.12)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.13)]*
- Antiemetic effect *[see Warnings and Precautions (5.14)]*
- Suicide *[see Warnings and Precautions (5.15)]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions (5.16)]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions (5.16)]*

The most common adverse reactions in clinical trials (≥ 10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia.

The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were somnolence,

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nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia *[see Adverse Reactions (6.5)]*.

The data described in this section are derived from a clinical trial database consisting of 9712 adult and pediatric patients exposed to one or more doses of RISPERDAL® for the treatment of schizophrenia, bipolar mania, autistic disorder, and other psychiatric disorders in pediatrics and elderly patients with dementia. Of these 9712 patients, 2626 were patients who received RISPERDAL® while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with RISPERDAL® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

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 WHOART 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® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for RISPERDAL® 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

Adult Patients with Schizophrenia

Table 1 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with schizophrenia in three 4- to 8-week, double-blind, placebo-controlled trials.

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Table 1. Adverse Reactions in ≥1% of RISPERDAL®-Treated Adult Patients with Schizophrenia in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Event		
	RISPERDAL®		
Body System Adverse Reaction	**2-8 mg per day (N=366)**	**>8-16 mg per day (N=198)**	**Placebo (N=225)**
Body as a whole - general disorders			
Back pain	3	2	<1
Fatigue	3	1	0
Chest pain	3	1	2
Fever	2	1	1
Asthenia	1	1	<1
Syncope	<1	1	<1
Edema	<1	1	0
Cardiovascular disorders, general			
Hypotension postural	2	<1	0
Hypotension	<1	1	0
Central and peripheral nervous system disorders			
Parkinsonism*	12	17	6
Dizziness	10	4	2
Dystonia*	5	5	2
Akathisia*	5	5	2
Dyskinesia	1	1	<1
Gastrointestinal system disorders			
Dyspepsia	10	7	6
Nausea	9	4	4
Constipation	8	9	7
Abdominal pain	4	3	0
Mouth dry	4	<1	<1
Saliva increased	3	1	<1
Diarrhea	2	<1	1
Hearing and vestibular disorders			
Earache	1	1	0
Heart rate and rhythm disorders			
Tachycardia	2	5	0
Arrhythmia	0	1	0
Metabolic and nutritional disorders			
Weight increase	1	<1	0
Creatine phosphokinase increased	<1	2	<1
Musculoskeletal system disorders			
Arthralgia	2	3	<1
Myalgia	1	0	0
Platelet, bleeding and clotting disorders			
Epistaxis	<1	2	0
Psychiatric disorders			
Anxiety	16	12	11
Somnolence	14	5	4
Anorexia	2	0	<1
Red blood cell disorders			
Anemia	<1	1	0
Reproductive disorders, male			
Ejaculation failure	<1	1	0
Respiratory system disorders			

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Rhinitis	7	11	6
Coughing	3	3	3
Upper respiratory tract infection	2	3	<1
Dyspnea	2	2	0
Skin and appendages disorders			
Rash	2	4	2
Seborrhea	<1	2	0
Urinary system disorders			
Urinary tract infection	<1	3	0
Vision disorders			
Vision abnormal	3	1	<1

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Schizophrenia

Table 2 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with schizophrenia in a 6-week double-blind, placebo-controlled trial.

Table 2. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients with Schizophrenia in a Double-Blind Trial

	Percentage of Patients Reporting Event RISPERDAL®		
Body System Adverse Reaction	**1-3 mg per day (N=55)**	**4-6 mg per day (N=51)**	**Placebo (N=54)**
Central and peripheral nervous system disorders			
Parkinsonism*	13	16	6
Tremor	11	10	6
Dystonia*	9	18	7
Dizziness	7	14	2
Akathisia*	7	10	6
Gastrointestinal system disorders			
Saliva increased	0	10	2
Psychiatric disorders			
Somnolence	24	12	4
Anxiety	7	6	0

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradykinesia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

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

Adult Patients with Bipolar Mania

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Table 3 lists the adverse reactions reported in 1% or more of RISPERDAL®-treated adult patients with bipolar mania in four 3-week, double-blind, placebo-controlled monotherapy trials.

Table 3. Adverse Reactions in ≥1% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Monotherapy Trials

	Percentage of Patients Reporting Event	
Body System Adverse Reaction	**RISPERDAL® 1-6 mg per day (N=448)**	**Placebo (N=424)**
Body as a whole - general disorders		
Fatigue	2	<1
Fever	1	<1
Asthenia	1	<1
Edema	1	<1
Central and peripheral nervous system disorders		
Parkinsonism*	20	6
Dystonia*	11	3
Akathisia*	9	3
Tremor	6	4
Dizziness	5	5
Gastrointestinal system disorders		
Nausea	5	2
Dyspepsia	4	2
Saliva increased	3	<1
Diarrhea	3	2
Mouth dry	1	1
Heart rate and rhythm disorders		
Tachycardia	1	<1
Liver and biliary system disorders		
SGOT increased	1	<1
Musculoskeletal disorders		
Myalgia	2	2
Psychiatric disorders		
Somnolence	12	4
Anxiety	2	2
Reproductive disorders, female		
Lactation nonpuerperal	1	0
Respiratory disorders		
Rhinitis	2	2
Skin and appendages disorders		
Acne	1	0
Vision disorders		
Vision abnormal	2	<1

* Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

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Table 4 lists the adverse reactions reported in 2% or more of RISPERDAL®-treated adult patients with bipolar mania in two 3-week, double-blind, placebo-controlled adjuvant therapy trials.

Table 4. Adverse Reactions in ≥2% of RISPERDAL®-Treated Adult Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Adjuvant Therapy Trials

	Percentage of Patients Reporting Event	
Body System Adverse Reaction	**RISPERDAL® + Mood Stabilizer (N=127)**	**Placebo + Mood Stabilizer (N=126)**
Body as a whole – general disorders		
Chest pain	2	2
Fatigue	2	2
Central and peripheral nervous system disorders		
Parkinsonism*	9	4
Dizziness	8	2
Dystonia*	6	3
Akathisia*	6	0
Tremor	5	2
Gastrointestinal system disorders		
Nausea	6	5
Diarrhea	6	4
Saliva increased	4	0
Abdominal pain	2	0
Heart rate and rhythm disorders		
Palpitation	2	0
Metabolic and nutritional disorders		
Weight increase	2	2
Psychiatric disorders		
Somnolence	12	5
Anxiety	4	2
Respiratory disorders		
Pharyngitis	5	2
Coughing	3	1
Skin and appendages disorders		
Rash	2	2
Urinary system disorders		
Urinary incontinence	2	1
Urinary tract infection	2	1

* Parkinsonism includes extrapyramidal disorder, hypokinesia and bradykinesia. Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Akathisia includes hyperkinesia and akathisia.

Pediatric Patients with Bipolar Mania

Table 5 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients with bipolar mania in a 3-week double-blind, placebo-controlled trial.

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Table 5. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients with Bipolar Mania in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Event		
	RISPERDAL®		
Body System Adverse Reaction	**0.5-2.5 mg per day (N=50)**	**3-6 mg per day (N=61)**	**Placebo (N=58)**
Body as a whole - general disorders			
Fatigue	18	30	3
Central and peripheral nervous system disorders			
Dizziness	16	13	5
Dystonia*	8	13	2
Parkinsonism*	2	7	2
Akathisia*	0	7	2
Gastrointestinal system disorders			
Abdominal pain	18	15	5
Dyspepsia	16	5	3
Nausea	16	13	7
Vomiting	12	10	7
Diarrhea	8	7	2
Heart rate and rhythm disorders			
Tachycardia	0	5	2
Psychiatric disorders			
Somnolence	42	56	19
Appetite increased	4	7	2
Anxiety	0	8	3
Reproductive disorders, female			
Lactation nonpuerperal	2	5	0
Respiratory system disorders			
Rhinitis	14	13	10
Dyspnea	2	5	0
Skin and appendages disorders			
Rash	0	7	2
Urinary system disorders			
Urinary incontinence	0	5	0
Vision disorders			
Vision abnormal	4	7	0

* Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis. Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradykinesia. Akathisia includes hyperkinesia and akathisia.

