PRODUCT MONOGRAPH

PrRISPERDAL®*

risperidone tablets House Standard
0.25, 0.5, 1, 2, 3 and 4 mg

risperidone tartrate oral solution
risperidone 1 mg/mL

PrRISPERDAL®* M-TAB®*
risperidone orally disintegrating tablets
0.5, 1, 2, 3 and 4 mg

Antipsychotic Agent

Janssen Inc.
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Toronto, Ontario
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www.janssen.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 0.25, 0.5, 1, 2, 3 and 4 mg	Lactose
	solution 1 mg/mL	None
	orally disintegrating tablets 0.5, 1, 2, 3 and 4 mg	aspartame *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

ADULTS

Schizophrenia
RISPERDAL® (risperidone) is indicated for the acute treatment and maintenance treatment of schizophrenia and related psychotic disorders. In controlled clinical trials, RISPERDAL® was found to improve both positive and negative symptoms of schizophrenia.

RISPERDAL® has been shown to be effective in maintaining clinical improvement during long-term therapy (1 year).

Severe Dementia - Symptomatic management of inappropriate behaviour
RISPERDAL® may be useful in severe dementia for the short-term symptomatic management of inappropriate behaviour due to aggression and/or psychosis. Other behavioural disturbances seen in this patient population as well as disease stage remained unaffected by RISPERDAL® treatment (see ***Product Monograph Part II*: CLINICAL TRIALS**).

Physicians are advised to assess the risks and benefits of the use of RISPERDAL® in elderly patients with dementia, taking into account risk predictors for stroke or existing cardiovascular comorbidities in the individual patient (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Bipolar Disorder - Mania
RISPERDAL® is indicated as monotherapy for the acute management of manic episodes associated with Bipolar I disorder.

The efficacy of RISPERDAL® in the treatment of acute bipolar mania was established in three 3-week, placebo-controlled trials. The safety and effectiveness of RISPERDAL® for long-term use, and for prophylactic use in bipolar disorder have not been evaluated. Physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Geriatrics (> 65 years of age):
See **WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions Box** and **Special Populations**.

Pediatrics (< 18 years of age):
The safety and efficacy of RISPERDAL® in children under the age of 18 have not been established.

CONTRAINDICATIONS

RISPERDAL® is contraindicated in patients who are hypersensitive to this drug or to any ingredients in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. 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 (see WARNINGS AND PRECAUTIONS - Special Populations, Use in Geriatric Patients with Dementia).

General

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing RISPERDAL® for patients who will be experiencing conditions which may contribute to an elevation or reduction of core temperature, e.g., exercising strenuously, exposure to extreme heat or cold, receiving concomitant medication with anticholinergic activity, or being subject to dehydration (see **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions**).

Phenylketonurics

Phenylalanine is a component of aspartame. RISPERDAL® M-TAB® tablets contain phenylalanine (0.14, 0.28, 0.42-0.56, 0.63 and 0.84 mg) per 0.5, 1, 2, 3 and 4 mg tablets, respectively.

QT Interval

As with other antipsychotics, caution should be exercised when RISPERDAL® is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval.

Carcinogenesis and Mutagenesis

Carcinogenesis

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 maximum recommended human dose (MRHD) (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 tumours occurred.

Table 1.1 Summary of Carcinogenicity Studies in Mice and Rats

Tumour 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- to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine 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 tumours is unknown (see **WARNINGS AND PRECAUTIONS - Endocrine and Metabolism).**

Mutagenicity

Risperidone had no mutagenic effects when tested by the DNA-repair test in rat hepatocytes, the Ames reverse mutation test in *Salmonella typhimurium* and *Escherichia coli*, the mammalian cell gene mutation test in mouse lymphoma cells, the sex-linked recessive lethal test in *Drosophila melanogaster*, the chromosome aberration test in human lymphocytes and Chinese hamster lung cells, and the micronucleus test in the mouse bone marrow 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 behaviour 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.

Cardiovascular

During clinical trials, RISPERDAL® has been observed to cause orthostatic hypotension and tachycardia, especially during the initial dose titration period and the first few weeks of treatment. Rare cases of syncope, cardiac arrhythmias and first degree AV-block have been reported. Clinically significant hypotension has also been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. The likelihood of excessive hypotension or syncope can be minimized by limiting the initial dose of the drug to 1-2 mg per day, o.d. or b.i.d., in adult patients and to 0.25 to 0.5 mg b.i.d. in special patient populations, and by increasing the dose slowly (see **DOSAGE AND ADMINISTRATION**). A dose reduction should be considered if hypotension occurs.

Patients with a history of clinically significant cardiac disorders were excluded from clinical trials. Therefore, RISPERDAL® should be used with caution in patients with cardiovascular diseases (e.g., heart failure, history of myocardial infarction or ischemia, cerebrovascular disease, conduction abnormalities) and other conditions such as dehydration and hypovolemia. Special care should be taken to avoid hypotension in patients with a history of cerebrovascular insufficiency or ischemic heart disease, and in patients taking medications to lower blood pressure. Monitoring of orthostatic vital signs should be considered in all such patients.

Endocrine and Metabolism

Hyperglycemia and Diabetes Mellitus

As with some other antipsychotics, hyperglycemia, diabetes mellitus and exacerbation of pre-existing diabetes, in some cases serious and associated with ketoacidosis or hyperosmolar coma or death, have been reported during the use of RISPERDAL® (see **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions**).

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.

Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia and diabetes mellitus including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia and diabetes mellitus 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 antidiabetic treatment despite discontinuation of the suspect drug. 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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Hyperprolactinemia

Antipsychotic drugs elevate prolactin levels with the effect persisting during chronic administration.

Schizophrenia: In controlled clinical trials, prolactin levels were higher in patients treated with RISPERDAL® than in haloperidol-treated patients; however, the incidence of solicited adverse events considered to be possibly prolactin related in patients treated with RISPERDAL® (≤10 mg/day) was low (< 6%), and similar to that in haloperidol-treated patients (see Table 1.2, **ADVERSE REACTIONS**).

Bipolar disorder: In controlled clinical trials, patients treated with RISPERDAL® had higher prolactin levels than patients treated with haloperidol. The incidence of potentially prolactin-related adverse events in patients treated with 1-6 mg/day RISPERDAL® was 2.3%, and greater than what was reported for patients on placebo (0.5%) or haloperidol (0%) (see **ADVERSE REACTIONS**).

Since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, RISPERDAL® should only be administered to patients with previously detected breast cancer if the benefits outweigh the potential risks. Caution should also be exercised when considering RISPERDAL® treatment in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhea, galactorrhea, and menorrhagia (see **ADVERSE REACTIONS**).

In carcinogenicity studies, the administration of risperidone resulted in an increase in the incidence of mammary neoplasms in both rats and mice. In addition, adenomas of the endocrine pancreas in male rats and pituitary adenomas in female mice have been noted (see ***Product Monograph Part II:*** **TOXICOLOGY**). These changes have been attributed to elevated prolactin levels and have also been observed with other dopamine receptor antagonists. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date, neither clinical studies nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Weight Gain

Significant weight gain has been reported in both clinical trials and post-marketing. Monitoring weight gain is advised when RISPERDAL® is being used (see **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions**).

Schizophrenia: In pooled 6- to 8-week placebo-controlled clinical trials, which compared RISPERDAL® and placebo in the treatment of schizophrenia, 18% of patients treated with RISPERDAL® and 9% of placebo-treated patients met a weight gain criterion of ≥ 7% of baseline body weight. This difference was statistically significant. With continued treatment, weight gain (mean: 2.3 kg in long-term studies) has been seen.

Bipolar disorder: In the 3-week controlled clinical trials, the incidence of weight increases of ≥ 7% was similar among patients treated with placebo, risperidone and haloperidol (2.5%, 2.6% and 3.5%, respectively). The incidence of patients with weight increases of ≥ 7% was higher with longer treatment duration: 16.7% in patients who received an additional 9 weeks of

risperidone during open-label treatment extensions and 15% and 11% in patients treated for a total of 12 weeks with risperidone and haloperidol, respectively.

Gastrointestinal

Antiemetic Effect

Consistent with its dopamine antagonistic effects, RISPERDAL® may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage with other drugs, or may mask symptoms of disease such as brain tumour, or intestinal obstruction or Reye's syndrome.

Genitourinary

Priapism

Rare cases of priapism have been reported with RISPERDAL®. This adverse reaction, as with other psychotropic drugs, did not appear to be dose dependent and did not correlate with the duration of treatment. The most likely mechanism of priapism is a relative decrease in sympathetic tone.

Hematologic

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.

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 (see **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions**).

Hepatic/Biliary/Pancreatic

Although the pharmacokinetics of RISPERDAL® in patients with hepatic impairment were comparable to those in young volunteers, the free fraction of risperidone was increased by about 35% (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics** and **Table 1.8**). Since this may lead to a more pronounced pharmacological effect, lower starting doses and lower maximal doses are recommended in patients with any degree of hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Neurologic

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including RISPERDAL®.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular blood pressure, tachycardia, cardiac arrhythmias, and diaphoresis). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms. 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 all antipsychotic drugs including RISPERDAL®, 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 recurrence of NMS has been reported.

Tardive Dyskinesia (TD)
A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD. It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD. In clinical studies, the observed incidence of drug-induced parkinsonism was lower with RISPERDAL® than with haloperidol. In the optimal clinical dose range, the difference between risperidone and haloperidol was significant. The risk of developing TD may be less with RISPERDAL®. In longer-term clinical studies, RISPERDAL® was associated with a lower incidence of treatment-emergent dyskinesia compared to haloperidol.

The risk of developing TD 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 less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for established cases of TD. The syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. However, antipsychotic drug treatment itself may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown.

In view of these considerations, RISPERDAL® should be prescribed in a manner that is most likely to minimize the risk of TD. As with any antipsychotic drug, RISPERDAL® should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of TD develop during treatment with RISPERDAL®, withdrawal of the

drug should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential Effect on Cognitive and Motor Performance
Since RISPERDAL® may cause somnolence, patients should be cautioned against driving a car or operating hazardous machinery until they are reasonably certain that RISPERDAL® does not affect them adversely.

Schizophrenia: In controlled clinical trials (see Tables 1.3 and 1.4, **ADVERSE REACTIONS**), the incidence of somnolence in patients on RISPERDAL® was clinically similar to placebo (3-4% of patients on RISPERDAL® ≤10 mg versus 1% of patients on placebo).

Bipolar disorder: In controlled clinical trials for the acute management of manic episodes (see Table 1.7, **ADVERSE REACTIONS**), the incidence of somnolence was higher in patients treated with RISPERDAL® compared to placebo or haloperidol (12% of patients on RISPERDAL® 1-6 mg/day versus 4% of patients on placebo and 4% of patients on haloperidol).

Seizures
Antipsychotic drugs are known to lower the seizure threshold. In clinical trials, seizures have occurred in a few patients treated with RISPERDAL®. Therefore, caution should be used in administering RISPERDAL® to patients having a history of seizures or other predisposing factors.

Use in Patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB)
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL®, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, in addition to extrapyramidal symptoms.

Psychiatric
Suicide
The possibility of suicide or attempted suicide is inherent in psychosis and bipolar mania, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Renal
The pharmacokinetics of RISPERDAL® were significantly altered in patients with renal disease. In patients with moderate to severe renal disease, clearance of risperidone and its active metabolite 9-hydroxyrisperidone, combined, decreased by 60%, compared to young, healthy subjects (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics** and **Table 1.8**). Therefore, lower starting doses and lower maximal doses of risperidone are recommended in patients with any degree of renal impairment. It may also be useful to monitor renal function in these patients (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women: The safety of RISPERDAL® during pregnancy has not been established. In animal studies, risperidone did not show direct reproductive toxicity. However, due to its prolactin-elevating and CNS-depressant activities, reproductive performance and pup survival were adversely affected in rats. Risperidone was not teratogenic in either rats or rabbits.

