

RISPERIDONE TABLETS, USP

Rx only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Risperidone Tablets, USP safely and effectively. See full prescribing information for Risperidone Tablets, USP.

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

Recent Major Changes

Warnings and Precautions (5.6)

Indications and Usage

- Risperidone is atypical antipsychotic indicated for:
- Treatment of schizophrenia (1.1)
 - As monotherapy or adjunctive therapy with lithium or valproate, for the treatment of acute manic or mixed episodes associated with bipolar I disorder (1.2)
 - Treatment of irritability associated with autistic disorder (1.3)

Dosage and Administration

	Initial Dose	Target Dose	Effective Dose Range
Schizophrenia: adults (2.1)	2 mg	4 to 8 mg	4 to 16 mg
Schizophrenia: adolescents (2.1)	0.5 mg	3 mg	1 to 6 mg
Bipolar mania: adults (2.2)	2 to 3 mg	1 to 6 mg	1 to 6 mg
Bipolar mania: in children and adolescents (2.2)	0.5 mg	1 to 2.5 mg	1 to 6 mg
Irritability associated with autistic disorder (2.3)	0.25 mg (Weight < 20 kg)	0.5 mg (< 20 kg)	0.5 to 3 mg
	0.5 mg (Weight ≥ 20 kg)	1 mg (≥ 20 kg)	

- Severe Renal or Hepatic Impairment in Adults: Use a lower starting dose of 0.5 mg twice daily. May increase to dosages above 1.5 mg twice daily at intervals of at least one week. (2.4)

Dosage Forms and Strengths

- Tablets: 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg. (3)

Contraindications

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

Full Prescribing Information: Contents*

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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. Risperidone is not approved for the treatment of patients with dementia-related psychosis. (See Warnings and Precautions (5.1))

- INDICATIONS AND USAGE
 - SchizophreniaRisperidone tablets are indicated for the treatment of schizophrenia. Efficacy was established in 4 short-term trials in adults, 2 short-term trials in adolescents (ages 13 to 17 years), and one long-term maintenance trial in adults (See Clinical Studies (14.1)).
 - Bipolar Mania

Monotherapy

Risperidone tablets are indicated for the treatment of acute manic or mixed episodes associated with bipolar I Disorder. Efficacy was established in 2 short-term trials in children and adolescents (ages 10 to 17 years) (See Clinical Studies (14.2)).

Adjunctive Therapy

Risperidone tablets adjunctive therapy with lithium or valproate is indicated for the treatment of acute manic or mixed episodes associated with bipolar I Disorder. Efficacy was established in one short-term trial in adults (See Clinical Studies (14.3)).

 - Irritability Associated with Autistic Disorder

Risperidone tablets are indicated for the treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-harm/injuries, temper tantrums, and quickly changing moods. Efficacy was established in 3 short-term trials in children and adolescents (ages 5 to 17 years) (See Clinical Studies (14.4)).
- DOSAGE AND ADMINISTRATION

Table 1. Recommended Daily Dosage by Indication

	Initial Dose	Titration (Increments)	Target Dose	Effective Dose Range
Schizophrenia: adults (2.1)	2 mg	1 to 2 mg	4 to 8 mg	4 to 16 mg
Schizophrenia: adolescents (2.1)	0.5 mg	0.5 to 1 mg	3 mg	1 to 6 mg
Bipolar mania: adults (2.2)	2 to 3 mg	1 mg	1 to 6 mg	1 to 6 mg
Bipolar mania: children and adolescents (2.2)	0.5 mg	0.5 to 1 mg	1 to 2.5 mg	1 to 6 mg
Irritability in autistic disorder (2.3)	0.25 mg Can increase to 0.5 mg by Day 4. (body weight less than 20 kg)	After Day 4, at 1 mg by Day 4 weeks. 0.25 mg (body weight less than 20 kg)	0.5 mg (body weight less than 20 kg)	0.5 to 3 mg
	0.5 mg Can increase to 1 mg by Day 4. (body weight greater than or equal to 20 kg)	0.5 mg (body weight greater than or equal to 20 kg)	1 mg (body weight greater than or equal to 20 kg)	

Severe Renal and Hepatic Impairment in Adults: use a lower starting dose of 0.5 mg twice daily. May increase to dosages above 1.5 mg twice daily at intervals of one week or longer.