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6.3 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Autistic Disorder

Table 6 lists the adverse reactions reported in 5% or more of RISPERDAL®-treated pediatric patients treated for irritability associated with autistic disorder in two 8-week, double-blind, placebo-controlled trials.

Table 6. Adverse Reactions in ≥5% of RISPERDAL®-Treated Pediatric Patients Treated for Irritability Associated with Autistic Disorder in Double-Blind, Placebo-Controlled Trials

	Percentage of Patients Reporting Event	
Body System Adverse Reaction	**RISPERDAL® 0.5-4.0 mg per day (N=76)**	**Placebo (N=80)**
Body as a whole - general disorders		
Fatigue	42	13
Fever	20	19
Central and peripheral nervous system disorders		
Dystonia*	12	6
Tremor	12	1
Dizziness	9	3
Parkinsonism*	8	0
Automatism	7	1
Dyskinesia	7	0
Gastrointestinal system disorders		
Vomiting	25	21
Saliva increased	22	6
Constipation	21	8
Mouth dry	13	6
Nausea	8	8
Heart rate and rhythm disorders		
Tachycardia	7	0
Metabolic and nutritional disorders		
Weight increase	5	0
Psychiatric disorders		
Somnolence	67	23
Appetite increased	49	19
Anxiety	16	15
Anorexia	8	8
Confusion	5	0
Respiratory system disorders		
Rhinitis	36	23
Upper respiratory tract infection	34	15
Coughing	24	18
Skin and appendages disorders		
Rash	11	8
Urinary system disorders		
Urinary incontinence	22	20

* Dystonia includes dystonia, hypertonia, oculogyric crisis, muscle contractions involuntary, tetany, laryngismus, tongue paralysis, and torticollis.
Parkinsonism includes extrapyramidal disorder, hypokinesia, and bradycardia.

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6.4 Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL®

The following adverse reactions occurred in < 1% of the adult patients and in < 5% of the pediatric patients treated with RISPERDAL® in the above double-blind, placebo-controlled clinical trial data sets. In addition, the following also includes adverse reactions reported in RISPERDAL®-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia and bipolar mania studies in pediatric patients with psychiatric disorders other than schizophrenia, bipolar mania, or autistic disorder, and studies in elderly patients with dementia.

Body as a Whole, General Disorders: edema peripheral, pain, influenza-like symptoms, leg pain, malaise, allergy, crying abnormal, allergic reaction, rigors, allergy aggravated, anaphylactoid reaction, hypothermia

Central Nervous System Disorders: gait abnormal, speech disorder, coma, ataxia, dysphonia, stupor, cramps legs, vertigo, hypoesthesia, tardive dyskinesia, neuroleptic malignant syndrome

Endocrine Disorders: hyperprolactinemia, gynecomastia

Gastrointestinal System Disorders: dysphagia, flatulence

Heart Rate and Rhythm Disorders: AV block, bundle branch block

Liver and Biliary Disorders: SGPT increased, hepatic enzymes increased

Metabolic and Nutritional Disorders: thirst, hyperglycemia, xerophthalmia, generalized edema, diabetes mellitus aggravated, diabetic coma

Musculoskeletal Disorders: muscle weakness, rhabdomyolysis

Platelet, Bleeding, and Clotting Disorders: purpura

Psychiatric Disorders: insomnia, agitation, emotional lability, apathy, nervousness, concentration impaired, impotence, decreased libido

Reproductive Disorders, Female: amenorrhea, menstrual disorder, leukorrhea

Reproductive Disorders, Male: ejaculation disorder, abnormal sexual function, priapism

Resistance Mechanism Disorders: otitis media, viral infection

Respiratory Disorders: respiratory disorder

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Skin and Appendages Disorders: skin ulceration, skin discoloration, rash erythematous, skin exfoliation, rash maculopapular, erythema multiforme

Urinary Disorders: micturition frequency

Vascular Disorders: cerebrovascular disorder

Vision Disorders: conjunctivitis

White Cell Disorders: leucopenia, granulocytopenia

6.5 Discontinuations Due to Adverse Reactions

Schizophrenia - Adults

Approximately 7% (39/564) of RISPERDAL®-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more RISPERDAL®-treated patients were:

Table 7. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Schizophrenia Trials

	RISPERDAL®		
Adverse Reaction	**2-8 mg/day (N=366)**	**>8-16 mg/day (N=198)**	**Placebo (N=225)**
Dizziness	1.4%	1.0%	0%
Nausea	1.4%	0%	0%
Agitation	1.1%	1.0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0.5%	0%
Dystonia	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Hypotension postural	0.3%	0.5%	0%
Tachycardia	0.3%	0.5%	0%
Akathisia	0%	1.0%	0%

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Schizophrenia - Pediatrics

Approximately 7% (7/106), of RISPERDAL®-treated patients discontinued treatment due to an adverse event in a double-blind, placebo-controlled trial, compared with 4% (2/54) placebo-treated patients. The adverse reactions associated with discontinuation for at least one RISPERDAL®-treated patient were somnolence (2%), dizziness (2%), anorexia (1%), anxiety (1%), ataxia (1%), hypotension (1%), and palpitation (1%).

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Bipolar Mania - Adults

In double-blind, placebo-controlled trials with RISPERDAL® as monotherapy, approximately 6% (25/448) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 5% (19/424) of placebo-treated patients. The adverse reactions associated with discontinuation in RISPERDAL®-treated patients were:

Table 8. Adverse Reactions Associated With Discontinuation in 2 or More RISPERDAL®-Treated Adult Patients in Bipolar Mania Clinical Trials

Adverse Reaction	RISPERDAL® 1-6 mg/day (N=448)	Placebo (N=424)
Parkinsonism	0.4%	0%
Somnolence	0.2%	0%
Dizziness	0.2%	0%
Dystonia	0.2%	0%
SGOT increased	0.2%	0.2%
SGPT increased	0.2%	0.2%

Bipolar Mania - Pediatrics

In a double-blind, placebo-controlled trial 12% (13/111) of RISPERDAL®-treated patients discontinued due to an adverse event, compared with 7% (4/58) of placebo-treated patients. The adverse reactions associated with discontinuation in more than one RISPERDAL®-treated pediatric patient were somnolence (5%), nausea (3%), abdominal pain (2%), and vomiting (2%).

Autistic Disorder - Pediatrics

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n = 156), one RISPERDAL®-treated patient discontinued due to an adverse reaction (Parkinsonism), and one placebo-treated patient discontinued due to an adverse event.

6.6 Dose Dependency of Adverse Reactions in Clinical Trials

Extrapyramidal Symptoms

Data from two fixed-dose trials in adults with schizophrenia provided evidence of dose-relatedness for extrapyramidal symptoms associated with RISPERDAL® treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day), including (1) a Parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

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Dose Groups	Placebo	RISPERDAL® 2 mg	RISPERDAL® 6 mg	RISPERDAL® 10 mg	RISPERDAL® 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	11%	15%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day):

Dose Groups	RISPERDAL® 1 mg	RISPERDAL® 4 mg	RISPERDAL® 8 mg	RISPERDAL® 12 mg	RISPERDAL® 16 mg
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	11%	17%	18%	20%

Other Adverse Reactions

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectile dysfunction, ejaculation disorder, sexual function abnormal, fatigue, and skin discoloration.

6.7 Changes in Body Weight

The proportions of RISPERDAL® and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the RISPERDAL® (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

Changes in body weight were also evaluated in pediatric patients *[see Use in Specific Populations (8.4)]*

6.8 Changes in ECG

Between-group comparisons for pooled placebo-controlled trials in adults revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were

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associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In pooled placebo-controlled acute mania trials in adults, there were small decreases in mean heart rate, similar among all treatment groups.

In the two placebo-controlled trials in children and adolescents with autistic disorder (aged 5 - 16 years) mean changes in heart rate were an increase of 8.4 beats per minute in the RISPERDAL® groups and 6.5 beats per minute in the placebo group. There were no other notable ECG changes.

In a placebo-controlled acute mania trial in children and adolescents (aged 10 – 17 years), there were no significant changes in ECG parameters, other than the effect of RISPERDAL® to transiently increase pulse rate (< 6 beats per minute). In two controlled schizophrenia trials in adolescents (aged 13 – 17 years), there were no clinically meaningful changes in ECG parameters including corrected QT intervals between treatment groups or within treatment groups over time.