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 risperidone therapy is unknown (see ***Product Monograph Part II*: TOXICOLOGY – Reproductive and Developmental Toxicology**).

Reversible extrapyramidal symptoms in the neonate were observed following post-marketing use of risperidone during the last trimester of pregnancy.

RISPERDAL® should not be used during pregnancy unless the expected benefits to the patient markedly outweigh the potential risks to the fetus.

Nursing Women: Risperidone appeared in the milk of lactating dogs. The concentration of risperidone was similar in milk and plasma, while that of 9-hydroxyrisperidone was higher in the milk than in plasma. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk.

Nursing should not be undertaken while a patient is receiving RISPERDAL®.

Pediatrics (< 18 years of age): The safety and efficacy of RISPERDAL® in children under the age of 18 have not been established.

Geriatrics (> 65 years of age): Geriatric patients generally have decreased renal, hepatic and cardiac function, and an increased tendency to postural hypotension. Therefore, lower starting doses, lower rates of dose adjustment and lower maximal doses are recommended in these patients.

Risperidone is substantially excreted by the kidneys. Thus, 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, caution should be taken in dose selection and titration. It may also be useful to monitor renal function in these patients (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics** and **Table 1.8**).

In schizophrenic patients, doses exceeding 3 mg per day are not recommended. In patients with behavioural disturbances due to severe dementia, the optimal dose is 0.5 mg b.i.d. (1.0 mg per day) and the maximal dose is 1 mg b.i.d. (2.0 mg per day).

Use in Geriatric Patients with Dementia
See **INDICATIONS AND CLINICAL USE**.

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. In six placebo-controlled trials with RISPERDAL® in this population, the incidence of mortality was 4.0% for RISPERDAL®-treated patients compared to 3.1% for placebo-treated patients.

Concomitant Use with Furosemide

In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96), furosemide alone (4.1%; mean age 80 years, range 67-90) or placebo without furosemide (2.9%; mean age 88 years, range 71-100). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAEs) in Elderly Patients with Dementia

Analysis of clinical trials in elderly patients with dementia suggests that the use of RISPERDAL® in dementia patients may be associated with an increased incidence of reports of CVAEs such as stroke and transient ischemic attacks, including fatalities. In placebo-controlled trials, there was a significantly higher incidence of CVAEs in patients treated with RISPERDAL® compared to placebo-treated patients (see ADVERSE REACTIONS). There is insufficient information to determine whether CVAEs in elderly patients with dementia are associated specifically with RISPERDAL® or other antipsychotic agents.

Therefore, physicians are advised to assess risks and benefits of the use of RISPERDAL® in elderly patients with dementia taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be advised to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems (see INDICATIONS AND CLINICAL USE, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

All treatment options should be considered without delay, including discontinuation. Furthermore, caution should be exercised in prescribing RISPERDAL® to patients with vascular comorbidities, such as hypertension and cardiovascular disease (see **WARNINGS AND PRECAUTIONS - Cardiovascular**).

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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Schizophrenia and Related Psychotic Disorders

Adverse Events Associated with Discontinuation of Treatment

An estimated 9% of approximately 1800 patients who received RISPERDAL® (risperidone) in controlled clinical trials discontinued treatment due to adverse reactions. The more common events causing discontinuation included: **Psychiatric** (4.1%): primarily psychosis, agitation, suicide attempt, somnolence; **Neurological** (3.2%): primarily extrapyramidal disorder, dizziness; and **Cardiovascular** (1.2%): primarily hypotension. Other events leading to discontinuation included: tachycardia/palpitations (0.6%), nervousness (0.4%), nausea (0.3%) and insomnia (0.3%).

Commonly Observed Adverse Events in Short-term Clinical Trials

The most frequent adverse reactions reported during clinical trials with RISPERDAL® were insomnia, agitation, extrapyramidal disorder, anxiety, headache and rhinitis (see Tables 1.3 and 1.4). In some instances, it has been difficult to differentiate adverse events from symptoms of the underlying psychosis.

Serious Adverse Events

The most serious adverse reactions reported were rare cases of syncope, cardiac arrhythmias, first degree AV-block, and seizures.

Extrapyramidal Symptoms

Parkinsonian side effects reported were usually mild but dose related; they were reversible upon dose reduction and/or administration of antiparkinsonian medication.

Vital Sign Changes

Hypotension (including orthostatic) and tachycardia (including reflex tachycardia) have been observed following the administration of RISPERDAL® (see **WARNINGS AND PRECAUTIONS - Cardiovascular**).

ECG Changes

Electrocardiograms were evaluated in patients treated with RISPERDAL® (N=380), haloperidol (N=126) and placebo (N=120). In the RISPERDAL® group, eight patients had a slight increase in QTc intervals from less than 450 msec at baseline to intervals ranging from 450 to 474 msec during treatment. Changes of this type were not seen in placebo-treated patients but were observed in three haloperidol-treated subjects.

Hyperprolactinemia

RISPERDAL® elevated plasma prolactin levels. Associated manifestations, namely amenorrhea, galactorrhea, and menorrhagia, have occurred.

In controlled clinical trials prolactin levels were higher in patients treated with RISPERDAL® than in haloperidol-treated patients; however, the incidence of solicited adverse events considered to be possibly prolactin-related in patients treated with RISPERDAL® (≤ 10 mg/day) was low (< 6%), and similar to that in haloperidol-treated patients.

Table 1. 2 Prolactin-related adverse events solicited from women and men in the two fixed-dose schizophrenia trials

	RISPERDAL® (mg/day)			Placebo
	1 – 2	4 - 6	8 - 10	
Women	**N=78**	**N=90**	**N=98**	**N=14**
Amenorrhea	5 (6%)	4 (4%)	6 (6%)	1 (7%)
Galactorrhea	1 (1%)	2 (2%)	2 (2%)	0
Men	**N=238**	**N=223**	**N=219**	**N=74**
Ejaculatory dysfunction	7 (3%)	6 (3%)	9 (4%)	2 (3%)
Erectile dysfunction	6 (2%)	9 (4%)	6 (3%)	1 (1%)
Gynecomastia	2 (1%)	0	1 (<1%)	1 (1%)

Note: Adverse events were solicited using the UKU questionnaire. See Kleinberg DL, Davis JM, De Coster R, Van Baelen B, Brecher M. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999;19(1):57-61.

Weight Gain

In a pool of 6- to 8-week placebo-controlled clinical trials, which compared RISPERDAL® and placebo in the treatment of schizophrenia, 18% of patients treated with RISPERDAL® and 9% of placebo-treated patients met a weight gain criterion of ≥7% of baseline body weight. This difference was statistically significant. With continued treatment, weight gain (mean: 2.3 kg in long-term studies) has been seen.

Other Adverse Events

Erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, and rash have also been reported during treatment with RISPERDAL®. As with other antipsychotics, cases of water intoxication, either due to polydipsia or to syndrome of inappropriate secretion of antidiuretic hormone (SIADH), have occasionally been reported during treatment with RISPERDAL®.

Adverse Events in North American Studies

Table 1.3 enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among patients treated with RISPERDAL® receiving doses of ≤ 10 mg/day as among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL® at fixed doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the flexible dose study. Table 1.3 shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ substantially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

Table 1.3: Treatment-emergent adverse experience incidence in 6- to 8-week controlled clinical trials in schizophrenia[1]

Body System/ Preferred Term	RISPERDAL® ≤ 10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Neurological			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculoskeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤10 mg/day' group and placebo, the data for individual dose groups in fixed-dose trials do suggest a dose/response relationship.

Adverse Events in All International Trials

Table 1.4 lists the overall incidence of adverse reactions noted for all international controlled clinical trials including the North American trials. Some adverse events were reported at a higher incidence in the North American trials than appear in Table 1.3, due to differences in reporting practices and/or methodology.

Table 1.4: Adverse reactions reported at a frequency of ≥ 1% in all international trials in schizophrenia[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=1202)	RISPERDAL® > 10 mg/day (N=535)	Placebo (N=176)
Psychiatric			
Insomnia	13%	10%	16%
Agitation	9%	7%	16%
Anxiety	7%	6%	7%
Somnolence	4%	2%	1%
Nervousness	2%	2%	3%
Impaired concentration	1%	0%	0%
Aggressive reaction	1%	1%	3%
Suicide attempt	1%	2%	1%
Psychosis	1%	1%	0%
Neurological			
Extrapyramidal disorder	7%	13%	7%
Headache	6%	3%	10%
Dizziness	3%	2%	1%
Hyperkinesia (includes akathisia)	2%	3%	2%
Tremor	1%	2%	2%
Rigidity	1%	2%	2%
Hypokinesia	1%	1%	1%
Dystonia	1%	2%	1%
Oculogyric crisis	1%	1%	1%
Dyskinesia	1%	1%	1%
Gastrointestinal			
Constipation	3%	2%	2%
Nausea	3%	1%	2%
Vomiting	2%	2%	3%
Increased salivation	2%	2%	1%
Dyspepsia	1%	2%	3%
Anorexia	1%	0%	1%
Abdominal pain	1%	0%	1%
Respiratory			
Rhinitis	3%	1%	3%
Coughing	1%	1%	1%
Special Senses			
Abnormal vision	2%	0%	1%
Cardiovascular			
Tachycardia	1%	2%	0%
Other			
Fatigue	2%	1%	1%

[1] Events reported by at least 1% of patients treated with RISPERDAL® are rounded to the nearest %.

Adverse Reactions During Long-Term Treatment

Long-term clinical trials with RISPERDAL® were carried out in 1235 chronic schizophrenic patients, with 671 patients receiving the drug for at least one year. The pattern of adverse events observed in patients receiving RISPERDAL® in long-term clinical trials is consistent with those observed in short-term trials.

Adverse events were collected through spontaneous reporting, open questioning or utilization of the UKU side effect rating scale. Listed (in decreasing order) are those events which developed or showed deterioration during treatment compared to baseline in at least 10% of patients. **Psychic:** asthenia/lassitude/increased fatiguability, concentration difficulties, sleepiness/sedation, reduced duration of sleep, increased duration of sleep, failing memory, increased dream activity, insomnia; **Autonomic:** orthostatic dizziness, constipation, nausea/vomiting, polyuria/polydipsia, palpitations/tachycardia, reduced salivation, accommodation disturbances, increased tendency to sweating, diarrhea, micturition disturbances; **Other:** weight gain, weight loss, amenorrhea, ejaculatory dysfunction, erectile dysfunction, diminished sexual desire, tension headache, headache, increased sexual desire, orgastic dysfunction, pruritus.

Behavioural Disturbances in Severe Dementia

Adverse Events Associated with Discontinuation of Treatment

In the fixed-dose, dose-response study, 95/617 patients discontinued treatment due to an adverse event. The most frequently reported adverse events were somnolence, extrapyramidal symptoms (EPS), and agitation, with somnolence and EPS being dose-related.

Table 1.5 Adverse events leading to discontinuation in trials in elderly patients with dementia

Adverse Event	Placebo	RISPERDAL®		
	(N=161) %	0.5 mg/day (N=147) %	1 mg/day (N=147) %	2 mg/day (N=162) %
Somnolence	1.9	0	4.8	6.8
Extrapyramidal symptoms (EPS)	1.2	1.4	3.4	3.7
Agitation	2.5	2	1.4	3.7

Incidence of Adverse Events

Table 1.6 enumerates adverse events from the fixed-dose, dose-response study that were more frequent in the RISPERDAL® groups than in the placebo group and/or were dose-related.