- Schizophrenia
- Usual Initial Dose
- Risperidone tablets can be administered once or twice daily. Initial dosing is 2 mg per day. May increase the dose at intervals of 24 hours or greater, in increments of 1 to 2 mg per day, as tolerated, to a recommended dose of 4 to 8 mg per day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4 to 16 mg per day. However, doses above 8 mg per 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 were generally not recommended. In a single study supporting once-daily dosing, the efficacy of risperidone was generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg per day has not been evaluated in clinical trials (See Clinical Studies (14.1)).
- Adolescents
- The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg per day, as tolerated, to a recommended dose of 3 mg per day. Although efficacy has been demonstrated in studies of adolescents with schizophrenia at doses between 1 mg to 6 mg per day, no additional benefit was observed above 3 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied. Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance Therapy

While it is unknown how long a patient with schizophrenia should remain on risperidone tablets, the effectiveness of the risperidone tablets 2 mg per day to 8 mg per day at dosing regimens was demonstrated in a controlled trial in adult 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)). Both adult and adolescent patients who respond acutely should generally be maintained on their effective tablets should be titrated slowly. It may be necessary to increase the risperidone tablets dose when needed for maintenance treatment.

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 risperidone tablets, 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 risperidone tablets, or treating patients with concomitant antipsychotics.

- Bipolar Mania
- Usual Dose
- Adults
- The initial dose range is 2 mg to 3 mg per day. The dose may be adjusted at intervals of 24 hours or greater, in increments of 1 mg per day. The effective dose range is 1 mg to 6 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 mg to 6 mg per day (See Clinical Studies (14.2, 14.3)). Risperidone tablets doses higher than 6 mg per day were not studied.

Pediatrics

The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg per day, as tolerated, to a recommended target dose of 1 mg to 2.5 mg per day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 mg and 6 mg per day, no additional benefit was observed above 2.5 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied.

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 long-term management of a patient who improves during treatment of an acute manic episode with risperidone tablets. While it is generally agreed that pharmacological treatment beyond an acute response should be 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 risperidone tablets in such longer-term treatment (i.e., beyond 3 weeks). The physician who elects to use risperidone tablets 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 dosage of risperidone tablets should be individualized according to the response and tolerability of the patient. The total daily dose of risperidone tablets can be administered once daily, or half the total daily dose can be administered twice daily.

For patients with body weight less than 20 kg, initiate dosing at 0.25 mg per day. For patients with body weight greater than or equal to 20 kg, initiate dosing at 0.5 mg per day. After a minimum of four days, the dose may be increased to 0.5 mg per day for patients less than 20 kg and 1 mg per day for patients greater than or equal to 20 kg. Maintain this dose for a minimum of 14 days. In patients not achieving sufficient clinical response, the dose may be increased in increments of 0.25 mg or greater to 0.25 mg per day for patients less than 20 kg, or increments of 0.5 mg per day for patients greater than or equal to 20 kg. The effective dose range is 0.5 mg to 3 mg per day. No dosing data are available for children who weigh less than 15 kg.

Once sufficient clinical response has been achieved and maintained, consider gradually lowering the dose to achieve the optimal balance of efficacy and safety. The physician who elects to use risperidone tablets 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 one-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

2.4 Dosing in Patients with Severe Renal or Hepatic Impairment

For patients with severe renal impairment (Cr < 30 mL/min) or hepatic impairment (10-15 points on Child Pugh System), the initial starting dose is 0.5 mg twice daily. The dose may be increased in increments of 0.5 mg or less, administered twice daily. For doses above 1.5 mg twice daily, increase in intervals of one week or greater (See Use in Specific Populations (8.6 and 8.7)).