6.9 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RISPERDAL®; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: anaphylactic reaction, angioedema, atrial fibrillation, diabetic ketoacidosis in patients with impaired glucose metabolism, intestinal obstruction, jaundice, mania, QT prolongation, and sleep apnea.

Other adverse events reported since market introduction, which were temporally related to RISPERDAL® but not necessarily causally related, include the following: pancreatitis, pituitary adenoma, pulmonary embolism, precocious puberty, cardiopulmonary arrest, and sudden death.

7 DRUG INTERACTIONS

7.1 Centrally-Acting Drugs and Alcohol

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

7.2 Drugs with Hypotensive Effects

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

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7.3 Levodopa and Dopamine Agonists

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

7.4 Amitriptyline

Amitriptyline did not affect the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined.

7.5 Cimetidine and Ranitidine

Cimetidine and ranitidine increased the bioavailability of 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 RISPERDAL® may decrease the clearance of risperidone.

7.7 Lithium

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

7.8 Valproate

Repeated oral doses of 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 (C_{max}) after concomitant administration of RISPERDAL®.

7.9 Digoxin

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

7.10 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs *[see Clinical Pharmacology (12.3)]*. 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 ($n \cong 70$) 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.

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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) 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 physician should re-evaluate the dosing of RISPERDAL®. 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 RISPERDAL® and erythromycin.

7.11 Carbamazepine and Other Enzyme Inducers

Carbamazepine co-administration decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of RISPERDAL® may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with RISPERDAL® may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of RISPERDAL® treatment.

7.12 Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, 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 risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the

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MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III 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 3 times the MRHD on a mg/m^2 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 Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number 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 impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 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 agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of RISPERDAL® during the last trimester of pregnancy.

RISPERDAL® 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® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast-feed.

8.4 Pediatric Use

The efficacy and safety of RISPERDAL® in the treatment of schizophrenia were demonstrated in 417 adolescents, aged 13 – 17 years, in two short-term (6 and 8 weeks, respectively) double-blind controlled trials *[see Indications and Usage (1.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]*. Additional safety and efficacy information was also assessed in one long-term (6-month) open-label extension study in 284 of these adolescent patients with schizophrenia.

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Safety and effectiveness of RISPERDAL® in children less than 13 years of age with schizophrenia have not been established.

The efficacy and safety of RISPERDAL® in the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in 169 children and adolescent patients, aged 10 – 17 years, were demonstrated in one double-blind, placebo-controlled, 3-week trial *[see Indications and Usage (1.2), Adverse Reactions (6.2), and Clinical Studies (14.2)]*.

Safety and effectiveness of RISPERDAL® in children less than 10 years of age with bipolar disorder have not been established.

The efficacy and safety of RISPERDAL® in the treatment of irritability associated with autistic disorder were established in two 8-week, double-blind, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years *[see Indications and Usage (1.3), Adverse Reactions (6.3) and Clinical Studies (14.4)]*. Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania who were of similar age and weight, and who received similar dosages of RISPERDAL® as patients treated for irritability associated with autistic disorder.

The safety and effectiveness of RISPERDAL® in pediatric patients less than 5 years of age with autistic disorder have not been established.

Tardive Dyskinesia

In clinical trials in 1885 children and adolescents treated with RISPERDAL®, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of RISPERDAL® treatment *[see also Warnings and Precautions (5.4)]*.

Weight Gain

In a long-term, open-label extension study in adolescent patients with schizophrenia, weight increase was reported as a treatment-emergent adverse event in 14% of patients. In 103 adolescent patients with schizophrenia, a mean increase of 9.0 kg was observed after 8 months of RISPERDAL® treatment. The majority of that increase was observed within the first 6 months. The average percentiles at baseline and 8 months, respectively, were 56 and 72 for weight, 55 and 58 for height, and 51 and 71 for body mass index.

In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed, which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The

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majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index.

In one 3-week, placebo-controlled trial in children and adolescent patients with acute manic or mixed episodes of bipolar I disorder, increases in body weight were higher in the RISPERDAL® groups than the placebo group, but not dose related (1.90 kg in the RISPERDAL® 0.5-2.5 mg group, 1.44 kg in the RISPERDAL® 3-6 mg group, and 0.65 kg in the placebo group). A similar trend was observed in the mean change from baseline in body mass index.

When treating pediatric patients with RISPERDAL® for any indication, weight gain should be assessed against that expected with normal growth. *[See also Adverse Reactions (6.7)]*

Somnolence

Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. Somnolence was the most commonly observed adverse event in the clinical trial of bipolar disorder in children and adolescents, as well as in the schizophrenia trials in adolescents. As was seen in the autistic disorder trials, these events were most often of early onset and transient in duration. *[See also Adverse Reactions (6.1, 6.2, 6.3)]* Patients experiencing persistent somnolence may benefit from a change in dosing regimen *[*see *Dosage and Administration (2.1, 2.2, 2.3)]*.

Hyperprolactinemia, Growth, and Sexual Maturation

RISPERDAL® has been shown to elevate prolactin levels in children and adolescents as well as in adults *[see Warnings and Precautions (5.6)]*. In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania, 49% of patients who received RISPERDAL® had elevated prolactin levels compared to 2% of patients who received placebo. Similarly, in placebo-controlled trials in children and adolescents (aged 10 to 17 years) with bipolar disorder, or adolescents (aged 13 to 17 years) with schizophrenia, 82–87% of patients who received RISPERDAL® had elevated levels of prolactin compared to 3-7% of patients on placebo. Increases were dose-dependent and generally greater in females than in males across indications.

In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.

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The long-term effects of RISPERDAL® on growth and sexual maturation have not been fully evaluated.

8.5 Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.4, 2.5)]*. While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg twice daily followed by careful titration *[see Warnings and Precautions (5.7)]*. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.4)]*.

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 RISPERDAL® when compared to patients treated with RISPERDAL® alone or with 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 RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. *[See Boxed Warning and Warnings and Precautions (5.1)]*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

RISPERDAL® (risperidone) is not a controlled substance.

9.2 Abuse

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited

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experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

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

10 OVERDOSAGE

10.1 Human Experience

Premarketing experience included eight reports of acute RISPERDAL® overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

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

10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of RISPERDAL® M-TAB®Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those

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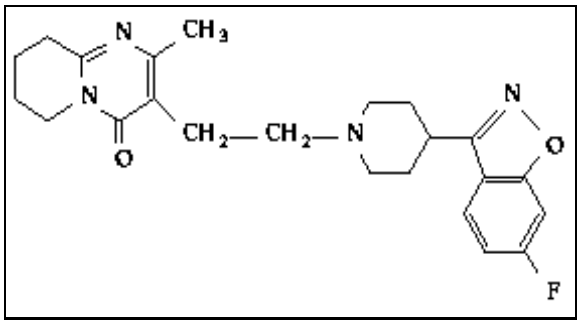
of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

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

11 DESCRIPTION

RISPERDAL® contains risperidone, 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-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® Tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. RISPERDAL® tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). The 0.25 mg, 0.5 mg, 2 mg, 3 mg, and 4 mg tablets also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

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RISPERDAL® is also available as a 1 mg/mL oral solution. RISPERDAL® Oral Solution contains the following inactive ingredients: tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (coral), 3 mg (coral), and 4 mg (coral) strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 2 mg, 3 mg, and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of RISPERDAL®, 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 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

12.2 Pharmacodynamics

The clinical effect from RISPERDAL® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$ *[see Clinical Pharmacology (12.1)]* may explain some of the other effects of RISPERDAL®.

12.3 Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

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Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, RISPERDAL® can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

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

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

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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.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone *[see Drug Interactions (7.12)]*. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given RISPERDAL® do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with RISPERDAL® may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone *[see Drug Interactions (7.11)]*. 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 7.12)]*.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease *[see Dosage and Administration (2.4) and Warnings and Precautions (5.15)]*.

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Hepatic Impairment

While the pharmacokinetics of risperidone 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 both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease *[see Dosage and Administration (2.4)* and *Warnings and Precautions (5.15)]*.