Table 1.6: Treatment-emergent adverse events in the fixed-dose study in elderly patients with dementia

Body System/ Preferred Term	Placebo	RISPERDAL®		
		0.5 mg/day	1 mg/day	2 mg/day
	(N=161) %	(N=147) %	(N=147) %	(N=162) %
Body as a Whole				
Edema peripheral	6	16	13	18
Psychiatric				
Somnolence	8	10	17	27
Neurological				
Extrapyramidal symptoms (EPS)	8	7	13	22
Respiratory				
Rhinitis	5	5	6	10
Dyspnea	1	1	1	5
Cardiovascular				
Hypotension	3	2	3	5
Tachycardia	1	1	0	2

Events are rounded to the nearest %.

Other adverse events which occurred with a high incidence but with similar frequencies in the patients treated with RISPERDAL® and placebo included injury (28 to 38%), falls (13 to 25%), urinary tract infection (13 to 21%), and purpura (10 to 17%).

Cerebrovascular Adverse Events (CVAEs) in Elderly Patients with Dementia

In 6 placebo-controlled dementia trials for elderly patients taking RISPERDAL® for 4 to 12 weeks within the approved dosage range, the pooled incidence rate of CVAEs was 3%, compared to 1% for age-matched patients taking placebo. Five patients died in the RISPERDAL® group (5/1009) versus 1 patient in the placebo group (1/712) (see **INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Post-marketing for the Elderly Dementia Population

Review of the global post-marketing database for the elderly dementia patient population (over 2.4 million patient-years as of October 2002) identified approximately 37 cases of cerebrovascular adverse events such as strokes and transient ischemic attacks. Of these cases, 16 were fatal.

There is insufficient information to determine whether CVAEs in elderly patients with dementia are associated specifically with RISPERDAL® or other antipsychotic agents.

Bipolar Disorder – Mania

Adverse Events Associated with Discontinuation of Treatment

In the 3-week placebo-controlled trials, a total of 4.2% of patients discontinued from the studies because of an adverse event: 4.1% for placebo, 4.8% for RISPERDAL® and 2.8% for haloperidol. The most common adverse event leading to discontinuation was manic reaction: 1.0% for placebo and 1.6% for RISPERDAL®.

Incidence of Adverse Events

In the 3-week placebo-controlled trials, in which patients received dosages of 1-6 mg/day risperidone, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of ≥5% and at least twice placebo) included extrapyramidal disorder, hyperkinesia, dystonia and somnolence. Adverse events that occurred in these trials with an incidence of ≥1% and more frequently in patients treated with risperidone than placebo are shown in Table 1.7.

Table 1.7: Treatment-emergent adverse events reported in double-blind monotherapy trials in bipolar disorder (≥1% and more frequent than placebo)

Adverse Event System Organ Class Adverse Event Preferred Term	PLACEBO (N=409) n (%)	RISPERDAL® (N=434) n (%)
Total no. subjects with Emerging Adverse Event	232 (56.7)	305 (70.3)
Central and peripheral nervous system disorders	99 (24.2)	200 (46.1)
Extrapyramidal disorder	25 (6.1)	85 (19.6)
Headache	30 (7.3)	39 (9.0)
Hyperkinesia	10 (2.4)	37 (8.5)
Tremor	15 (3.7)	28 (6.5)
Dizziness	20 (4.9)	24 (5.5)
Dystonia	2 (0.5)	22 (5.1)
Hypertonia	4 (1.0)	16 (3.7)
Muscle contractions involuntary	1 (0.2)	5 (1.2)
Psychiatric disorders	78 (19.1)	103 (23.7)
Somnolence	15 (3.7)	53 (12.2)
Manic reaction	11 (2.7)	13 (3.0)
Gastrointestinal system disorders	63 (15.4)	82 (18.9)
Nausea	4 (1.0)	18 (4.1)
Dyspepsia	9 (2.2)	16 (3.7)
Saliva increased	2 (0.5)	13 (3.0)
Mouth dry	4 (1.0)	5 (1.2)
Body as a whole - general disorders	44 (10.8)	51 (11.8)
Fatigue	3 (0.7)	8 (1.8)
Pain	6 (1.5)	8 (1.8)
Fever	3 (0.7)	6 (1.4)
Asthenia	3 (0.7)	5 (1.2)
Edema	1 (0.2)	5 (1.2)
Respiratory system disorders	30 (7.3)	33 (7.6)
Rhinitis	5 (1.2)	6 (1.4)
Sinusitis	1 (0.2)	6 (1.4)
Skin and appendages disorders	15 (3.7)	23 (5.3)
Acne	0	5 (1.2)
Musculoskeletal system disorders	14 (3.4)	16 (3.7)
Myalgia	7 (1.7)	8 (1.8)

Note: Incidence is based on the number of subjects, not the number of events.
Note: Incidence for female reproductive disorders is based on the number of female subjects (placebo, N=181; risperidone, N=180).

Table 1.7: Treatment-emergent adverse events reported in double-blind monotherapy trials in bipolar disorder (≥1% and more frequent than placebo) (continued)

Adverse Event System Organ Class Adverse Event Preferred Term	PLACEBO (N=409) n (%)	RISPERDAL® (N=434) n (%)
Cardiovascular disorders, general	12 (2.9)	14 (3.2)
Hypertension	8 (2.0)	9 (2.1)
Vision disorders	6 (1.5)	11 (2.5)
Vision abnormal	3 (0.7)	8 (1.8)
Heart rate and rhythm disorders	5 (1.2)	10 (2.3)
Tachycardia	2 (0.5)	6 (1.4)
Reproductive disorders, female	5 (2.8)	8 (4.4)
Lactation nonpuerperal	0	5 (2.8)
Liver and biliary system disorders	2 (0.5)	6 (1.4)
SGOT increased	1 (0.2)	5 (1.2)

See footnotes on the first page of the table.

Suicide

In the 3-week double-blind phase of controlled clinical trials, suicide-related adverse events occurred at an incidence of 0.45% for patients treated with risperidone (2 patients/448) compared to 0 for patients treated with placebo (0 patients/424). Suicide attempt and completed suicide occurred in one patient each.

The incidence of suicide-related adverse events was 0.67% (3 patients/446) during 9 weeks of open-label risperidone treatment. Suicide attempts were reported for two patients and completed suicide occurred in one patient.

Hyperprolactinemia

In controlled clinical trials, patients treated with RISPERDAL® had higher prolactin levels than patients treated with placebo or haloperidol. Associated manifestations that occurred in fewer than 1% of patients treated with RISPERDAL® during the bipolar clinical trials, which are not listed in Table 1.7, included ejaculation failure, abnormal sexual function, decreased libido, and impotence.

Extrapyramidal symptoms in bipolar disorder clinical trials

Adverse events related to extrapyramidal symptoms (EPS) were reported more frequently in all clinical trials for bipolar disorder than schizophrenia, regardless of study population demographics, and this may be consistent with a greater susceptibility to EPS-related adverse reactions in bipolar patients that has been observed in clinical practice. The lower mean body

weight and body mass index (BMI) of an Indian study population (RIS-IND-2) and a higher mean risperidone dose may have contributed to a higher incidence of EPS-related AEs in this trial (45%, mean modal dose 5.6 mg/day; mean modal dose is the average of individual subjects' most frequent daily dose) compared to the US (36.6%, mean modal dose 4.0 mg/day) and international (31.2%, mean modal dose 4.2 mg/day) trials. EPS-related adverse events in all studies were usually mild, dose-related and reversible upon dose reduction and/or administration of antiparkinsonian medication.

Abnormal Hematologic and Clinical Chemistry Findings

In one study in which testosterone levels were measured, testosterone decreased below the normal range in 6 out of 85 patients.

Post-Market Adverse Drug Reactions

Adverse events reported since market introduction of RISPERDAL®, which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: edema, angioedema, increased hepatic enzyme levels, skin manifestations of allergy including cases of Stevens-Johnson syndrome, systemic manifestations of allergy including a case of anaphylactic shock, neuroleptic malignant syndrome, body temperature dysregulation, urinary incontinence, gynecomastia, seizures, tardive dyskinesia, hypertension, priapism, thrombopenia, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder including cerebrovascular accident, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated and pulmonary embolism.

Hyperglycemia and exacerbation of pre-existing diabetes have been reported during RISPERDAL® treatment. Diabetic ketoacidosis, diabetes mellitus and hypoglycemia have also been reported very rarely (see **WARNINGS AND PRECAUTIONS - Endocrine and Metabolism**).

As with other neuroleptics, sudden death, torsades de pointes, ventricular tachycardia, arrhythmia, cardiopulmonary arrest and QT prolongation have been reported during RISPERDAL® treatment. Many of the patients had pre-existing cardiovascular disease, were on concomitant medications known to prolong the QT interval, had risk factors for QT prolongation, took an overdose of risperidone, and/or were morbidly obese. Very rarely, QT prolongation has been reported in the absence of confounding factors.

Significant weight gain has been reported in both clinical trials and post-marketing (see **WARNINGS AND PRECAUTIONS - Endocrine and Metabolism**).

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including RISPERDAL®. Agranulocytosis has also been reported (see **WARNINGS AND PRECAUTIONS - Hematologic**).

DRUG INTERACTIONS

Overview

Given the primary central nervous system effects of RISPERDAL®, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. Because of its potential

for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive medications.

Caution is advised when prescribing RISPERDAL® with drugs known to prolong the QT interval.

Drug-Drug Interactions

Concomitant Use with Furosemide

See **WARNINGS AND PRECAUTIONS**, **Special Populations** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Carbamazepine and Other CYP 3A4 Enzyme Inducers

Carbamazepine has been shown to decrease substantially the plasma levels of risperidone and its active metabolite, 9-hydroxyrisperidone (n=11). Similar effects may be observed with other CYP 3A4 hepatic enzyme inducers. Consequently, in the presence of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dose of RISPERDAL® may have to be adjusted. On discontinuation of these drugs, the dosage of RISPERDAL® should be re-evaluated and, if necessary, decreased.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

The metabolism of RISPERDAL®, a substrate of the hepatic cytochrome P450 isozyme 2D6 (CYP 2D6), is affected by the debrisoquine hydroxylation polymorphism (see **ACTION AND CLINICAL PHARMACOLOGY** – **Pharmacokinetics**). CYP 2D6 is also responsible for the metabolism of a variety of drugs, including phenothiazines, antidepressants (tricyclics and SSRIs), antiarrhythmics and some β-blockers. Consequently, potential interaction between RISPERDAL® and drugs that are also substrates of CYP 2D6, should also be considered.

Fluoxetine and Paroxetine: Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone but less so of risperidone and 9-hydroxyrisperidone combined. Pharmacokinetic interaction with fluoxetine was examined in a study which measured steady-state plasma levels of risperidone and its metabolites before and following 3 weeks of co-treatment with fluoxetine (n=10). The addition of fluoxetine resulted in about a 2- to 3-fold increase in peak and AUC levels of risperidone and about a 50% increase in peak and AUC levels for risperidone and 9-hydroxyrisperidone combined. Similarly, pharmacokinetic interaction with paroxetine was examined in a study which measured steady-state plasma levels of risperidone and its metabolites before and following 4 weeks of co-treatment with paroxetine (n=10). After 4 weeks of paroxetine treatment, the sum of the concentrations of risperidone and 9-hydroxyrisperidone increased significantly by 45% over baseline. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®.

Erythromycin: Erythromycin, a CYP 3A4 inhibitor, did not change the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined. Risperidone was administered as a single dose of 1 mg with multiple doses of erythromycin (500 mg q.i.d.) in healthy volunteers (n=18).

The Effect of Other Drugs on the Metabolism of Risperidone

Galantamine and Donepezil: The cholinesterase inhibitors, galantamine (n=15) and donepezil (n=24), did not show an effect on the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined. Galantamine 12 mg o.d. was co-administered with risperidone 0.5 mg o.d. in healthy elderly volunteers. Donepezil 5 mg o.d. was co-administered with risperidone 0.5 mg b.i.d. in healthy male volunteers.

