



### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**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, Metabolic Changes (5.5) September 2011

#### INDICATIONS AND USAGE

- RISPERIDONE 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)

#### DOSE AND ADMINISTRATION

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

#### DOSE FORMS AND STRENGTHS

- Tablets: 0.25 mg, 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. RISPERIDONE is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome (5.3)
- Tardive dyskinesia (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 (5.6)
- Orthostatic hypotension (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotics, including RISPERIDONE. 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 RISPERIDONE 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)
- Thrombotic Thrombocytopenic Purpura (TTP) (5.13)
- Disruption of body temperature regulation (5.14)
- Antiemetic Effect (5.15)
- Suicide (5.16)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies (5.17)
- Diseases or conditions that could affect metabolism or hemodynamic responses (5.17)

#### ADVERSE REACTIONS

The most common adverse reactions in clinical trials (≥ 10%) were somnolence, increased appetite, fatigue, insomnia, sedation, parkinsonism, akathisia, vomiting, cough, constipation, nasopharyngitis, drooling, rhinorrhea, dry mouth, abdominal pain upper, dizziness, nausea, anxiety, headache, nasal congestion, rhinitis, tremor, and rash. (6)

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

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779 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)

#### 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. Analysis of 17 placebo-controlled trials in elderly 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 18-week trial, the risk 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. Observations suggest that older patients with dementia-related psychosis treated with conventional antipsychotic drugs may experience mortality. Not extend the findings of increased mortality in observational studies. These findings are based on analyses that do not adjust for differences in baseline characteristics of patients in clear. RISPERIDONE is not approved for the treatment of patients with dementia-related psychosis. (See BOXED WARNING.)

##### INDICATIONS AND USAGE

**1.1 Schizophrenia**  
Adult  
RISPERIDONE is indicated for the acute and maintenance treatment of schizophrenia (see Clinical Studies (14.1)).

Adolescents  
RISPERIDONE 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  
RISPERIDONE 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)).

**1.3 Irritability Associated with Autistic Disorder**  
Pediatrics  
RISPERIDONE is indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years (see Clinical Studies (14.3)).

**2.1 Schizophrenia**  
Usual Initial Dose  
RISPERIDONE can be administered once or twice daily. Initial dosing is generally 2 mg/day. Dose increases should occur at intervals not less than 24 hours. In increments of 1-2 mg/day, as tolerated, to a recommended dose of 2 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.

**2.2 Dosage and Administration**  
Schizophrenia  
Usual Initial Dose  
RISPERIDONE can be administered once or twice daily. Initial dosing is generally 2 mg/day. Dose increases should occur at intervals not less than 24 hours. In increments of 1-2 mg/day, as tolerated, to a recommended dose of 2 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.

**2.3 Irritability Associated with Autistic Disorder - Pediatrics**  
The safety and effectiveness of RISPERIDONE in pediatric patients with autistic disorder less than 5 years of age have not been established.

**2.4 Dosage in Specific Populations**  
Elderly or debilitated; severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dose 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 occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

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

**5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis**  
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. 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, the risk of stroke was higher in risperidone-treated patients than in placebo-treated patients 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 (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 hyperreflexia, muscle rigidity, altered mental status, and autonomic instability (irregular heartbeat, changes in blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnosis of NMS should be considered in patients in whom 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, untreated electrolyte imbalance, or severe dehydration) and features of the syndrome (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 requires discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy. (2) Intensive symptomatic treatment and 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 clinical 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 rule out 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 not known.

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, RISPERIDONE 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

### See 17 for PATIENT COUNSELING INFORMATION.

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\*Sections or subsections omitted from the full prescribing information are not listed

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

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

**Hyperglycemia and Diabetes Mellitus**  
Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including 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. However, in clinical trials, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiologic 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 thereafter. 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 required continuation of anti-diabetic treatment despite discontinuation of RISPERIDONE.

Pooled data from three double-blind, placebo-controlled schizophrenia studies and four double-blind, placebo-controlled bipolar mania studies are presented in Table 1a.

**Change in Random Glucose from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects with Schizophrenia or Bipolar Mania**

	Placebo	1 to 8 mg/day	>8 to 16 mg/day
Mean change from baseline (mg/dL)	n=555	n=742	n=164
Serum Glucose	-1.4	0.8	0.6
<b>Proportion of patients with shifts</b>			
Serum Glucose	0.6%	4.3%	0%
(<140 mg/dL to ≥200 mg/dL)	(3/252)	(37/202)	(0/158)

In longer-term, controlled and uncontrolled studies, RISPERIDONE was associated with a mean change in glucose of 2.8 mg/dL at Week 24 (n=151) and 4.1 mg/dL at Week 48 (n=119). Pooled data from the placebo-controlled, 3- to 8-week study in children and adolescents with schizophrenia (13 to 17 years of age), bipolar mania (10 to 17 years of age), or autistic disorder (5 to 16 years of age) are presented in Table 1b.