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients *[see Dosage and Administration (2.4)]*.

Pediatric

The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

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 corrected for body weight or not) or race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63 mg/kg, 2.5 mg/kg, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

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Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which 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 MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

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14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (twice-daily schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2 mg/day, 6 mg/day, 10 mg/day, and 16 mg/day, on a twice-daily schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1 mg/day, 4 mg/day, 8 mg/day, 12 mg/day, and 16 mg/day, on a twice-daily schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None

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of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a once-daily schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Pediatrics

The efficacy of RISPERDAL® in the treatment of schizophrenia in adolescents aged 13–17 years was demonstrated in two short-term (6 and 8 weeks), double-blind controlled trials. All patients met DSM-IV diagnostic criteria for schizophrenia and were experiencing an acute episode at time of enrollment. In the first trial (study #1), patients were randomized into one of three treatment groups: RISPERDAL® 1-3 mg/day (n = 55, mean modal dose = 2.6 mg), RISPERDAL® 4-6 mg/day (n = 51, mean modal dose = 5.3 mg), or placebo (n = 54). In the second trial (study #2), patients were randomized to either RISPERDAL® 0.15-0.6 mg/day (n = 132, mean modal dose = 0.5 mg) or RISPERDAL® 1.5–6 mg/day (n = 125, mean modal dose = 4 mg). In all cases, study medication was initiated at 0.5 mg/day (with the exception of the 0.15-0.6 mg/day group in study #2, where the initial dose was 0.05 mg/day) and titrated to the target dosage range by approximately Day 7. Subsequently, dosage was increased to the maximum tolerated dose within the target dose range by Day 14. The primary efficacy variable in all studies was the mean change from baseline in total PANSS score.

Results of the studies demonstrated efficacy of RISPERDAL® in all dose groups from 1-6 mg/day compared to placebo, as measured by significant reduction of total PANSS score. The efficacy on the primary parameter in the 1-3 mg/day group was comparable to the 4-6 mg/day group in study #1, and similar to the efficacy demonstrated in the 1.5–6 mg/day group in study #2. In study #2, the efficacy in the 1.5-6 mg/day group was statistically

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significantly greater than that in the 0.15-0.6 mg/day group. Doses higher than 3 mg/day did not reveal any trend towards greater efficacy.

14.2 Bipolar Mania - Monotherapy

Adults

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in two short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the YMRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

Pediatrics

The efficacy of RISPERDAL® in the treatment of mania in children or adolescents with Bipolar I disorder was demonstrated in a 3-week, randomized, double-blind, placebo-controlled, multicenter trial including patients ranging in ages from 10 to 17 years who were experiencing a manic or mixed episode of bipolar I disorder. Patients were randomized into one of three treatment groups: RISPERDAL® 0.5-2.5 mg/day (n = 50, mean modal dose = 1.9 mg), RISPERDAL® 3-6 mg/day (n = 61, mean modal dose = 4.7 mg), or placebo (n = 58). In all cases, study medication was initiated at 0.5 mg/day and titrated to the target dosage range by Day 7, with further increases in dosage to the maximum tolerated dose within the targeted dose range by Day 10. The primary rating instrument used for assessing efficacy in this study was the mean change from baseline in the total YMRS score.

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Results of this study demonstrated efficacy of RISPERDAL® in both dose groups compared with placebo, as measured by significant reduction of total YMRS score. The efficacy on the primary parameter in the 3-6 mg/day dose group was comparable to the 0.5-2.5 mg/day dose group. Doses higher than 2.5 mg/day did not reveal any trend towards greater efficacy.

14.3 Bipolar Mania – Combination Therapy

The efficacy of RISPERDAL® with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in adult patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of YMRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

14.4 Irritability Associated with Autistic Disorder

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of these subjects were under 12 years of age and most weighed over 20 kg (16-104.3 kg).

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Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of autism, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

The results of these trials are as follows:

(1) In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=101), aged 5 to 16 years, received twice daily doses of placebo or RISPERDAL® 0.5-3.5 mg/day on a weight-adjusted basis. RISPERDAL®, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day), significantly improved scores on the ABC-I subscale and on the CGI-C scale compared with placebo.

(2) In the other 8-week, placebo-controlled trial in children with autistic disorder (n=55), aged 5 to 12 years, RISPERDAL® 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day), significantly improved scores on the ABC-I subscale compared with placebo.

Long-Term Efficacy

Following completion of the first 8-week double-blind study, 63 patients entered an open-label study extension where they were treated with RISPERDAL® for 4 or 6 months (depending on whether they received RISPERDAL® or placebo in the double-blind study). During this open-label treatment period, patients were maintained on a mean modal dose of RISPERDAL® of 1.8-2.1 mg/day (equivalent to 0.05 - 0.07 mg/kg/day).

Patients who maintained their positive response to RISPERDAL® (response was defined as ≥ 25% improvement on the ABC-I subscale and a CGI-C rating of 'much improved' or 'very much improved') during the 4-6 month open-label treatment phase for about 140 days, on average, were randomized to receive RISPERDAL® or placebo during an 8-week, double-blind withdrawal study (n=39 of the 63 patients). A pre-planned interim analysis of data from patients who completed the withdrawal study (n=32), undertaken by an independent Data Safety Monitoring Board, demonstrated a significantly lower relapse rate in the RISPERDAL® group compared with the placebo group. Based on the interim analysis results, the study was terminated due to demonstration of a statistically significant effect on relapse prevention. Relapse was

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defined as ≥ 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline of the randomized withdrawal phase).

16 HOW SUPPLIED/STORAGE AND HANDLING

RISPERDAL® (risperidone) Tablets

RISPERDAL® (risperidone) Tablets are imprinted "JANSSEN" on one side and either "Ris 0.25", "Ris 0.5", "R1", "R2", "R3", or "R4" according to their respective strengths.

0.25 mg dark yellow, capsule-shaped tablets: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50, hospital unit dose blister packs of 100 NDC 50458-301-01.

0.5 mg red-brown, capsule-shaped tablets: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, hospital unit dose blister packs of 100 NDC 50458-302-01.

1 mg white, capsule-shaped tablets: bottles of 60 NDC 50458-300-06, hospital unit dose blister packs of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange, capsule-shaped tablets: bottles of 60 NDC 50458-320-06, hospital unit dose blister packs of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow, capsule-shaped tablets: bottles of 60 NDC 50458-330-06, hospital unit dose blister packs of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green, capsule-shaped tablets: bottles of 60 NDC 50458-350-06, hospital unit dose blister packs of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) Oral Solution

RISPERDAL® (risperidone) 1 mg/mL Oral Solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R0.5", "R1", "R2", "R3", or "R4" according to their respective strengths. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are packaged in blister packs of 4 (2 X 2) tablets. Orally Disintegrating Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-395-28, long-term care blister packaging of 30 tablets NDC 50458-395-30.

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1 mg light coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-315-28, long-term care blister packaging of 30 tablets NDC 50458-315-30.

2 mg coral, square, biconvex tablets: 7 blister packages (4 tablets each) per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

RISPERDAL® 1 mg/mL Oral Solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

17.1 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration *[see Warnings and Precautions (5.7)]*.

17.2 Interference with Cognitive and Motor Performance

Since RISPERDAL® 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 RISPERDAL® therapy does not affect them adversely *[see Warnings and Precautions (5.9)]*.

17.3 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

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17.4 Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL® *[see Use in Specific Populations (8.3)]*.

17.5 Concomitant Medication

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

17.6 Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL® *[see Drug Interactions (7.1)]*.

17.7 Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

INSERT NEW CODE
Revised July 2009
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RISPERDAL® Tablets are manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico 00778
RISPERDAL® Oral Solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium
RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico 00778

RISPERDAL® Tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and Oral Solution are manufactured for:
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RISPERDAL® CONSTA® (risperidone) LONG-ACTING INJECTION

Initial U.S. Approval: 2003

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

See full prescribing information for complete boxed warning.