Cimetidine and Ranitidine: Risperidone was administered as a single dose of 1 mg with multiple doses of either cimetidine (400 mg b.i.d.) or ranitidine (150 mg b.i.d.) in healthy young adult volunteers (n=12). The effect of the drug interaction of cimetidine and ranitidine on risperidone and 9-hydroxyrisperidone combined was minimal.

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

Topiramate:

Healthy Volunteers: A drug-drug interaction study between risperidone and topiramate was conducted in 12 healthy volunteers (6 males, 6 females), ages 28-40 years, with single-dose administration of risperidone (2 mg) and multiple doses of topiramate (titrated up to 200 mg/day). In the presence of topiramate, systemic exposure of risperidone and 9-hydroxyrisperidone combined was reduced such that mean $AUC_{0-\infty}$ was 11% lower and mean C_{max} was statistically significantly (18%) lower. In the presence of topiramate, systemic exposure of risperidone was statistically significantly reduced such that mean C_{max} and $AUC_{0-\infty}$ were 29% and 23% lower, respectively. The pharmacokinetics of 9-hydroxyrisperidone were unaffected. The effects of a single dose (2 mg/day) of risperidone on the pharmacokinetics of multiple doses of topiramate have not been studied.

Patients with Bipolar Disorder: A drug-drug interaction study conducted in 52 patients with various types of bipolar disorder (24 males, 28 females), ages 19-56 years, evaluated the steady-state pharmacokinetics of risperidone and topiramate when administered concomitantly. Eligible subjects were stabilized on a risperidone dose of 1-6 mg/day for 2 to 3 weeks. Topiramate was then titrated up to escalating doses of 100, 250 and 400 mg/day along with risperidone for up to 6 weeks. Risperidone was then tapered and discontinued over 4 weeks while maintaining topiramate (up to 400 mg/day). There was a statistically significant reduction in risperidone systemic exposure (16% and 33% for AUC_{12} and 13% and 34% for C_{max} at the 250 and 400 mg/day doses, respectively). Minimal alterations were observed in the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined and of 9-hydroxyrisperidone. Topiramate systemic exposure was slightly reduced (12.5% for mean C_{max} and 11% for mean AUC_{12}) in the presence of risperidone, which achieved statistical significance. There were no clinically significant changes in the systemic exposure of risperidone and 9-hydroxyrisperidone combined or of topiramate. The effects of higher doses of topiramate (>400 mg/day) are unknown. Therefore, if combination therapy is chosen, patients receiving both risperidone and topiramate should be closely monitored.

Effects of Risperidone on the Metabolism of Other Drugs

Lithium: RISPERDAL® (3 mg b.i.d.) did not show an effect on the pharmacokinetics of lithium (400, 450 or 560 mg b.i.d.) (n=13).

Valproate: RISPERDAL® (4 mg o.d.) did not show an effect on the pharmacokinetics of valproate (1000 mg/day) (n=9). However, more subjects reported adverse events with the risperidone-valproate therapy compared to the placebo-valproate group in the clinical trial.

Digoxin: The effect of RISPERDAL® (0.5 mg/day administered b.i.d.) on the steady-state plasma concentrations of digoxin (0.125 mg/day) was examined in a double-blind, two-way, crossover trial in healthy elderly volunteers (median age 68 years, range 61 to 75 years, n=19). RISPERDAL® did not affect the steady-state pharmacokinetics of digoxin, and concurrent administration of the two drugs was well tolerated.

In vitro studies, in which risperidone was given in the presence of various, highly protein-bound agents, indicated that clinically relevant changes in protein binding would not occur either for RISPERDAL® or for any of the drugs tested.

Drug-Food Interactions
RISPERDAL® oral solution is compatible with the following beverages: water, coffee, orange juice and low-fat milk. However, it is not compatible with cola or tea. Also see **DOSAGE AND ADMINISTRATION**.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Refer to **Special Populations** for dosing recommendations in the following patients:

- Patients prone to hypotension
- Geriatrics
- Patients with renal impairment
- Patients with hepatic impairment

Recommended Dose and Dosage Adjustment
Adults
Schizophrenia and Related Psychotic Disorders
RISPERDAL® can be administered on either a o.d. or b.i.d. schedule, generally beginning with 1 to 2 mg per day. The dose should be adjusted gradually over several days based on clinical response to a target dose of 4 to 6 mg per day. Some patients may benefit from lower initial doses and/or a slower adjustment schedule.

Further dosage adjustments, if indicated, should generally occur at intervals of not less than one week since steady state for the active metabolite would not be achieved for approximately one week in the typical patient. When dosage adjustments are necessary, small increments/decrements of 1 mg are recommended.
In controlled clinical trials, optimal therapeutic effects were seen in the 4 to 8 mg per day dose range. However, clinical experience indicates that in the majority of patients adequate therapeutic effect is achieved at the 6 mg per day dose. Doses above 10 mg per day have not been shown to be more efficacious than lower doses and were associated with more

extrapyramidal symptoms and other adverse events.

The safety of RISPERDAL® has not been established above 16 mg total daily dose, administered twice daily. If administered once daily, safety has not been established beyond a single dose of 8 mg.

Switching From Other Antipsychotics
When medically appropriate, gradual discontinuation of the previous treatment, while RISPERDAL® therapy is initiated, is recommended. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing antiparkinsonian medications should be re-evaluated periodically.

Maintenance Therapy
It is recommended that responding patients be continued on RISPERDAL® at the lowest dose needed to maintain remission. Patients should be reassessed periodically to determine the need for maintenance treatment. While there is no body of evidence available to answer the question of how long the patient should be treated with RISPERDAL®, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs.

Behavioural Disturbances in Severe Dementia
Physicians are advised to assess the risks and benefits of the use of RISPERDAL® in elderly patients with dementia, taking into account risk predictors for stroke or existing cardiovascular comorbidities in the individual patient (see **INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Discontinuation should be considered if signs and symptoms of cerebrovascular adverse events occur.

A starting dose of RISPERDAL® 0.25 mg b.i.d. is recommended. This dosage should be adjusted by increments of 0.25 mg per day approximately every 2 to 4 days. The optimal dose is 0.5 mg b.i.d. (1.0 mg per day) for most patients. Some patients, however, may benefit from higher doses up to a maximum of 1.0 mg b.i.d. (2.0 mg per day).

Periodic dosage adjustments (increase or decrease) or discontinuation of treatment should be considered because of the instability of the symptoms treated.

Since there is no experience in younger patients, dosage recommendations cannot be made.

Bipolar Mania
RISPERDAL® should be administered on a once-daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, based on clinical response and tolerability, should occur at intervals of not less than 24 hours and in dosage increments or decrements of 1 mg per day. RISPERDAL® doses higher than 6 mg per day were not studied in patients with bipolar disorder.
In two controlled trials, the most common daily dose was 1-4 mg/day. In each of the three controlled trials, RISPERDAL® was effective across the dose range used, although the effect size in the 3-4 mg/day mean modal dose group was larger than in the 5-6 mg/day mean modal dose group (mean modal dose is the average of the most frequent daily dose across the three trials).

The safety and effectiveness of RISPERDAL® for long-term use and for prophylactic use in bipolar disorder have not been evaluated. Physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Special Populations

Geriatrics
Risperidone is substantially excreted by the kidneys. Thus, 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, caution should be taken in dose selection and titration. It may also be useful to monitor renal function in these patients (see **WARNINGS AND PRECAUTIONS - Special Populations, ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics** and **Table 1.8**).

In elderly schizophrenic patients, the doses of RISPERDAL® should be adjusted slowly from a 0.25 mg b.i.d. starting dose to a maximum daily dose of 3 mg. Since the elimination of RISPERDAL® is somewhat slower in these patients, the potential for accumulation should be considered (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics** and **Table 1. 8**).

Patients Prone to Hypotension
Caution should be exercised in patients prone to hypotension and the use of lower starting doses of 0.25 to 0.5 mg b.i.d. should be considered.

Patients with Impaired Liver Function
RISPERDAL® should be used with caution in patients with hepatic impairment.

Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone and this may result in an enhanced effect. In general, starting and consecutive dosing should be halved, and dose titration should be slower for patients with hepatic impairment, administered on a b.i.d. schedule.

In patients with schizophrenia and related psychotic disorders with impaired liver function, the starting dose should be 0.25 to 0.5 mg b.i.d. This dosage can be individually adjusted in 0.5 mg b.i.d. increments to 1 to 2 mg b.i.d. Increases to dosages above 1.5 mg b.i.d. should generally occur at intervals of at least 1 week (see **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic, ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics** and **Table 1.8**).

Patients with Impaired Kidney Function
RISPERDAL® should be used with caution in patients with renal impairment.

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. In general, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal impairment, administered on a b.i.d. schedule. The recommended initial dose is 0.5 mg b.i.d. and dosage increases should be in increments of no more than 0.5 mg b.i.d. Increases to dosages above 1.5 mg b.i.d. should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate (see

WARNINGS AND PRECAUTIONS - Renal, ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and **Table 1.8**).

Missed Dose
The missed dose should be taken at the next scheduled dose. Doses should not be doubled.

Administration
RISPERDAL® may be given as tablets or oral solution. RISPERDAL® M-TAB® is given as orally disintegrating tablets. All may be taken with or without meals. In order to avoid orthostatic hypotension, the dose of RISPERDAL® should be adjusted gradually.

RISPERDAL® M-TAB® tablets should not be split into halves.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Cases of overdose have been reported with RISPERDAL®; the estimated doses were between 20 and 360 mg. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, namely drowsiness, sedation, tachycardia, hypotension and extrapyramidal symptoms. In overdose, QT-prolongation, widened QRS complex, convulsions, hyponatremia and hypokalemia were also reported. Torsades de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

Treatment of Overdosage
Since there is no specific antidote to RISPERDAL®, treatment is primarily supportive. A patent airway must be established and maintained to ensure adequate ventilation and oxygenation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. Epinephrine should not be used since beta stimulation may worsen hypotension in the setting of RISPERDAL®-induced alpha blockade. In cases of severe extrapyramidal reactions, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

In managing overdosage, the physician should consider the possibility of multiple drug involvement.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to serotonin type 2 (5-HT_2), dopamine type 2 (D_2), and α_1-adrenergic receptors. Risperidone binds with a lower affinity to the α_2-adrenergic and histamine H_1 receptors. Risperidone does not bind to dopamine D_1 receptors and has no affinity (when tested at concentrations $>10^{-5}$ M) for muscarinic cholinergic receptors. Due to the lack of muscarinic receptor binding, risperidone is not expected to produce anticholinergic adverse effects.

Receptor occupancy was also demonstrated *in vivo* in humans. Using positron emission tomography, risperidone was shown to block both 5-HT_{2A} and dopamine D_2 receptors in three healthy volunteers. Although risperidone is a potent D_2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy in animal models than classical antipsychotics. Risperidone has also been found to be one of the most potent known antagonists of 5-HT_{2A} (cloned human receptor); 5-HT_{2A} antagonism has been shown to reverse deficits in several *in vivo* animal models predictive of novel antipsychotic activity (PCP-induced social deficit, microdialysis assessment of dopamine output in prefrontal cortex, glutamate antagonist-induced hyperlocomotion). Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side-effect liability.

Pharmacokinetics

Absorption: Risperidone was well absorbed after oral administration, had high bioavailability, and showed dose-proportionality in the therapeutic dose range, although inter-individual plasma concentrations varied considerably. Mean peak plasma concentrations of risperidone and 9-hydroxyrisperidone were reached at about 1 hour and 3 hours, respectively, after drug administration. Food did not affect the extent of absorption; thus, risperidone can be given with or without meals.

Distribution: Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. Steady-state concentrations of risperidone and 9-hydroxyrisperidone were reached within 1-2 days and 5-6 days, respectively. In plasma, risperidone is bound to albumin and alpha$_1$-acid glycoprotein (AGP). The plasma protein binding of risperidone is approximately 88%, that of the metabolite 77%.