**Change in Fasting Glucose from Three Placebo-Controlled, 3- to 6-Week, Fixed-Dose Studies in Children and Adolescents with Schizophrenia (13 to 17 Years of Age), Bipolar Mania (10 to 17 Years of Age), or Autistic Disorder (5 to 17 Years of Age)**

	Placebo	RISPERIDONE 0.5 to 6 mg/day	
Mean change from baseline (mg/dL)	n=133	n=135	
Serum Glucose	-1.3	2.6	
<b>Proportion of patients with shifts</b>			
Serum Glucose	0%	0.8%	
(<100 mg/dL to ≥120 mg/dL)	(0/64)	(1/120)	

In longer-term, uncontrolled, open-label extension pediatric studies, RISPERIDONE was associated with a mean change in fasting glucose of +5.2 mg/dL at Week 24 (n=119) and +6.8 mg/dL at Week 48 (n=86) and (b) non-fasting triglycerides of +15.2 mg/dL at Week 24 (n=103) and +16.8 mg/dL at Week 48 (n=120).

Pooled data from 3 placebo-controlled, 3- to 8-week, fixed- or flexible-dose studies in children and adolescents with schizophrenia (13 to 17 years of age), bipolar mania (10 to 17 years of age), or autistic disorder (5 to 16 years of age) are presented in Table 2a.

**Change in Random Lipids from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects with Schizophrenia or Bipolar Mania**

	Placebo	RISPERIDONE 1 to 8 mg/day	>8 to 16 mg/day
Mean change from baseline (mg/dL)	n=559	n=742	n=158
Change from baseline	0.6	6.9	1.8
LDL	n=222	n=222	n=222
Change from baseline	-17.4	4.9	-8.3
<b>Proportion of patients with shifts</b>			
Cholesterol	2.7%	4.3%	3.3%
(<200 mg/dL to ≥240 mg/dL)	(10/368)	(22/156)	(6/96)
Triglycerides	1.1%	2.7%	2.5%
(<150 mg/dL to ≥200 mg/dL)	(5/418)	(12/185)	(1/121)

In longer-term, controlled and uncontrolled studies, RISPERIDONE was associated with a mean change in weight of +4.3 kg at Week 24 (n=395) and +5.3 kg at Week 48 (n=203).

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in associated pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, syndrome, and/or prolactinemia 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.

Preclinical data from rat experiments indicate that approximately 70% of human breast cancer cells are dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with breast cancer. In addition, hyperprolactinemia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERIDONE should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.8)

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<sup>3</sup>) should discontinue RISPERIDONE and have their WBC followed until recovery.

Clinically significant hypotension has been observed with concomitant use of RISPERIDONE 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 RISPERIDONE. 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 RISPERIDONE should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.8)

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<sup>3</sup>) should discontinue RISPERIDONE and have their WBC followed until recovery.

Clinically significant hypotension has been observed with concomitant use of RISPERIDONE and antihypertensive medication.

**5.9 Potential for Cognitive and Motor Impairment**  
Sedation is a common adverse event associated with RISPERIDONE treatment, especially when administered by oral administration. This adverse event is dose-related, and in a study

utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERIDONE 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 RISPERIDONE 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERIDONE has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably sure that RISPERIDONE therapy does not affect them adversely.

**5.10 Seizures**  
Postmarketing testing in adult patients with schizophrenia, seizures occurred in 0.3% (2/607) of RISPERIDONE-treated patients, in 1 association with hypotension. RISPERIDONE should be used cautiously in patients with a history of seizures.

**5.11 Dysphagia**  
Postmarketing testing in adult patients with schizophrenia, seizures occurred in 0.3% (2/607) of RISPERIDONE-treated patients, in 1 association with hypotension. RISPERIDONE should be used cautiously in patients with a history of seizures.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of mortality and morbidity in patients with advanced Alzheimer's dementia. RISPERIDONE and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)).

**5.12 Priapism**  
Priapism has been reported during postmarketing surveillance (see ADVERSE REACTIONS (6.8)). Severe priapism may require surgical intervention.

**5.13 Thrombotic Thrombocytopenic Purpura (TTP)**  
A single case of TTP was reported in a 28-year-old female patient receiving RISPERIDONE in a large, open, non-randomized study of risperidone or olanzapine in patients with advanced Alzheimer's dementia. She eventually recovered after receiving plasmapheresis. The relationship to RISPERIDONE therapy is unknown.

**5.14 Disruption of 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 RISPERIDONE use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