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

----------RECENT MAJOR CHANGES----------

Boxed Warning	October 2008
Indications and Usage, Bipolar Disorder (1.2)	May 2009
Dosage and Administration, Bipolar Disorder (2.2)	May 2009
Warnings and Precautions (5.1)	October 2008
Warnings and Precautions, Leukopenia, Neutropenia, and Agranulocytosis (5.8)	May 2009
Warnings and Precautions, Priapism (5.12)	October 2008
Warnings and Precautions, Suicide (5.17)	May 2009

----------INDICATIONS AND USAGE----------

RISPERDAL® CONSTA® is an atypical antipsychotic indicated:

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

----------DOSAGE AND ADMINISTRATION----------

- For patients who have never taken oral RISPERDAL®, tolerability should be established with oral RISPERDAL® prior to initiating treatment with RISPERDAL® CONSTA® (2)
- Administer by deep intramuscular (IM) deltoid or gluteal injection. Each injection should be administered by a health care professional using the appropriate enclosed safety needle (1-inch for deltoid administration alternating injections between the two arms and 2-inch for gluteal administration alternating injections between the two buttocks). Do not administer intravenously. (2)
- 25 mg intramuscular (IM) every 2 weeks. Patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks. (2)
- Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL® CONSTA®, and continued for 3 weeks (and then discontinued) to ensure adequate therapeutic plasma concentrations from RISPERDAL® CONSTA®. (2)
- Upward dose adjustment of RISPERDAL® CONSTA® should not be made more frequently than every 4 weeks. Clinical effects of each upward dose adjustment should not be anticipated earlier than 3 weeks after injection. (2)
- Avoid inadvertent administration into a blood vessel. (5.15)
- See Full Prescribing Information Section 2.6 for instructions for use.

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

- Known hypersensitivity to 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)
- Hyperglycemia and Diabetes Mellitus- in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking risperidone. Patients with diabetes mellitus should have glucose levels monitored regularly. Patients with risk factors for diabetes mellitus should undergo fasting glucose testing at the beginning of treatment and periodically during treatment. All patients taking risperidone should be monitored for symptoms of hyperglycemia. Symptomatic patients should undergo fasting glucose testing. (5.5)
- Hyperprolactinemia: Risperidone treatment may elevate prolactin levels. Long-standing hyperprolactinemia, when associated with hypogonadism, can lead to decreased bone density in men and women. (5.6)
- Orthostatic hypotension: associated with dizziness, tachycardia, bradycardia, and syncope can occur, especially during initial dose titration with oral risperidone. Use caution in patients with cardiovascular disease, cerebrovascular disease, and conditions that could affect hemodynamic responses. (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotics, including RISPERDAL. Patients with history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood cell count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® CONSTA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.8)
- Potential for cognitive and motor impairment: has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. (5.9)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.10)
- Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. (5.11)
- Priapism: has been reported. Severe priapism may require surgical intervention. (5.12)
- Thrombotic Thrombocytopenic Purpura (TTP): has been reported. (5.13)
- Avoid inadvertent administration into a blood vessel (5.15)
- Suicide: There is increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. (5.17)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies: has been reported. Manifestations include mental status changes, motor impairment, extrapyramidal symptoms, and features consistent with Neuroleptic Malignant Syndrome. (5.18)
- Diseases or conditions that could affect metabolism or hemodynamic responses: Use with caution in patients with such medical conditions (e.g., recent myocardial infarction or unstable cardiac disease) (5.18)

----------ADVERSE REACTIONS----------

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

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

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

----------DRUG INTERACTIONS----------

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

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- Clozapine may decrease clearance of risperidone. (7.6)
- Fluoxetine and paroxetine increase plasma concentrations of risperidone. (7.11)
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. (7.12)

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® CONSTA®(risperidone) is not approved for the treatment of patients with dementia-related psychosis. [*See Warnings and Precautions (5.1)*]

1 INDICATIONS AND USAGE

1.1 Schizophrenia

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

1.2 Bipolar Disorder

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

2 DOSAGE AND ADMINISTRATION

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

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

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2.1 Schizophrenia

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

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

2.2 Bipolar Disorder

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

2.3 General Dosing Information

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

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

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

In patients with clinical factors such as hepatic or renal impairment or certain drug interactions that increase risperidone plasma concentrations *[see Drug Interactions (7.11)]*, dose reduction as low as 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

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

2.4 Dosage in Special Populations

Elderly

For elderly patients treated with RISPERDAL® CONSTA®, the recommended dosage is 25 mg IM every 2 weeks. Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL® CONSTA® and should be continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site *[see Clinical Pharmacology (12.3)]*.

Renal or Hepatic Impairment

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

Patients with renal impairment may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have an increase in the free fraction of the risperidone, possibly resulting in an enhanced effect *[see Clinical Pharmacology (12.3)]*. Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on

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the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). These patients should avoid sodium depletion or dehydration, and circumstances that accentuate hypotension (alcohol intake, high ambient temperature, etc.). Monitoring of orthostatic vital signs should be considered *[see Warnings and Precautions (5.7)]*.

2.5 Reinitiation of Treatment in Patients Previously Discontinued

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

2.6 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients from other antipsychotics to RISPERDAL® CONSTA®, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of RISPERDAL® CONSTA® to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun *[see Clinical Pharmacology (12.3)]*. For patients who have never taken oral RISPERDAL®, it is recommended to establish tolerability with oral RISPERDAL® prior to initiating treatment with RISPERDAL® CONSTA®. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

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

Co-administration of carbamazepine and other CYP 3A4 enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of the sum of risperidone and 9-hydroxyrisperidone combined, which could lead to decreased efficacy of RISPERDAL® CONSTA® treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers *[see Drug Interactions (7.11)]*. At the initiation of therapy with carbamazepine or other known CYP 3A4 hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL® CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of RISPERDAL® CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 inducers to adjust for the expected

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increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL® CONSTA® and discontinuing from carbamazepine or other CYP3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. The efficacy of the12.5 mg dose has not been investigated in clinical trials.

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

2.8 Instructions for Use

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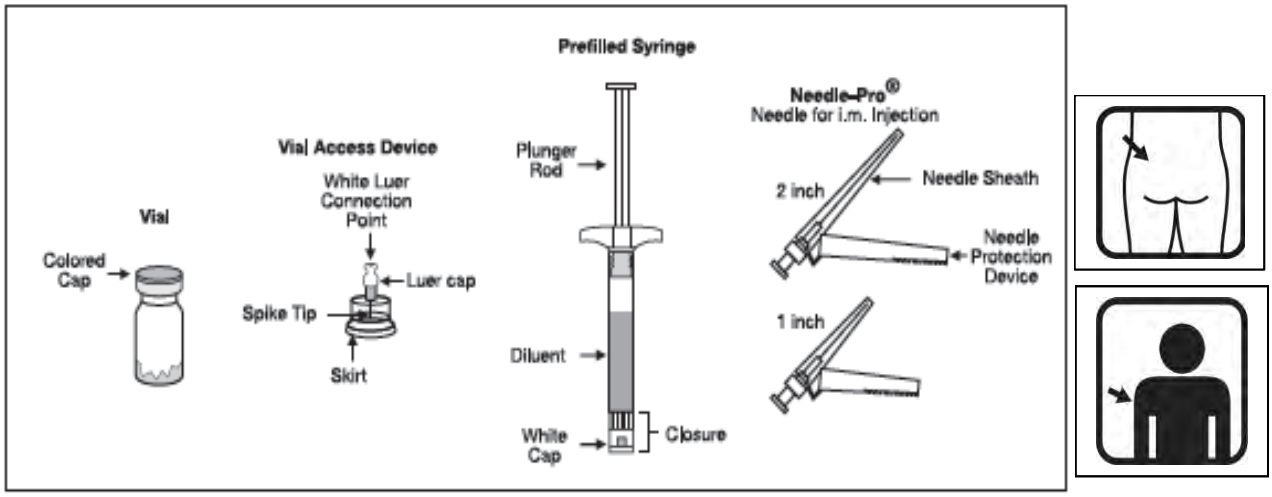
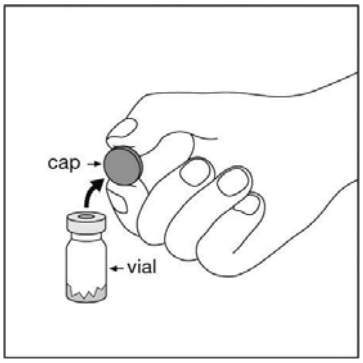


RISPERDAL® CONSTA® must be reconstituted **only** in the diluent supplied in the dose pack, and must be administered with **only** the appropriate needle supplied in the dose pack for gluteal (2-inch needle) or deltoid (1-inch needle) administration. All components are required for administration. Do not substitute any components of the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.