Metabolism: Risperidone is extensively metabolized in the liver by CYP 2D6 to a major active metabolite, 9-hydroxyrisperidone, which appears approximately equi-effective with risperidone with respect to receptor-binding activity. (A second minor pathway is N-dealkylation.) Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. The hydroxylation of risperidone is dependent upon debrisoquine 4-hydroxylase, i.e., the metabolism of risperidone is sensitive to the debrisoquine hydroxylation type genetic polymorphism. Consequently, the concentrations of parent drug and active metabolite differ substantially in extensive and poor metabolizers. However, the concentration of risperidone and 9-hydroxyrisperidone combined did not differ substantially between extensive and poor metabolizers, and elimination half-lives were similar in all subjects (approximately 20 to 24 hours).

Excretion: One week after administration, 70% of the dose is excreted in the urine and 14% in

the faeces. In urine, risperidone plus 9-hydroxyrisperidone represents 35-45% of the dose. The remainder is inactive metabolites.

Special Populations and Conditions

Table 1.8 summarizes the pharmacokinetic parameters observed in various subpopulations:

Table 1.8: Median pharmacokinetic parameters of risperidone and 9-hydroxyrisperidone combined following a single, 1 mg oral dose of risperidone in different patient populations

Parameters	Young	Elderly	Liver disease	Renal disease	
				Moderate	Severe
N	8	12	8	7	7
age (yr) range	30 25-35	69 65-78	51 35-73	57 34-68	52 29-66
T_{max}, h	2	1.5	1	1	2
C_{max}, ng/mL	9.1	10.2	8.5	13	13.3
$t_{½}$, h	17	23	16	25	29
$AUC_{0-\infty}$, ng.h/mL	132	189	145	272	417
Cl_{ren}, mL/min/1.73 m^2	55	41	57	17	9.5
risperidone, % unbound	16	14	22	14	16
$Cl_{oral,}$ mL/min	127	89	119	61	40

N: number of subjects
T_{max}: time to peak plasma concentration
C_{max}: peak plasma concentration
$t_{½}$: elimination half-life
$AUC_{0-\infty}$: area under plasma concentration time curve
Cl_{ren}: renal clearance
Cl_{oral}: oral clearance

The results indicate that a 1 mg dose of risperidone produced modest pharmacokinetic changes in elderly subjects, including reduced clearance of the active antipsychotic fraction by about 30%. In patients with impaired liver function, the unbound fraction of risperidone was increased by about 35% due to diminished concentrations of both α_1-AGP and albumin. In patients with impaired renal function, the changes were substantial; C_{max} and AUC of risperidone and 9-hydroxyrisperidone combined were increased by about 40% and 160% respectively, half-life was prolonged by about 60% and clearance decreased by about 60%.

Plasma Levels in Patients with Severe Dementia

The plasma levels of risperidone and its major metabolite, 9-hydroxyrisperidone, were determined at steady state. Blood samples were obtained from 85% of all trial patients receiving risperidone. Blood samples were drawn prior to the morning dose. Thus, the plasma levels shown in Table 1.9 represent trough levels.

Table 1.9: Median trough plasma levels of risperidone and 9-hydroxyrisperidone-combined at steady state in patients with severe dementia

Dose (mg/day) (b.i.d. dosing)	Median trough plasma levels (ng/mL)
0.5	5.8
1.0	14.3
2.0	24.0

The plasma concentration of risperidone and 9-hydroxyrisperidone combined was dose proportional over the dosing range of 0.5 to 2 mg daily dose (0.25 to 1 mg b.i.d.).

STORAGE AND STABILITY

RISPERDAL® tablets and RISPERDAL® M-TAB® orally disintegrating tablets should be stored between 15 - 30°C. Protect from light and moisture.

RISPERDAL® oral solution should be stored between 15 - 30°C. Protect from light and freezing.

RISPERDAL® should be kept out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging
RISPERDAL® is available as the following:

Film-Coated Tablets
0.25 mg risperidone as yellow, oblong, biconvex tablets, marked "JANSSEN" on one side and "Ris 0.25" on the other side. Bottles of 100.

0.5 mg risperidone as brownish-red, half-scored, oblong, biconvex tablets, marked "JANSSEN" on one side and "Ris 0.5" on the other side. Bottles of 100.

1 mg risperidone as white, oblong, biconvex tablets, marked "Ris" and "1" on one side. Tablets may be scored. Blisters of 60, bottles of 500.

2 mg risperidone as orange, scored, oblong, biconvex tablets, marked "Ris" and "2" on one side. Blisters of 60, bottles of 500.

3 mg risperidone as yellow, scored, oblong, biconvex tablets, marked "Ris" and "3" on one side. Blisters of 60, bottles of 250.

4 mg risperidone as green, scored, oblong, biconvex tablets, marked "Ris" and "4" on one side. Bottles of 60.

Oral Solution
RISPERDAL® 1 mg/mL oral solution is supplied in 30 mL bottles, with a plastic child-resistant closure and a calibrated (in milligrams and millilitres) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL. Calibration marks every 0.25 mL up to 3 mL are printed on this pipette.

Patient Instructions (including illustrations) for using the RISPERDAL calibrated dispensing pipette are provided (see ***Product Monograph Part III*: CONSUMER INFORMATION**). Tests indicate that RISPERDAL® oral solution is compatible with the following beverages: water, coffee, orange juice and low-fat milk. However, it is NOT compatible with cola or tea.

RISPERDAL® M-TAB® Orally Disintegrating Tablets
0.5 mg risperidone as light coral, round, biconvex tablets marked "R0.5". Blisters of 28 per carton.
1 mg risperidone as light coral, square, biconvex tablets marked "R1". Blisters of 28 per carton.
2 mg risperidone as biconvex tablets marked "R2". Tablets manufactured prior to 2006 are light coral and round. Tablets manufactured from 2006 onwards are coral and square. Blisters of 28 per carton.
3 mg risperidone as coral, round, biconvex tablets marked "R3". Blisters of 28 per carton.
4 mg risperidone as coral, round, biconvex tablets marked "R4". Blisters of 28 per carton.

Composition
RISPERDAL® tablets are available in 6 strengths containing 0.25, 0.5, 1, 2, 3 or 4 mg risperidone per tablet.

The following inactive ingredients are common to all tablet strengths: lactose, corn starch, microcrystalline cellulose, hydroxypropyl methylcellulose, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulphate and propylene glycol.

In addition, all tablet strengths except the 1 mg contain talc and titanium dioxide.

Colourants are present in the tablets as follows:
0.25 mg: yellow ferric oxide
0.5 mg: red ferric oxide
1 mg: none present
2 mg: FD & C Yellow #6 Aluminum Lake
3 mg: D & C Yellow #10
4 mg: D & C Yellow #10, FD & C Blue #2 Aluminum Lake

RISPERDAL® is also available as an oral solution containing risperidone 1 mg/mL as risperidone tartrate. The inactive ingredients for this solution are: tartaric acid, benzoic acid, sodium hydroxide and purified water.

RISPERDAL® M-TAB® orally disintegrating tablets are available in 5 strengths containing 0.5, 1, 2, 3 and 4 mg risperidone per tablet. The following inactive ingredients are common to all tablet strengths: polacrilex resin, gelatin, mannitol, glycine, simethicone, carbomer 934P, sodium hydroxide, aspartame, red ferric oxide and peppermint oil. The 2 mg tablets manufactured from 2006 onwards and the 3 and 4 mg tablets also contain xanthan gum.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

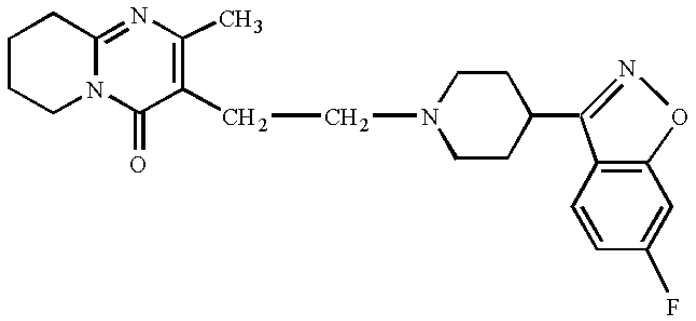
Drug Substance

Proper name: risperidone

Chemical name: 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

Molecular formula and molecular mass: $C_{23}H_{27}FN_4O_2$; 410.49

Structural formula:



Physicochemical properties: Risperidone is a white or almost white powder. It is practically insoluble in water (pH=8.7), freely soluble in dichloromethane, and soluble in methanol and 0.1N HCl.

Ionization Constant: $pKa_1 = 8.24$
$pKa_2 = 3.11$

Partition Coefficient: log P = 3.04

Melting Point: 169 - 173°C

CLINICAL TRIALS

Schizophrenia

Short-Term Clinical Trials

The efficacy of RISPERDAL® in the management of the manifestations of schizophrenia was established in three well-controlled, short-term (6- to 8-week), double-blind clinical trials of psychotic inpatients who met the DSM-III-R criteria of schizophrenia.

Psychiatric signs and symptoms were assessed according to the following rating scales: PANSS (Positive and Negative Syndrome Scale) total score and positive and negative subscales, BPRS (Brief Psychiatric Rating Scale) total score and psychosis cluster (conceptual disorganization, hallucinatory behaviour, suspiciousness, and unusual thought content), CGI-S (Clinical Global Impression - Severity of Illness) and SANS (Scale for Assessing Negative Symptoms).

The results of the trials follow:

A 6-week, double-blind, flexible-dose trial (N=160) compared RISPERDAL® up to 10 mg per day with haloperidol up to 20 mg per day or placebo. The mean daily dose of RISPERDAL® was 7.8 mg at endpoint. RISPERDAL® was statistically significantly superior to placebo on the BPRS total score and psychosis cluster, as well as on the SANS and CGI-S.

An 8-week, double-blind, fixed-dose trial (N=1356) compared 5 doses of RISPERDAL® (1, 4, 8, 12 and 16 mg per day) with haloperidol 10 mg per day or placebo. The higher doses generally produced better results than the 1 mg dose. On the PANSS total score and negative subscale, as well as on the BPRS total score, a bell-shaped dose response relationship was established with optimal therapeutic responses occurring at the 4 mg and 8 mg doses. On the PANSS positive subscale and BPRS psychosis cluster, the dose-response relationship was linear (i.e., increasing doses produced increasing efficacy).

An 8-week, double-blind, fixed-dose trial (N=513) compared 4 doses of RISPERDAL® (2, 6, 10 or 16 mg per day) with haloperidol 20 mg per day or placebo. RISPERDAL® was statistically significantly superior to placebo on all scales measured (PANSS total score and positive and negative subscales, BPRS total score and psychosis cluster and CGI-S), although the difference between the 2 mg daily dose and placebo did not reach statistical significance in each case. The most consistent response on all measures was seen with the 6 mg per day dose, and there was no indication that the larger doses provided greater benefits.

The efficacy and safety of once-daily RISPERDAL® were established in a 4-week, placebo-controlled trial. Inpatients (N=246) who met the DSM-IV criteria of schizophrenia received fixed doses of RISPERDAL®, 4 or 8 mg per day, or placebo. Both RISPERDAL® groups were superior to placebo on several measures, including 'clinical response' (≥20% reduction in PANSS total score), PANSS total score and the BPRS psychosis cluster (derived from PANSS). Patients receiving 8 mg per day RISPERDAL® did generally better than those receiving the 4 mg per day dose.

In all studies, parkinsonian adverse events were mild but dose related. RISPERDAL® elevated serum prolactin levels. Due to the α_1-adrenergic blocking activity, orthostatic hypotension with compensatory tachycardia was also observed.