2.5 Dose Adjustments for Specific Drug Interactions

When risperidone tablets are co-administered with enzyme inducers (e.g., carbamazepine), the dose of risperidone tablets should be increased up to double the patient's usual dose. It may be necessary to decrease the risperidone tablets dose when enzyme inducers such as carbamazepine are discontinued (See Drug Interactions (7.1)). Similar effect may be expected with co-administration of risperidone tablets with other enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital).

When fluoxetine or paroxetine is co-administered with risperidone tablets, the dose of risperidone tablets should be reduced. The risperidone tablets dose should not exceed 8 mg per day in adults when co-administered with these drugs. When initiating therapy, risperidone tablets should be titrated slowly. It may be necessary to increase the risperidone tablets dose when enzyme inhibitors such as fluoxetine or paroxetine are discontinued (See Drug Interactions (7.1)).

3 DOSAGE FORMS AND STRENGTHS

Risperidone Tablets are available in the following strengths and colors: 0.25 mg (dark yellow), 0.5 mg (reddish-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green). 0.25 mg tablets are round and red and all are capsule shaped. All are debossed with "7" on one side and either "221", "222", "223", "224", "225", or "226" on the other side according to their respective strengths.

4 CONTRAINDICATIONS

Risperidone is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the risperidone formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone is a metabolite of risperidone.

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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in drug-treated patients of between 1.5 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 have found that, similar

- Warnings and Precautions
- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis: Risperidone is not approved for use in patients with dementia-related psychosis (5.2)
 - Neuroleptic Malignant Syndrome: Manage with immediate discontinuation of risperidone and close monitoring. (5.3)
 - Tardive dyskinesia: Consider discontinuing risperidone if clinically indicated. (5.4)
 - Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
 - Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.5)
 - Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
 - Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.5)
 - Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. (5.6)
 - Orthostatic hypotension: For patients at risk, consider a lower starting dose and slower titration. (5.7)
 - Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts in patients with a history of clinically significant low white blood cell count (WBC). Consider discontinuing risperidone if a clinically significant decline in WBC occurs in the absence of other causative factors. (5.8)
 - Potential for cognitive and motor impairment: Use caution when operating machinery. (5.10)
 - Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.11)

The most common adverse reactions in clinical trials (≥5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, and pharyngitis. (5.12)

Weight Gain: Significant weight gain has been reported. Monitor weight gain. (5.5)

To report SUSPECTED ADVERSE REACTIONS, contact Jubilant Cadista Pharmaceuticals Inc. at 1-800-313-4623 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

- Drug Interactions
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. Increase the risperidone dose up to double the patient's usual dose. Titrate slowly. (7.1)
 - Fluoxetine, paroxetine, and other CYP 2D6 enzyme inhibitors increase plasma concentrations of risperidone. Reduce the initial dose. Do not exceed a final dose of 8 mg per day of risperidone. (7.1)

Use in Specific Populations

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised: 06/2025

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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.

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 tursamide plus risperidone versus compared to patients treated with risperidone alone or placebo plus tursamide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed.

Risperidone is not approved for the treatment of dementia-related psychosis (See Boxed Warning).

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

Cerebrovascular adverse reactions (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. Risperidone is not approved for the treatment of patients with dementia-related psychosis. (See Boxed Warning and Warnings and Precautions (5.1))

5.3 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal syndrome complex, has been reported with risperidone treatment. Clinical manifestations of NMS are hyperreflexia, rigidity, muscle rigidity, altered mental status including delirium, and 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.

If NMS is suspected, immediately discontinue risperidone and provide symptomatic treatment and supportive care. The outcome is unknown.

5.4 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting 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 predict which patients will 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 increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. The lowest dose and the shortest duration of treatment with antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but less potentially harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment with antipsychotics, including risperidone. Periodically reassess the need for continued treatment.

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

5.5 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

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

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including risperidone, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including risperidone, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients may require continued treatment with antidiabetic medications. Patients who are starting treatment with atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including risperidone, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients may require continued treatment with antidiabetic medications. 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Annex No.

Autistic Disorder - Pediatrics

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n = 156), open-label extension studies did not report any adverse events in reaction (Parkinsonism), and one placebo-treated patient discontinued due to an adverse event.