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

1. Flip off the plastic colored cap from the vial.



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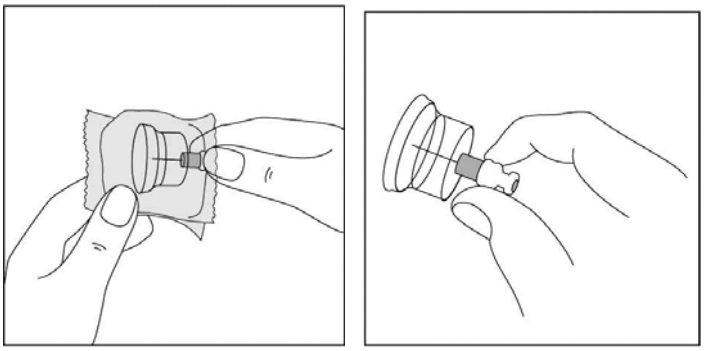
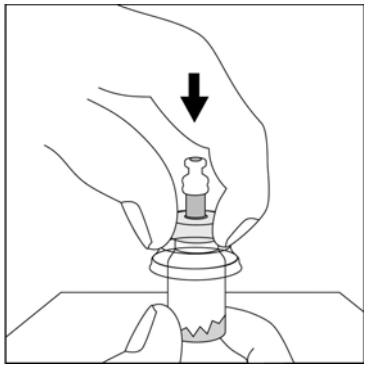
2. Peel back the blister pouch and remove the SmartSite® Needle-Free Vial Access Device by holding the white luer cap. Do not touch the spike tip of the access device at any time.



3. Place vial on a hard surface. Hold the base of the vial. Orient the SmartSite® Access Device vertically over the vial so that the spike tip is at the center of the vial's rubber stopper. With a straight downward push, press the spike tip of the SmartSite® Access Device through the center of the vial's rubber stopper until the device securely snaps onto the vial top.



4. Swab the syringe connection point (blue circle) of the SmartSite® Access Device with preferred antiseptic prior to attaching the syringe to the SmartSite® Access Device.

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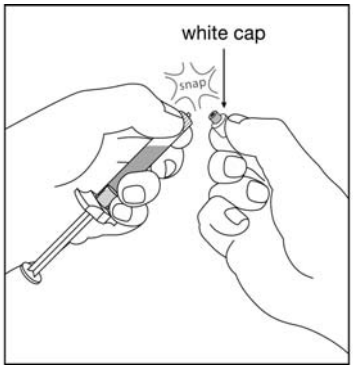
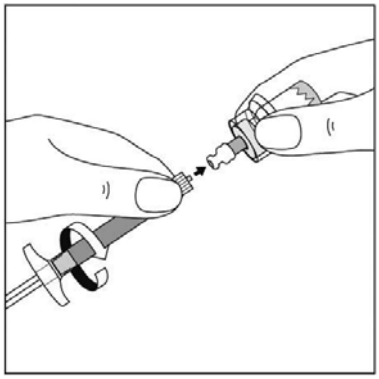
5. The prefilled syringe has a white cap consisting of 2 parts: a knurled collar and a smooth cap. To open the syringe, hold the syringe by the knurled collar and **snap** off the smooth cap **(DO NOT TWIST OFF THE CAP)**. Remove the white cap together with the rubber tip cap inside.



For all syringe assembly steps, hold the syringe only by the white collar, located at the tip of the syringe. Be careful to not overtighten components when assembling. Overtightening connections may cause syringe component parts to loosen from the syringe body.

6. While holding the **white collar** of the syringe, **press** the syringe tip into the blue circle of the SmartSite® Access Device and **twist** in a clockwise motion to attach the syringe to the SmartSite® Access Device. Hold the skirt of the SmartSite® Access Device during attachment to prevent it from spinning. Keep the syringe and SmartSite® Access Device aligned.



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

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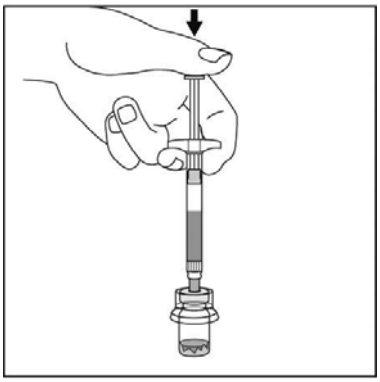
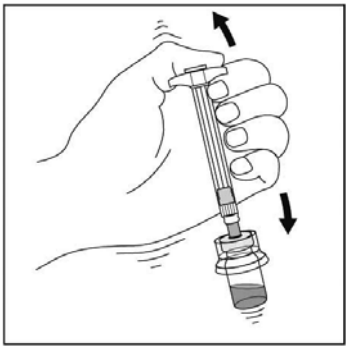
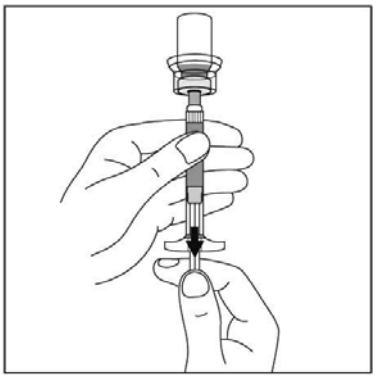


8. Shake the vial vigorously while holding the plunger rod down with the thumb for a minimum of 10 seconds to ensure a homogeneous suspension. When properly mixed, the suspension appears uniform, thick, and milky in color. The particles will be visible in liquid, but no dry particles remain.



9. Do not store the vial after reconstitution or the suspension may settle. *If 2 minutes pass before injection, re-suspend by shaking vigorously.*

10. Invert the vial completely and slowly withdraw the suspension from the vial into the syringe. Tear section of the vial label at the perforation and apply detached label to syringe for identification purposes.



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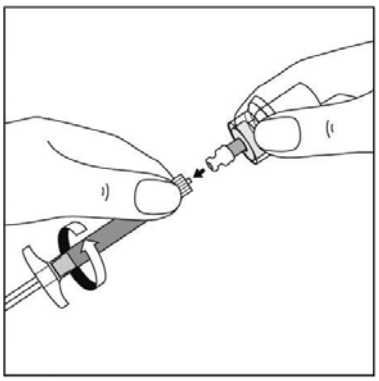
11. While holding the **white collar** of the syringe, unscrew the syringe from the SmartSite® Access Device. Discard both the vial and access device appropriately.

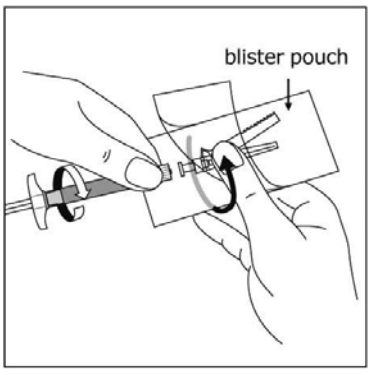


12. Select the appropriate needle:

    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)

13. Peel the blister pouch of the Needle-Pro® device open halfway. Grasp sheath using the plastic peel pouch. While holding the **white collar** of the syringe, attach the luer connection of the Needle-Pro® device to the syringe with an easy clockwise twisting motion.



14. *If 2 minutes pass before injection, re-suspend by shaking vigorously.*

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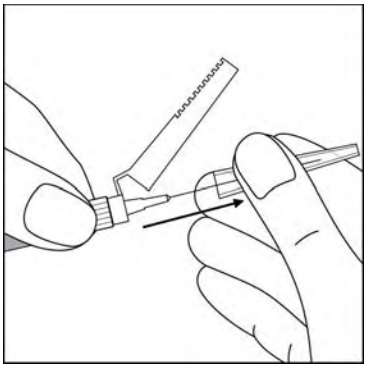
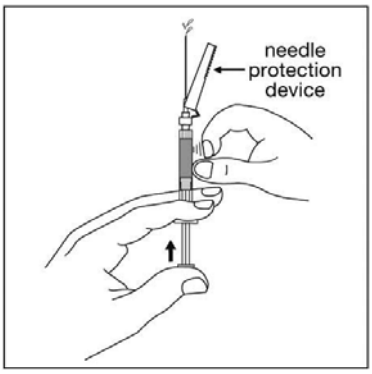
15. While holding the **white collar** of the syringe, pull the sheath away from the needle- do not twist the sheath because it could result in loosening the needle.