Long-Term Clinical Trials

Long-term efficacy and safety of RISPERDAL® were demonstrated in a double-blind, randomized, parallel-group trial (N=365) (duration 1 to 2 years) which compared time to relapse during maintenance treatment with RISPERDAL® (1-8 mg/day, mean = 5 mg/day) and haloperidol (2.5-20 mg/day, mean = 8 mg/day) in chronic patients who met the DSM-IV criteria of schizophrenia or schizoaffective disorder and had been stable for at least one month. There was a statistically significant difference between the RISPERDAL® and the haloperidol treatment groups for distribution of time to relapse (mean = 452 days vs. 391 days).

The pattern of adverse events observed in patients receiving RISPERDAL® in long-term clinical trials is consistent with those observed in short-term trials.

Behavioural Disturbances in Severe Dementia

The effect of RISPERDAL® upon the management of behavioural disturbances in geriatric patients with severe dementia was evaluated in two well-controlled clinical trials. The first study was a fixed-dose, dose-response study in which RISPERDAL®, at daily doses of 0.5, 1.0 and 2.0 mg per day, was compared to placebo (N=617). The second study was a flexible-dose study in which RISPERDAL® was compared to haloperidol and placebo (N=344). The duration of the studies was 12 weeks. In both studies, patients had to meet the DSM-IV criteria for Alzheimer's and/or vascular dementia. The scales used to assess symptomatic efficacy included the BEHAVE-AD (Behavioural Pathology in Alzheimer's Disease Rating Scale), the CMAI (Cohen-Mansfield Agitation Inventory) and the CGI-C (Clinical Global Impression-Change). Potential extrapyramidal adverse events were assessed by the ESRS (Extrapyramidal Symptom Rating Scale).

In the fixed-dose study, 73%, 16% and 12% of patients were diagnosed with Alzheimer's, vascular and mixed dementia, respectively. At baseline, the MMSE (Mini-Mental State Examination) scores ranged from 6.0 to 7.8, and more than 95% of patients were at least at stage 6 on the FAST (Functional Assessment Staging). The median ages of the patients treated with RISPERDAL® ranged from 82 to 84 years with an overall range of 60 to 105 years. RISPERDAL®, 1.0 and 2.0 mg per day, given b.i.d., decreased significantly both verbal and physical aggression and psychotic behaviour. The differences between the 0.5 mg dose and placebo did not reach statistical significance. The incidence of extrapyramidal adverse events was significantly higher with RISPERDAL®, 2.0 mg per day, than with placebo. The difference between RISPERDAL® 0.5 mg and 1.0 mg per day and placebo was not significant.

In the flexible-dose study, 67%, 26% and 7% of patients were diagnosed with Alzheimer's, vascular and mixed dementia, respectively. At baseline, the MMSE scores ranged from 7.9 to 8.8, and 61% and 31% of patients were at stage 6 and stage 7 on the FAST, respectively. The median age of the patients treated with RISPERDAL® was 81 years (range 68 to 97 years).

RISPERDAL®, at a mean endpoint dose of 1.1 mg per day, given b.i.d., decreased significantly aggressive behaviour but not psychosis. ESRS scores, assessing extrapyramidal symptoms, were similar in patients treated with RISPERDAL® and placebo.

RISPERDAL® had no effect on any of the other behaviours assessed by the BEHAVE-AD, namely activity disturbances, anxieties and phobias, or affective disturbances. Furthermore, the drug had no effect on either the MMSE scores or the FAST.

Bipolar Disorder – Mania

The efficacy of RISPERDAL® in the acute treatment of manic episodes associated with Bipolar I disorder was demonstrated in 3 double-blind, placebo-controlled monotherapy trials. The trials included initially hospitalized patients who met the DSM-IV criteria for Bipolar I disorder with manic episodes (with or without psychotic features).

In all 3 trials, patients were randomized to placebo (n=409) or risperidone (n=434). One of the trials also included a group of patients treated with haloperidol (n=144). All 3 studies were 3 weeks in duration.

Flexible dosages of 1 mg to 6 mg/day were studied in these trials. Patients received an initial dose of 2 or 3 mg RISPERDAL® on Day 1, after which the dosage could be increased or decreased by 1 mg/day, based on the patient's response and tolerability. The primary rating instrument for assessing manic symptoms was the Young Mania Rating Scale (YMRS) and the primary outcome was the change from baseline in total YMRS score at the Week 3 endpoint (LOCF).

- At a flexible dosage range of 1-6 mg/day, the 3 trials demonstrated that RISPERDAL was statistically significantly superior to placebo in reducing manic symptoms as measured by the primary outcome, mean change in total YMRS score from baseline to endpoint (LOCF) over 3 weeks ($p<0.001$).
- In general, secondary efficacy outcomes were consistent with the primary outcome. The percentage of patients with a decrease of $\geq$50% in total YMRS score from baseline to endpoint (3 weeks, LOCF) was significantly higher for RISPERDAL® than for placebo in all studies.

Comparative Bioavailability Studies

Bioequivalence of Oral Formulations

Pharmacokinetic studies indicate that RISPERDAL® tablets and RISPERDAL® M-TAB® tablets are bioequivalent based on C_{max}, AUC_{last}, and AUC_{∞} measurements with respect to risperidone, 9-hydroxyrisperidone and risperidone and 9-hydroxyrisperidone combined. RISPERDAL® M-TAB® tablets can be used as an alternative to RISPERDAL® tablets.

RISPERDAL® M-TAB® orally disintegrating tablets and RISPERDAL® oral solution are bioequivalent to RISPERDAL® tablets.

DETAILED PHARMACOLOGY

RISPERDAL® (risperidone) represents a new generation of neuroleptic drugs combining potent serotonin type 2 (5-HT_2) and dopamine-D_2 antagonism.

In *in vitro* receptor binding assays, risperidone exhibited high binding affinity for the following receptor sites (K_i nM): 5-HT_2 (0.16), α_1-adrenergic (0.81), dopamine-D_2 (1.4), H_1-histaminergic (2.1), and α_2-adrenergic (7.5). Risperidone was inactive at muscarinic cholinergic receptor sites (K_i: >10,000 nM). Affinity for dopamine-D_2 binding sites in rat brain showed little regional variation and was comparable to the affinity for cloned human D_2 receptors.

Serotonin Antagonism

In rats, risperidone dose-dependently inhibited tryptamine-, mescaline-, 5-HTP-, and DOM (2,5-dimethoxy-4-methylamphetamine)-induced behavioural effects (ED_{50}: 0.014-0.049 mg/kg sc). Higher risperidone doses completely blocked the serotonin agonist-induced behavioural effects.

In drug discrimination studies, risperidone was a potent and selective antagonist of LSD and DOM (0.024-0.028 mg/kg sc), devoid of partial 5-HT_2 agonist activity and LSD-like abuse and dependence liability. Low doses of risperidone (0.01-0.16 mg/kg ip) increased deep slow wave sleep and decreased paradoxical sleep in rats.

Peripheral 5-HT_2 antagonism was reflected, at very low doses, in the antagonism of tryptamine-induced cyanosis in rats (ED_{50}: 0.0011 mg/kg sc) and serotonin-induced bronchospasm in guinea pigs (ED_{50}: 0.0027 mg/kg ip).

Dopamine-D_2 Antagonism

Risperidone dose-dependently antagonized apomorphine- and amphetamine-induced behavioural effects, namely apomorphine-induced climbing behaviour in mice (ED_{50}: 0.062 mg/kg ip), amphetamine-induced hyperactivity in rats (0.02-0.04 mg/kg), apomorphine-induced stereotypy in rats (ED_{50}: 3.2 mg/kg ip), and apomorphine-induced rotational behaviour in unilaterally 6-hydroxy-dopamine-lesioned mice (0.1-1.0 mg/kg dose range). Risperidone also reduced spontaneous locomotion (ED_{50}: 0.22 mg/kg sc) and conditioned avoidance responding (ED_{50}: 0.48 mg/kg ip) in rats and induced catalepsy in the 0.59-3.0 mg/kg (sc) dose range.

Risperidone increased the levels of the dopamine metabolites (DOPAC and HVA) in a dose-dependent manner in various brain regions.

In common with other neuroleptics, risperidone also produced effects that are related to blockade of peripheral dopamine-D_2 receptors. Risperidone was a potent antagonist of apomorphine-induced emesis in dogs (0.005-0.007 mg/kg following iv, sc, or po administration). After oral administration, the onset of action was rapid and the duration was 24 hours. *In vitro*, risperidone reversed dopamine-suppressed prolactin release in primary culture of rat anterior pituitary cells. *In vivo*, risperidone dose-dependently increased serum prolactin levels in rodents after single and repeated administration.

Combined 5-HT_2 and Dopamine-D_2 Antagonism

The combined 5-HT_2 and dopamine-D_2 antagonism of risperidone resulted in differences from specific dopamine-D_2 antagonists. Risperidone reduced both spontaneous and amphetamine-stimulated locomotor activity more gradually. Dopamine-D_2 receptor occupation and the extent of dopamine turnover potentiation varied according to brain region. Low doses of risperidone completely blocked 5-HTP-induced head twitches and discrimination stimulus effects of the hallucinogenic serotonin agonists DOM and LSD. Disinhibitory effects in amphetamine-treated rats were seen over a much wider dose range. Risperidone increased social interaction time. A sequential tryptamine-apomorphine challenge was more readily controlled.

Interaction with Histamine-H_1 and α-Adrenergic Receptors

Blockade of peripheral histamine-H_1 receptors by risperidone was evidenced by protection from compound 48/80-induced lethality in rats (ED_{50}: 0.014 mg/kg sc) although the very potent 5-HT_2 antagonism of risperidone might have contributed to this activity. Risperidone antagonized histamine-induced bronchospasm in guinea pigs (ED_{50}: 0.037 mg/kg ip).

Risperidone also blocked α_1-adrenoceptors as indicated by protection from norepinephrine-induced lethality in rats (ED_{50}: 0.074 mg/kg sc) and induction of palpebral ptosis (ED_{50}: 0.19 mg/kg sc).

Blockade of central α_2-adrenoceptors was found at 2.4 mg/kg in the xylazine test. Reversal of the antidiarrheal effect of clonidine at 0.67 mg/kg reflected blockade of peripheral α_2-adrenoceptors.

Cardiovascular effects, such as hypotension and reflex tachycardia observed in dogs, are considered to be predominantly consequences of vascular α_1-adrenoceptor blockade. These effects diminished or disappeared during chronic treatment, indicating the development of tachyphylaxis.

In anaesthetized mongrel dogs, risperidone produced dose-dependent vasodilation accompanied by an increase in cardiac contractility, aortic blood flow and cardiac output. The minimal effective dose (0.005 mg/kg) was similar to the antiemetic dose.

In conscious Labrador dogs, a single oral dose of 0.08 mg/kg (11 times the oral antiemetic dose) reduced systolic and diastolic pressure but did not affect heart rate. After a single oral dose of 0.31 mg/kg (44 times the oral antiemetic dose), the blood pressure lowering effect became more pronounced, heart rate increased and QT_c interval became prolonged but PQ and QRS intervals remained essentially uninfluenced.

Drug Interactions

After repeated administration of oral doses up to 10 mg/kg/day, risperidone did not interact *in vivo* with liver drug-metabolizing enzymes (cytochrome P-450, glucuronosyltransferase, and cytochrome c-reductase) that are known to be generally involved in the metabolism of drugs.

Pharmacology of the 9-Hydroxy Metabolite

Risperidone is predominantly metabolized to its 9-hydroxy derivative. This metabolite and its 2 enantiomers were comparable in potency, onset and duration of action, oral activity and pharmacological profile to risperidone.