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 risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing a fixed dose of risperidone (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:

Dose Groups	Placebo	Risperidone 2 mg	Risperidone 6 mg	Risperidone 10 mg	Risperidone 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	17%	21%	24%	35%

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

Dose Groups	Risperidone 1 mg	Risperidone 4 mg	Risperidone 8 mg	Risperidone 12 mg	Risperidone 16 mg
Parkinsonism	0.6	1.2	2.4	2.9	4.1
EPS Incidence	7%	17%	24%	18%	20%

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 spasms of the neck muscles, sometimes progressing to rigidity of the neck, the tongue, 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 subjects.

Other Adverse Reactions

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of risperidone (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.

Changes in Body Weight

Weight gain was observed in short-term, controlled trials and longer-term uncontrolled studies in adult and pediatric patients (see *Warnings and Precautions (5.5)*, *Adverse Reactions (6)*, and *In Specific Populations (8.4)*).

Changes in ECG Parameters

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 risperidone 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 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 8.8 beats per minute in the risperidone 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 risperidone 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of risperidone. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions include: alopecia, anaphylactic reaction, angioedema, atrial fibrillation, cardiopulmonary arrest, cataplexy, diabetic ketoacidosis in patients with impaired glucose metabolism, dyspnea, hypokalemia, hypothermia, ileus, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice, mania, pancreatitis, pituitary adenoma, precocious puberty, pulmonary embolism, QT prolongation, sleep apnea syndrome, somnambulism, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), sudden death, thrombocytopenia, thrombotic thrombocytopenic purpura, urinary retention, and water intoxication.

Postmarketing cases of extrapyramidal symptoms (dystonia and dyskinesia) have been reported in patients concomitantly taking methylphenidate and risperidone when there was an increase or decrease in dosage, initiation, or discontinuation of either or both medications.

7.0 DRUG INTERACTIONS

7.1 Pharmacokinetic-related Interactions

The dose of risperidone should be adjusted when used in combination with CYP2D6 enzyme inhibitors (e.g., fluoxetine, and paroxetine) and enzyme inducers (e.g., carbamazepine) (see *Table 18 and Dosage and Administration (2.5)*). Dose adjustment is not recommended for risperidone when co-administered with ranitidine, cimetidine, amitriptyline, or erythromycin (see *Table 18*).

Table 18. Summary of Effect of Coadministered Drugs on Exposure to Active Moiety (Risperidone + 9-Hydroxy-Risperidone) in Healthy Subjects or Patients with Schizophrenia

Coadministered Drug	Dosing Schedule		Effect on Active Moiety (Risperidone + 9-Hydroxy-Risperidone) (Ratio) ^a		Risperidone Dose Recommendation
	Coadministered Drug	Risperidone	AUC	C _{max}	
Enzyme (CYP2D6) Inhibitors					
Fluoxetine	20 mg/day	2 or 3 mg twice daily	1.4	1.5	Re-evaluate dosing. Do not exceed 8 mg/day
Paroxetine	10 mg/day	4 mg/day	1.3	-	Re-evaluate dosing. Do not exceed 8 mg/day
	20 mg/day	4 mg/day	1.6	-	Do not exceed 8 mg/day
	40 mg/day	4 mg/day	1.8	-	
Enzyme (CYP3A/ Pgp inducers) Inducers					
Carbamazepine	573 + 168 mg ^b daily	3 mg twice daily	0.51	0.55	Titrate dose upwards. Do not exceed twice the patient's usual dose
Enzyme (CYP3A) Inhibitors					
Ranitidine	150 mg twice daily	1 mg single dose	1.2	1.4	Dose adjustment not needed
Cimetidine	400 mg twice daily	1 mg single dose	1.1	1.3	Dose adjustment not needed
Erythromycin	500 mg four times daily	1 mg single dose	1.1	0.94	Dose adjustment not needed
Other Drugs					
Amitriptyline	50 mg twice daily	3 mg twice daily	1.2	1.1	Dose adjustment not needed

^aChange relative to reference

Effect of Risperidone on Other Drugs

Lithium

Repeated oral doses of risperidone (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). Dose adjustment for lithium is not recommended.