16. Tap the syringe gently to make any air bubbles rise to the top. De-aerate syringe by moving plunger rod carefully forward, with 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 within 2 minutes to avoid settling. Gluteal injection should be made into the upper-outer quadrant of the gluteal area. **DO NOT ADMINISTER INTRAVENOUSLY.**



WARNING: To avoid a needle stick injury with a contaminated needle, do not:

- intentionally disengage the Needle-Pro® device
- attempt to straighten the needle or engage Needle-Pro® device if the needle is bent or damaged
- mishandle the needle protection device that could lead to protrusion of the needle from it

17. After injection is complete, use only one hand and tabletop or other hard surface to snap needle into the orange needle protector device before discarding. Discard needle appropriately. Also discard the other (unused) needle.

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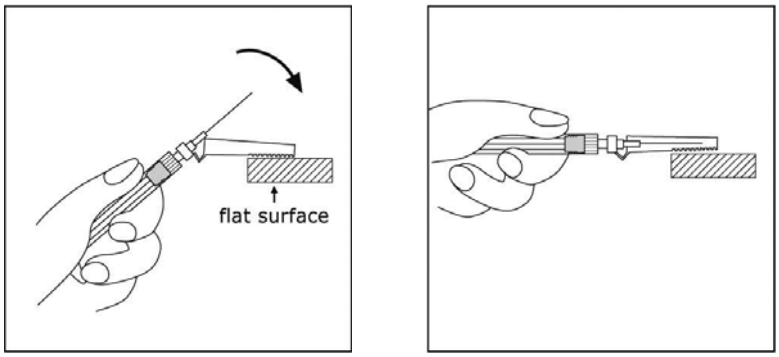

Upon suspension in the diluent, it is recommended to use RISPERDAL® CONSTA® immediately. RISPERDAL® CONSTA® must be used within 6 hours of suspension. Resuspension of RISPERDAL® CONSTA® will be necessary prior to administration, as settling will occur over time once the product is in suspension. Keeping the vial upright, shake vigorously back and forth for as long as it takes to resuspend the microspheres. Once in suspension, the product should not be exposed to temperatures above 77°F (25°C).

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

3 DOSAGE FORMS AND STRENGTHS

RISPERDAL® CONSTA® is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, and 50 mg risperidone. It is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL® CONSTA®, a SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety needles for intramuscular injection (a 21 G 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).

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL®CONSTA®(risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

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

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

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom 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 both 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

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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) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® CONSTA® should be prescribed in a manner that is 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 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical

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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 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 should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 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 cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

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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% (12/1499 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. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and a history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL® CONSTA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) 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

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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% (5/1499 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 (6.9)]*. Severe priapism may require surgical intervention.

5.13 Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). 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 (6.8)]*

5.16 Antiemetic Effect

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

5.17 Suicide

There is an increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. 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 hemodynamic 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 m^2) 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 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 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 a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks.

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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/m^2 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/m^2 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. Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study.

The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail in Section 13.1 (Carcinogenicity, Mutagenesis, Impairment of Fertility).

The relevance of these findings to human risk is unknown.

5.20 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- 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)]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*

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- 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)]*
- Priapism *[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)]*
- Antiemetic 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 Warnings and Precautions (5.18)]*
- Osteodystrophy and tumors in animals *[see Warnings and Precautions (5.19)]*

The most common adverse reactions in clinical trials in patients with schizophrenia (≥ 5%) 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, 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).

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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 were 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, placebo- or 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, or were experiencing an acute episode. After a 3-week period of treatment with open-label oral risperidone (n=440), subjects who demonstrated an initial response to oral risperidone in this period and those who were stable on risperidone (oral or long-acting injection) at study entry entered into a 26-week stabilization period of open-label RISPERDAL® CONSTA® (n=501). Subjects who demonstrated a maintained response during this period were then randomized into a 24-month double-blind, placebo-controlled period in which they received RISPERDAL® CONSTA® (n=154) or placebo (n=149) as monotherapy. Subjects who relapsed or who completed the double-blind period could choose to enter an 8-week open-label RISPERDAL® CONSTA® extension period (n=160).

Safety data are also presented from a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar 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 or Type II 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. At the start of this study, all patients (n = 275) entered into a 16-week open-label treatment phase in which they received RISPERDAL® CONSTA® in addition to continuing their treatment as usual, which consisted of various mood stabilizers (primarily lithium and

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valproate), 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 1 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.

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Table 1. Adverse Reactions in ≥ 2% of RISPERDAL® CONSTA®-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial

	Percentage of Patients Reporting Event		
System/Organ Class Adverse Reaction	**RISPERDAL® CONSTA® 25 mg (N=99)**	**50 mg (N=103)**	**Placebo (N=98)**
Eye disorders			
Vision blurred	2	3	0
Gastrointestinal disorders			
Constipation	5	7	1
Dry mouth	0	7	1
Dyspepsia	6	6	0
Nausea	3	4	5
Toothache	1	3	0
Salivary hypersecretion	4	1	0
General disorders and administration site conditions			
Fatigue*	3	9	0
Edema peripheral	2	3	1
Pain	4	1	0
Pyrexia	2	1	0
Infections and infestations			
Upper respiratory tract infection	2	0	1
Investigations			
Weight increased	5	4	2
Weight decreased	4	1	1
Musculoskeletal and connective tissue disorders			
Pain in extremity	6	2	1
Nervous system disorders			
Headache	15	21	12
Parkinsonism*	8	15	9
Dizziness	7	11	6
Akathisia*	4	11	6
Sedation*	5	6	3
Tremor	0	3	0
Syncope	2	1	0
Hypoesthesia	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	4	2	3
Sinus congestion	2	0	0
Skin and subcutaneous tissue disorders			
Acne	2	2	0
Dry skin	2	0	0

* 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.

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

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

Table 2. 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

	Percentage of Patients Reporting Event	
System/Organ Class Adverse Reaction	**RISPERDAL® CONSTA®** **(N=154)**	**Placebo** **(N=149)**
Investigations		
Weight increased	5	1
Nervous system disorders		
Dizziness	3	1
Vascular disorders		
Hypertension	3	1

Table 3 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.

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Table 3. 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

	Percentage of Patients Reporting Event	
System/Organ Class Adverse Reaction	**RISPERDAL® CONSTA® + Treatment as Usual[a] (N=72)**	**Placebo + Treatment as Usual[a] (N=67)**
General disorders and administration site conditions		
Gait abnormal	4	0
Infections and infestations		
Upper respiratory tract infection	6	3
Investigations		
Weight increased	7	1
Metabolism and nutrition disorders		
Decreased appetite	6	1
Increased appetite	4	0
Musculoskeletal and connective tissue disorders		
Arthralgia	4	3
Nervous system disorders		
Tremor	24	16
Parkinsonism[b]	15	6
Dyskinesia[b]	6	3
Sedation[c]	7	1
Disturbance in attention	4	0
Reproductive system and breast disorders		
Amenorrhea	4	1
Respiratory, thoracic and mediastinal disorders		
Cough	4	1

[a] Patients received double-blind RISPERDAL® CONSTA® or placebo in addition to continuing their treatment as usual, which included mood stabilizers, antidepressants, and/or anxiolytics.
[b] Parkinsonism includes muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia. Dyskinesia includes muscle twitching and dyskinesia.
[c] Sedation includes sedation and somnolence.

6.3 Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL® CONSTA®

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

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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 other studies, including double-blind, active-controlled and open-label studies in schizophrenia, and in the open-label phases of the bipolar disorder studies.