TOXICOLOGY

Acute Toxicity

Table 2.1: LD_{50} values for risperidone, 14 days after administration

Route	Species	Number and Sex of Animals	LD_{50} in mg/kg (limits)
ORAL	Mice	90M	82 (73-92)
		90F	63 (56-71)
	Rats	60M	113 (82-157)
		60F	57 (39-83)
	Dogs	32M&F	18 (14-24)
		2M	>10
INTRAVENOUS	Mice	60M	30 (26-33)
		70F	27 (23-31)
	Rats	70M	34 (31-38)
		70F	35 (32-39)
	Dogs	20M	14 (11-18)
		20F	18 (14-24)
SUBCUTANEOUS	Rats	60M	172 (132-225)
		60F	98 (59-162)

Toxicity was manifested by symptoms such as palpebral ptosis, prostration, catalepsy, sedation, hypothermia, and hypotonia at all doses, and clonic convulsions and loss of righting reflex at near lethal and lethal doses.

Occasionally, signs of gastrointestinal disturbance were present. Autopsy occasionally revealed gastric lesions and bleeding in rodents. All survivors recovered within the 14-day observation period.

The acute oral toxicity of 9-hydroxyrisperidone in rats was similar to that of the parent drug.

Subacute Toxicity

Oral Toxicity Study in Wistar Rats (3 months)

Groups of 20 male and 20 female Wistar rats were administered risperidone in the diet at doses of approximately 0, 0.63, 2.5 or 10 mg/100 g food/day. There was no drug-related mortality or effects on behaviour and physical appearance. There was an increase in body weight gain in females (low- and mid-dosed groups), a temporary and transient decrease in body weight gain in males (mid-dosed group), and a persistent decreased body weight gain in both high-dosed groups.

The following changes were observed in serum biochemistry: decreased aspartate aminotransferase in high-dosed males and mid- and high-dosed females; increased cholinesterase in high-dosed males.

In females the weight of the adrenals was decreased. In high-dosed males, the weight of the adrenals was increased and the weight of the kidneys was decreased. The major histological findings at autopsy included stimulation of the mammary gland (mid- and high-dosed male and all treated female rats), decreased glandular development of the uterus with decreased vaginal cornification and epithelial thickness, and inflammatory cell infiltration in the prostate (mid and high doses).

Oral Toxicity in Wistar Rats (3 months + 1 month recovery)
Groups of 10 male and 10 female Wistar rats (complemented with 5 male and 5 female rats in the control group and high-dosed group for a 1-month recovery period) were administered risperidone by gavage at 0 (vehicle), 0.16, 0.63, 2.5 and 10 mg/kg body weight/day. There was no drug-related mortality. The findings were qualitatively similar to those observed in the 3-month study using the dietary route of administration.

Laboratory examination revealed the following changes: a slight increase in hematocrit, hemoglobin and red blood cells (within the normal range); a slight increase, at the borderline of normal limits, in blood urea nitrogen in both males and females at 2.5 and 10 mg/kg body weight; a slight decrease in glucose (females at 10 mg/kg body weight), total protein (males and females at 10 mg/kg body weight), calcium, albumin and triglycerides (mostly within the normal range) at 10 mg/kg body weight in males. Urinalysis showed a slight decrease in specific gravity and creatinine in male and female rats dosed at 2.5 and 10 mg/kg body weight; a slightly increased pH (males and females dosed at 10 mg/kg body weight) and volume (males and females dosed at 2.5 and 10 mg/kg body weight); and increased appearance of bacteria at 10 mg/kg body weight (males and females).

Gross and histopathological examination displayed prolactin-dependent changes similar to those seen in the 3-month study, consisting of mammary gland stimulation, changes in the prostate, and uterine and vaginal changes.

After 1 month of recovery, most of the changes showed reversibility. Mammary gland stimulation was still present in the high-dosed animals.

Oral Toxicity in Beagle Dogs (3 months)
Groups of 4 male and 4 female Beagle dogs were administered risperidone orally in gelatin capsules at 0 (untreated), 0.31, 1.25 and 5 mg/kg body weight/day. All animals survived the 3-month study. Adverse clinical signs included dose-related sedation, miosis, soft faeces and congested conjunctiva. There was a transient decrease of body weight gain in high-dosed dogs during the first half of the study.

Hematological and serum analysis revealed: dose-dependent decrease of hematocrit, hemoglobin and red blood cells (within normal range) in medium- and high-dosed dogs; a dose-related moderate increase in haptoglobin (within the normal range) at all doses; and an increase of cholesterol and phospholipids at the medium and high doses.

Testicular and prostate weights decreased in a dose-related manner. Gross and histopathological examination revealed: increased presence of red blood cells in the spleen red pulp of the high-dosed group; decreased glandular development of the uterus and reduced epithelial thickness of the vagina in all dosed females; an immature aspect of the prostate and incomplete spermatogenesis in mid- and high-dosed male dogs.

Oral Toxicity in Beagle Dogs (3 months + 2 months recovery)
Groups of 6 male Beagle dogs were administered risperidone orally in capsules at 0 (untreated), 0.31, 1.25 and 5 mg/kg body weight/day. Four dogs/group were sacrificed after 3 months and the remaining 2 after 5 months. There was no drug-related mortality and findings were similar to those of the first 3-month study. A dose-related sedation and an initial body weight decrease at all doses were present.

Male dogs were studied in order to establish the effects of risperidone upon male genitalia and assess their reversibility.

Erythrocytic parameters decreased in a dose-related manner; the changes were reversible. Haptoglobin, cholesterol and phospholipid levels increased dose-dependently; the changes were reversible.

At the end of the treatment period only 2 low-dosed dogs ejaculated; at the end of the recovery period 2 low-dosed dogs were normal, 1 out of 2 medium-dosed dogs ejaculated normal sperm and 1 out of 2 high-dosed dogs ejaculated poor quality sperm (reduced sperm motility and concentration). At the end of the treatment period, testosterone levels were dose-dependently reduced. At the end of the recovery period, the levels were still reduced in the 2 high-dosed dogs.

Prostate and testicle weights were dose-dependently decreased and associated with immaturity. At the end of the recovery period, prostate weights remained slightly lower than in control animals. Dose-related increases in liver and spleen weights were reversible.

Chronic Toxicity
Oral Toxicity Study in Wistar Rats (12 months)
Groups of 20 male and 20 female Wistar rats were administered risperidone in the diet at doses of approximately 0, 0.63, 2.5 and 10 mg/100 g food/day. Doses expressed as mg/kg were lower. There was no drug-related mortality. High-dose males and females exhibited decreased weight gain. At 2.5 mg/kg, serum analysis revealed slightly decreased potassium and blood urea nitrogen levels and a slight increase in cholinesterase (within normal limits) in males; and decreased alanine aminotransferase level in females.

In addition to the changed serum variables seen at 2.5 mg/kg, dosing at 10 mg/kg resulted in a markedly decreased body weight gain; and a marginally reduced number of white blood cells and thrombocytes, decreased glucose, decreased urine creatinine and increased urine volume (within normal limits) in males, and decreased glucose, total protein and albumin in females. Most changes were slight.

Histopathology indicated changes in the prostate and mammary glands of medium- and high-dosed males and in the uterus, ovaries and mammary glands of all treated females. Medium- and high-dosed males showed diffuse hyperplasia of the pituitary, and in high-dosed males, the zona fasciculata of the adrenals was increased.

Oral Toxicity Study in Beagle Dogs (12 months)
Groups of 4 male and 4 female Beagle dogs were administered risperidone orally via gelatin capsules at doses of 0 (untreated), 0.31, 1.25 and 5 mg/kg body weight/day. All animals survived the 12-month study. At the low dose, the main effects were related to the expected pharmacological action of risperidone, i.e., sedation and an interaction with the endocrine system (male and female genital tract changes). Mid and high dosing produced a slight to moderate toxicity that is similar to that described in the 3-month studies.

Laboratory examination revealed slight anemia during the first 3 months (decreased hematocrit, hemoglobin and red blood cells); dose-dependent moderate increase of haptoglobin, cholesterol and phospholipids; and a slight decrease of potassium (high-dosed group).

Organ weight changes included increases in spleen and pituitary weight and decreases in the weight of testes and prostate. Histopathology examination showed changes in the male and female genital tract, namely prostatic changes (fibrosis and clear basal cells), degenerative changes in the testicles of some dogs, decreased glandular development of the uterus, and the absence of corpora lutea. In addition, an increased number of red blood cells were seen in the spleen.

Reproductive and Developmental Toxicology
Fertility and General Reproductive Performance in Wistar Rats
One hundred and ninety-two Wistar rats were divided into groups of 24 males and 24 females. Risperidone, at approximately 0, 0.31, 1.25 or 5 mg/kg body weight/day was administered orally through the diet to males for a minimum of 60 days prior to and during mating. Females were dosed for a minimum of 14 days prior to mating (with equivalently dosed males) and further during the first part of pregnancy up to day 8. No drug- or dose-related mortalities occurred.

Paternal and maternal effects were responsible for dose-dependent decreased and delayed mating behaviour (all doses), manifested by lower copulation indices, which caused lower pregnancy rates in rats receiving risperidone. However, where copulation occurred, the pregnancy rates were normal.

Fertility Study in Male Wistar Rats

One hundred and ninety-two Wistar rats were divided into groups of 24 males and 24 females. Risperidone, 0 (vehicle), 0.16, 0.63 and 2.5 mg/kg body weight/day was administered by gavage to male rats 60 days prior to and during mating to untreated female rats. No drug-related mortality occurred.

Fertility, gestation and copulation indices and the cohabitation-mating interval were comparable between groups. Litter data were comparable between groups and no teratogenic effects were present. These findings indicate no adverse effects on male fertility.

Fertility Study in Female Wistar Rats

One hundred and forty-four Wistar rats were divided into groups of 12 males and 24 females. Risperidone, 0 (vehicle), 0.16, 0.63 or 2.5 mg/kg body weight/day was administered by gavage to female rats from 14 days prior to mating (with untreated male rats) up to day 8 of pregnancy. All animals survived the study. A dose-related sedation was present in the medium- and high-dosed groups.

The cohabitation-mating interval was slightly increased in the low- and medium-dosed groups. The interval was clearly prolonged in the high-dosed group. However, the number of corpora lutea was not affected indicating a normal ovulation rate once ovulation occurred.

Fertility, copulation and pregnancy indices were comparable between groups, and in pregnant females, no adverse effects were observed in the offspring. No teratogenic effects were found.

Embryotoxicity and Teratogenicity Study in Sprague-Dawley Rats

Two Segment II studies were conducted in Sprague-Dawley rats. Groups of 24 female rats received risperidone 0 (vehicle), 0.63, 2.5 or 10 mg/kg body weight/day by gavage from day 6 through day 16 of pregnancy. There was no drug-related mortality.

The weights of the pups of the high-dosed group slightly decreased in one of the studies. Risperidone was not teratogenic at the doses studied.

Embryotoxicity and Teratogenicity Study in Wistar Rats

Groups of 36 female rats were administered risperidone 0 (vehicle), 0.63, 2.5 or 10 mg/kg body weight/day by gavage from day 8 through day 18 of pregnancy. Twelve females per group were allowed to deliver naturally, followed by an evaluation of the second generation, whereas the others were sacrificed at the end of the pregnancy period following a Caesarean section. There was no drug-related mortality. Dose-related sedation was present at all dosage levels.

In the low- and medium-dosage groups no adverse effects on the litter were present. In the high dosage group, there was maternal toxicity (decreased weight gain) associated with decreased pup weight and slightly delayed ossification (reduced number of visible metatarsal bones). During the lactation period, pup weights were slightly increased and survival rates were normal. Risperidone was not teratogenic at the doses studied.

In the undosed second generation, physical and behavioural development was comparable between groups and no adverse effects on fertility or on other reproduction parameters were observed.

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 risperidone therapy is unknown (see **WARNINGS AND PRECAUTIONS - Special Populations**).