Valproate

Repeated oral doses of risperidone (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 risperidone. Dose adjustment for valproate is not recommended.

Digoxin

Risperidone (0.25 mg digoxin) did not show a clinically relevant effect on the pharmacokinetics of digoxin. Dose adjustment for digoxin is not recommended.

7.2 Pharmacodynamic-related Interactions Centrally Acting Drugs and Alcohol

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

Drugs with Hypotensive Effects

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

Levodopa and Dopamine Agonists

Risperidone may antagonize the effects of levodopa and dopamine agonists.

Methylphenidate

Concomitant use with methylphenidate, when there is change in dosage of either medication, may increase the risk of extrapyramidal symptoms (EPS). Monitor for symptoms of EPS with concomitant use of risperidone and methylphenidate (see *Adverse Reactions (6.2)*).

Clozapine

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see *Clinical Considerations*). Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see *Data*). There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including risperidone, during pregnancy (see *Clinical Considerations*).

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medical database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3 times the MRHD of 16 mg/day based on mg/m² body surface area. maternal toxicity occurred at 4 times the MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 6 mg/kg/day or adults at 0.3 to 3 mg/kg/day, which was up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6 times the MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed orally throughout pregnancy at 1 and 0.6 mg/kg/day and 1.2 times the MRHD based on mg/m² body surface area. postnatal development and growth of the offspring were also delayed. Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 0.5 mg/kg/day which are 0.1 to 0.3 times the MRHD of 16 mg/day based on mg/m² body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5 times the MRHD based on mg/m² body surface area.

In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in pups of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats, regardless of whether or not the offspring were cross-fostered. Risperidone also appeared to impair maternal care in that offspring body weight and survival (from Day 14 to Day 21 in lactation) were reduced in offspring of rats exposed by drug-treated dams to 0.5 mg/kg/day risperidone compared to controls. In addition, the number of pups born to the dams was reduced. All of these effects occurred at 5 mg/kg which is 3 times the MRHD based on mg/m² and the only dose tested in the study.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3% and 4.7% of the maternal weight-adjusted dose. There are reports of decreased milk intake, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone (see *Clinical Considerations*). There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for risperidone and any potential adverse effects on the breastfed child from risperidone or from the mother's underlying condition.

Clinical Considerations

Infants exposed to risperidone through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential Infertility

Females

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

8.4 Pediatric Use

Approved Pediatric Indications

Schizophrenia

The efficacy and safety of risperidone in the treatment of schizophrenia were demonstrated in 417 adolescents, aged 13 to 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.

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

Bipolar I Disorder

The efficacy and safety of risperidone in the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in 169 children and adolescent patients, aged 10 to 17 years, were established in a double-blind, placebo-controlled, 8-week trial (see *Indications and Usage (1.2)*, *Adverse Reactions (6.1)*, and *Clinical Studies (14.2)*).

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

Autistic Disorder

The efficacy and safety of risperidone 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 (6.1)* 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 other psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania who were of similar age and weight, and who received similar dosages of risperidone as patients treated for irritability associated with autistic disorder.

A third study was a 6-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of a lower than recommended dose of risperidone in subjects 5 to 17 years of age with autistic disorder and associated irritability, and related behavioral symptoms. There were two weight-based, fixed doses of risperidone (high-dose and low-dose). The high dose was 1.25 mg per day for patients weighing 20 to < 45 kg, and it was 1.75 mg per day for patients weighing > 45 kg. The low dose was 0.625 mg per day for patients weighing 20 to < 45 kg, and it was 0.175 mg per day for patients weighing > 45 kg. The study demonstrated the efficacy of high-dose risperidone, but it did not demonstrate efficacy for low-dose risperidone.

Adverse Reactions in Pediatric Patients

Tardive Dyskinesia

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

Weight Gain

Weight gain has been observed in children and adolescents during treatment with risperidone. Clinical monitoring of weight is recommended during treatment.