Blood and lymphatic system disorders: anemia, neutropenia

Cardiac disorders: tachycardia, atrioventricular block first degree, palpitations, sinus bradycardia, bundle branch block left, bradycardia, sinus tachycardia, bundle branch block right

Ear and labyrinth disorders: ear pain, vertigo

Endocrine disorders: hyperprolactinemia

Eye disorders: conjunctivitis, visual acuity reduced

Gastrointestinal disorders: diarrhea, vomiting, abdominal pain, 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, 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

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

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

Psychiatric disorders: insomnia, agitation, anxiety, sleep disorder, depression, libido decreased, nervousness

Renal and urinary disorders: urinary incontinence

Reproductive system and breast disorders: oligomenorrhea, erectile dysfunction, galactorrhea, sexual dysfunction, ejaculation disorder, gynecomastia, breast discomfort, menstruation irregular, menstruation delayed, menstrual disorder

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

Skin and subcutaneous tissue disorders: rash, eczema, pruritus

Vascular disorders: hypotension, orthostatic hypotension

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).

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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 on the total score (sum 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 median 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 Body Weight

In the 12-week double-blind, placebo-controlled trial in patients with schizophrenia, 9% of patients treated with RISPERDAL® CONSTA®, compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint.

In the 24-month double-blind, placebo-controlled treatment period of a trial assessing the efficacy and safety of RISPERDAL® CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 11.6% of patients treated with RISPERDAL® CONSTA® compared with 2.8% of patients treated with placebo experienced a weight gain of >7% of body weight at endpoint.

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In the 52-week double-blind, placebo-controlled trial in patients with bipolar disorder, 26.8% of patients treated with RISPERDAL® CONSTA® as adjunctive treatment in addition to continuing their treatment as usual, compared with 27.3% of patients treated with placebo in addition to continuing their treatment as usual, experienced a weight gain of >7% of body weight at endpoint.

6.7 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 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.

6.8 Pain Assessment and Local Injection Site Reactions

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

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

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6.9 Postmarketing Experience

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

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

7 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 risperidone and 9-hydroxyrisperidone combined following concomitant administration with oral RISPERDAL®.

7.5 Cimetidine and Ranitidine

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

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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 (C_{max}) 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 (C_{max}) 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 $AUC_{0\text{-}12\ hour}$ at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral RISPERDAL® on the pharmacokinetics of topiramate.

7.11 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs *[see Clinical Pharmacology (12.3)]*. 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 (n≅70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

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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 physician should re-evaluate the dose of RISPERDAL® CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg RISPERDAL® CONSTA®, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. When RISPERDAL® CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[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®

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CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 enzyme inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL® CONSTA® and discontinuing from carbamazepine or other CYP 3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[See also DOSAGE AND ADMINSTRATION (2.5)]*

7.13 Drugs Metabolized by CYP 2D6

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 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/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the oral MRHD on a mg/m^2 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/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number 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

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drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m^2 basis.

No studies were conducted with RISPERDAL® CONSTA®.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy.

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.

8.5 Geriatric Use

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

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addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern *[see Warnings and Precautions (5.7)]*.

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

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

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

10 OVERDOSAGE

10.1 Human Experience

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

In premarketing experience with oral RISPERDAL®, there were eight reports of acute RISPERDAL® overdosage, with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an

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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, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to oral RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

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

11 DESCRIPTION

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-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:

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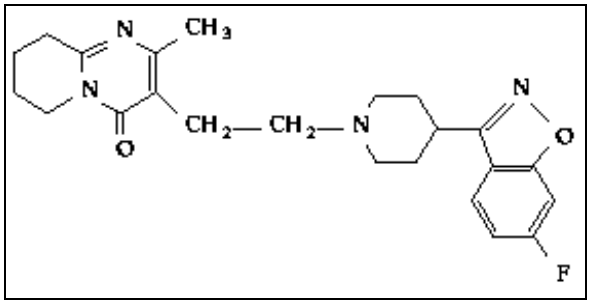

Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

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

The extended-release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 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® CONSTA® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of RISPERDAL® CONSTA®, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), $\alpha 1$ and $\alpha 2$ adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with

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lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 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® CONSTA® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$ *[see Clinical Pharmacology (12.1)]* may explain some of the other effects of RISPERDAL® CONSTA®.

12.3 Pharmacokinetics

Absorption

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

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

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

Distribution

Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α1-acid glycoprotein. The plasma protein binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each

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other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and of 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

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

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

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

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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 ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL® CONSTA® administration is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL® CONSTA®. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

Renal Impairment

In patients with moderate to severe renal disease treated with oral RISPERDAL®, clearance of the sum 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 both albumin and α_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

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appropriate when clinical factors warrant dose adjustment, such as in patients with hepatic impairment *[see Dosage and Administration (2.4)]*.

Elderly

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

Race and Gender Effects

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Oral

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m^2 basis. There was a significant increase in endocrine pancreatic adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m^2 basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m^2 basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m^2 basis), and in male rats at a dose 6 times the oral MRHD on a mg/m^2 basis.

Carcinogenesis - Intramuscular

RISPERDAL® CONSTA® was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with intramuscular (IM) injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times

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the IM MRHD on a mg/m^2 basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD.

Dopamine D_2 receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with RISPERDAL® CONSTA® every 2 weeks. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

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

Mutagenesis

No evidence of mutagenic potential for oral risperidone was found in the *in vitro* Ames reverse mutation test, *in vitro* mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* oral micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the *in vitro* chromosomal aberration test in human lymphocytes or in Chinese hamster cells.

In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for RISPERDAL® CONSTA®.

Impairment of Fertility

Oral risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two mating and fertility studies and a multigenerational study) at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the mating and fertility study in which males only were treated. In a subchronic study in Beagle dogs in which oral risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the oral MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses.

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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 the oral formulation of risperidone. In addition, the effectiveness of RISPERDAL® CONSTA® in the treatment of schizophrenia was established in a 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

Efficacy data were obtained from 400 patients with schizophrenia who were randomized to receive injections of 25 mg, 50 mg, or 75 mg RISPERDAL® CONSTA® or placebo every 2 weeks. During a 1-week run-in period, patients were discontinued from other antipsychotics and were titrated to a dose of 4 mg oral RISPERDAL®. Patients who received RISPERDAL® CONSTA® were given doses of oral RISPERDAL® (2 mg for patients in the 25-mg group, 4 mg for patients in the 50-mg group, and 6 mg for patients in the 75-mg group) for the 3 weeks after the first injection to provide therapeutic plasma concentrations until the main 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.

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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 manic rather than depressive symptoms. Based on their bipolar disorder history, subjects entering this study had had, on average, more manic episodes than depressive episodes.

14.3 Bipolar Disorder - Adjunctive Therapy

The effectiveness of RISPERDAL® CONSTA® as an adjunct to treatment with lithium or valproate for the maintenance treatment of Bipolar Disorder was established in a multi-center, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV criteria for Bipolar Disorder Type I and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12 months, including at least 2 episodes in the 6 months prior to the start of the study.

A total of 240 patients were treated during a 16-week open-label period with RISPERDAL® CONSTA® (starting dose of 25 mg, and titrated, if deemed clinically desirable, to 37.5 mg or 50 mg), as adjunctive therapy in addition to continuing their treatment as usual for their bipolar disorder, which consisted of mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. All oral antipsychotics were discontinued after the first three weeks of the initial RISPERDAL® CONSTA® injection. In the open-label phase, 124 (51.7%) were judged to be stable for at least the last 4 weeks and were randomized to double-blind treatment with either the same dose of RISPERDAL® CONSTA® or placebo in

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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.

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17 PATIENT COUNSELING INFORMATION

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

17.1 Orthostatic Hypotension

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

17.2 Interference with Cognitive and Motor Performance

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

17.3 Pregnancy

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

17.4 Nursing

Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® *[see Use in Specific Populations (8.2)]*.

17.5 Concomitant Medication

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

17.6 Alcohol

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

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Janssen Pharmaceutical Ltd.
Wallingstown, Little Island, County Cork, Ireland

Microspheres are manufactured by:
Alkermes, Inc.
Wilmington, Ohio

Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Ravensburg or Langenargen, Germany

or

Cilag AG
Schaffhausen, Switzerland

or

Ortho Biotech Products, L.P.
Raritan, NJ

RISPERDAL® CONSTA® is manufactured for:
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Titusville, NJ 08560