Data derive from short-term placebo-controlled trials and longer-term uncontrolled studies in children and adolescents with schizophrenia. In the short-term studies, bipolar disorder, autistic disorder, or other psychiatric disorders. In the short-term trials (3 to 8 weeks), the mean weight gain for risperidone-treated patients was 2 kg, compared to 0.6 kg for placebo-treated patients. In these trials, approximately 33% of the risperidone group had weight gain 27%, compared to 7% in the placebo group. In longer-term, uncontrolled, open-label pediatric studies, the mean weight gain was 5.5 kg at Week 24 and 8 kg at Week 48 (see *Warnings and Precautions (5.5)* and *Adverse Reactions (6.1)*).

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 frequent during the first week of treatment, and were more frequent in patients who were transient and with a median duration of 16 days. Somnolence was the most commonly observed adverse reaction 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 adverse reactions were most often of early onset and transient in duration (see *Adverse Reactions (6.1 and 6.2)*). Patients experiencing persistent somnolence may benefit from a change in dosing regimen (see *Dosage and Administration (2.1, 2.2, and 2.3)*).

Hyperprolactinemia

Risperidone 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 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 risperidone had elevated prolactin levels compared to 2% of patients who received placebo. Similarly, in placebo-controlled trials in children and adolescents (aged 10 to 16 years) with bipolar disorder, or adolescents (aged 13 to 17 years) with schizophrenia, 82-87% of patients who received risperidone 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.

In clinical trials in 1888 children and adolescents, galactorrhea was reported in 0.8% of risperidone-treated patients and gynecomasia was reported in 2.3% of risperidone-treated patients.

Growth and Sexual Maturation

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

Juvenile Animal Studies

Juvenile dogs were treated with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans), at doses of 0.31, 1.25, or 5 mg/kg/day, which are 1.3, 2.4, and 13.5 times the MRHD of 6 mg/day for children, based on mg/m² body surface area. Bone length and density were decreased with a no-effect dose of 0.31 mg/kg/day. This dose produced plasma AUC of risperidone plus its active metabolite paliperidone (BPRS total score) that were similar to those in children and adolescents receiving the MRHD of 6 mg/day. In addition, sexual maturation was delayed at all doses in both males and females. The male effects showed little or no reversibility in females after a 12 week drug-free recovery period.

Juvenile rats treated with oral risperidone from days 12 to 50 of age (equivalent to the period of infancy through adolescence in humans) showed impaired learning and memory performance (reversible only in females), with a no-effect dose of 0.63 mg/kg/day which is 0.5 times the MRHD of 6 mg/day for children, based on mg/m² body surface area. This dose produced plasma AUC of risperidone plus its active metabolite paliperidone (BPRS total score) that were similar to those in children and adolescents receiving the MRHD of 6 mg/day. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the MRHD of 6 mg/day for children.

5.6 Geriatric Use

Clinical studies of risperidone 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. After reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for elderly patients, 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 limited 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 clinical 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 renal function is 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)*).

8.6 Renal Impairment

In patients with moderate to severe (Clcr 59 to 15 mL/min) renal disease, clearance of the sum of risperidone and its active metabolite paliperidone was decreased by 80%, compared to young healthy subjects. Risperidone doses should be reduced in patients with renal disease (see *Dosage and Administration (2.4)*).

8.7 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 35% because of the diminished contribution of both albumin and α₁-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease (see *Dosage and Administration (2.4)*).

8.8 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to risperidone. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Risperidone is not a controlled substance.

9.2 Abuse

Risperidone has not been systematically studied in animals or humans for its potential for abuse. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited 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 risperidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

Risperidone 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 risperidone overdose with estimated doses ranging from 30 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 hypernatremia, hypotension, 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 risperidone overdose, with estimated doses 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 risperidone overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of risperidone and paroxetine.

10.2 Management of Overdose

For the most up to date information on the management of risperidone overdose, contact a certified poison control center (1-800-222-1222 or www.poisn.org). Provide supportive care including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdoses. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. There is no specific antidote to risperidone.

11 DESCRIPTION

Risperidone Tablets