Embryotoxicity and Teratogenicity Study in New Zealand White Rabbits
Groups of 15 female rabbits were administered risperidone at 0 (vehicle), 0.31, 1.25 or 5 mg/kg/day by gavage from day 6 through day 18 of pregnancy. Maternal toxicity was evidenced in the high dosage group by the death of 3 dams and by reduced body weight gain. At the doses studied, no embryotoxicity or teratogenic effects were seen.

Perinatal and Postnatal Study in Wistar Rats
Groups of 24 female Wistar rats were administered risperidone orally through the diet, at approximately 0, 0.31, 1.25 or 5 mg/100 g food/day from day 16 of pregnancy through a 3-week lactation period. There was no drug-related mortality. Both body weight and food consumption decreased at all dose levels during lactation in a dose-dependent way. Duration of gestation was normal in all groups.

The survival rate of pups was decreased in the high-dosed group with only 32% surviving. On day 4 of lactation, the body weight of pups in the high-dosed group was significantly less than that of controls.

Perinatal and Postnatal Study in Wistar Rats (with Second Generation Evaluation)
Groups of 24 female Wistar rats were administered risperidone 0 (vehicle), 0.16, 0.63 or 2.5 mg/kg body weight/day by gavage from day 18 of pregnancy through a 3-week lactation period. All females were allowed to deliver naturally. No drug-related mortality was noted. Maternal adverse effects were evidenced by a small but significant increase in duration of gestation and by decreased food consumption and weight gain during lactation in the high-dosed dams.

An increased number of stillborn pups was observed in the high-dosed group and survival was reduced at all doses probably due to decreased nursing.

In the non-dosed second generation (F_1), 10 females/group were mated with males from the same group. Pups were delivered by Caesarean section. There were no adverse effects on fertility or on other reproductive parameters. Observation of pups of the F_2 generation indicated no abnormalities.

Two-Generation Reproduction Study
One hundred and ninety-two Wistar rats were divided into groups of 24 males and 24 females. Risperidone, at approximately 0, 0.16, 0.63 or 2.5 mg/100 g food/day was administered orally through the diet to males for 60 days prior to and during mating. Females were dosed for 14 days prior to mating (with equivalently dosed males), during pregnancy and lactation until weaning of the first generation. There was no dosing of the second generation. No drug-related mortalities occurred.

The cohabitation-mating interval increased with increasing dose levels. However, the duration of gestation was comparable between groups. Pregnancy and copulation indices decreased significantly in the high-dosed rats but all mated females became pregnant. During pregnancy, body weight gain decreased in the medium- and high-dosed females. Dosing during lactation resulted in a reduced body weight of the high-dosed dams. Teratogenic effects were not evidenced at any dose.

Litter data including litter size, weight at birth, weight gain, and survival rate were comparable between controls and low- and medium-dosed rats. In the high-dosed rats, birth weight and survival rate were slightly lowered. The latter was related to decreased nursing behaviour. After weaning, physical and behavioural development were unaffected.

In the non-dosed second generation, no relevant adverse effects on fertility or on other reproduction parameters were noted.

Juvenile Toxicity Studies in Rats and Dogs

In a toxicity study in juvenile rats treated with oral risperidone (0, 0.04, 0.16, 0.63 or 2.5/1.25 mg/kg/day), increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs treated with oral risperidone (0, 0.31, 0.125 or 5 mg/kg/day), sexual maturation was delayed. Based on AUC, long bone growth was not affected in dogs at 3.6-times the maximum human oral exposure in adolescents (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human oral exposure in adolescents.

Mutagenicity

Risperidone had no mutagenic effects when tested by the DNA-repair test in rat hepatocytes, the Ames reverse mutation test in *Salmonella typhimurium* and *Escherichia coli*, the mammalian cell gene mutation test in mouse lymphoma cells, the sex-linked recessive lethal test in *Drosophila melanogaster*, the chromosome aberration test in human lymphocytes and Chinese hamster lung cells, and the micronucleus test in the mouse bone marrow cells.

Carcinogenicity

Carcinogenicity Study in Albino Swiss Mice (18 months)

Four groups of 50 male and 50 female mice received risperidone orally through the diet, at doses of approximately 0, 0.63, 2.5 or 10 mg/kg body weight/day. A slightly increased mortality was present in medium- and high-dosed females. In female mice at all doses, body weight gain was increased.

Hematological (decreased erythrocytic parameters and an increase in platelets) and serum biochemical changes (decrease in glucose and increase in cholinesterase; and in females only increase in cholesterol, phospholipids, haptoglobin, total protein, calcium and albumin) were similar to those observed in rat chronic toxicity studies.

Organ weight changes included increases in liver, spleen and heart weight. The weight of gonads in both sexes and the weight of adrenals in females were decreased.

Gross and histopathological examination demonstrated an increased incidence of non-neoplastic,

prolactin-dependent changes in the accessory sex glands (coagulating gland, seminal vesicle), pancreas, and pituitary gland in the medium- and high-dosed males. In females, at all doses, the changes involved increased (mammary gland, pituitary gland), or decreased (female genital tract) prolactin-dependent modifications.

Neoplastic changes: there was a positive trend for mammary adenocarcinomas and pituitary gland adenomas in females. Regarding prolactin-independent neoplasia, there was a positive trend for lung tumours in female animals (the incidence was within the range of historical controls).

Carcinogenicity Study in Wistar Rats (25 months)

Four groups of 50 male and 50 female rats received risperidone orally through the diet at doses of approximately 0, 0.63, 2.5 or 10 mg/100 g food/day. Mortality was increased in medium- and high-dosed males, and high-dosed females. In males at all doses and in mid- and high-dosed females, toxicity was expressed by decreased body weight gain, deterioration in general condition (males) and some changes in hematological and biochemical parameters. Organ weight changes included increased adrenal and decreased gonad weights.

Macroscopically, changes were seen in the mammary and pituitary gland, testes and uterus. Histopathological examination revealed prolactin-mediated non-neoplastic changes in the mammary gland, the pituitary gland and in the male and female genital tract at all doses, as well as renal pathology.

Neoplastic changes included a dose-related increase in mammary gland adenocarcinoma in both males and females and an increase in pancreatic endocrine adenoma in males. Neoplasms of the female genital tract (vagina, cervix, uterus) were decreased.

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PART III: CONSUMER INFORMATION

PrRISPERDAL®*
risperidone tablets
risperidone tartrate oral solution
PrRISPERDAL®* M-TAB®*
risperidone orally disintegrating tablets

This leaflet is Part III of a three-part "Product Monograph" published when RISPERDAL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RISPERDAL®. Contact your doctor or pharmacist if you have any questions about the drug.

If you are a caregiver helping someone to take RISPERDAL®, read this leaflet before you give the first dose.

ABOUT THIS MEDICATION

What the medication is used for:
RISPERDAL® belongs to a group of medicines called antipsychotic drugs.

Use in Schizophrenia
RISPERDAL® is used to treat the symptoms of schizophrenia and related psychotic disorders, which may include hallucinations (hearing or seeing things that are not there), delusions, unusual suspiciousness, emotional withdrawal. Patients suffering from schizophrenia may also feel depressed, anxious or tense.

Use in Inappropriate Behaviour Associated with Severe Dementia
RISPERDAL® may also be used for the short-term symptomatic management of behavioural disturbances such as verbal aggression (e.g., screaming, cursing) or physical aggression (e.g., kicking, hitting, biting, scratching, throwing things), as well as unusual suspiciousness and agitation in patients with severe dementia.

Use in Acute Mania Associated with Bipolar Disorder
RISPERDAL® may be used for the acute treatment of manic episodes associated with bipolar disorder. Signs and symptoms of bipolar mania include but are not limited to: feeling invincible or all powerful, inflated self-esteem, racing thoughts, easily lose your train of thought, overreaction to what you see or hear, misinterpretation of events, speeded-up activity, talking very quickly, talking too loudly, or talking more than usual, decreased need for sleep, and poor judgment.

The doctor has prescribed RISPERDAL® to help relieve the symptoms that are bothering you / the patient you are caring for. Although RISPERDAL® cannot cure the illness, it can keep the symptoms under control and reduce the risk of relapse as you / the patient you are caring for continues treatment.

What it does:
Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how RISPERDAL® works is unknown. However it seems to readjust the balance of dopamine and serotonin.

When it should not be used:
Do not take / give RISPERDAL® if an allergic reaction to the medicine or any of the nonmedicinal ingredients of the product has occurred.

Symptoms of an allergic reaction may include: itching, skin rash, swelling of the face, lips or tongue, shortness of breath. **If you experience any of these symptoms / if these symptoms are experienced by the patient you are caring for, your doctor / the treating physician should be contacted immediately.**

The safety and efficacy of RISPERDAL® in children under the age of 18 have not been established.

What the medicinal ingredient is:
risperidone

What the nonmedicinal ingredients are:
RISPERDAL® tablets: All tablets contain the following nonmedicinal ingredients: lactose, cornstarch, microcrystalline cellulose, hydroxypropyl methylcellulose, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulphate and propylene glycol. In addition, all tablet strengths except the 1 mg contain talc and titanium dioxide. The 0.25 mg tablets also contain yellow ferric oxide. The 0.5 mg tablets also contain red ferric oxide. The 2 mg tablets also contain FD & C Yellow #6 Aluminum Lake. The 3 mg tablets also contain D & C Yellow #10. The 4 mg tablets also contain D & C Yellow #10, FD & C Blue #2 Aluminum Lake.

RISPERDAL® oral solution: tartaric acid, benzoic acid, sodium hydroxide and purified water.

RISPERDAL® M-TAB® orally disintegrating tablets: All tablets contain the following nonmedicinal ingredients: polacrilex resin, gelatin, mannitol, glycine, simethicone, carbomer 934P, sodium hydroxide, aspartame, red ferric oxide and peppermint oil. The 2 mg tablets manufactured from 2006 onwards and the 3 and 4 mg tablets also contain xanthan gum.

Phenylketonurics: RISPERDAL® M-TAB® contains aspartame, which may not be suitable for those who cannot have phenylalanine (see **WARNINGS AND PRECAUTIONS**).

What dosage forms it comes in:
RISPERDAL® tablets: 0.25, 0.5, 1, 2, 3 and 4 mg.
RISPERDAL® oral solution: 1 mg/mL.
RISPERDAL® M-TAB® orally disintegrating tablets: 0.5, 1, 2,

3 and 4 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Studies with various medicines of the group to which RISPERDAL® belongs, when used in elderly patients with dementia, have been associated with an increased rate of death. Some of these studies included treatment with RISPERDAL®.

BEFORE you use RISPERDAL®, talk to your doctor or pharmacist if you / the patient you are caring for:

- have/has a history of stroke, mini-strokes, high cholesterol or high blood pressure;
- have/has diabetes or a family history of diabetes;
- are/is pregnant or planning to become pregnant;
- are/is breast-feeding;
- have/has ever had blackouts or seizures;
- have/has a history of kidney or liver problems;
- have/has a history of problems with the heart and/or blood vessels;
- are/is prone to hypotension;
- have/has Parkinson's disease;
- are/is taking or planning to take any other medicines (prescription or over-the-counter medicines);
- drink/drinks alcoholic beverages or use/uses drugs;
- cannot take phenylalanine because RISPERDAL® M-TAB® tablets contain aspartame, a source of phenylalanine;
- have/has or have had/has had breast cancer;
- have/has pituitary tumours;
- suffer/suffers from Alzheimer's Disease;
- suffer/suffers from Lewy body dementia;
- are/is dehydrated;
- exercise/exercises strenuously.

Elderly Patients with Dementia

Studies in elderly patients with dementia have shown that RISPERDAL® taken by itself or with furosemide is associated with a higher rate of death (see **Serious Warnings and Precautions Box**).

Tell your doctor if you are taking furosemide. Furosemide is a drug which is sometimes used to treat high blood pressure, some heart problems, or to treat swelling of parts of the body caused by the build-up of too much fluid.

In elderly patients with dementia, a sudden change in mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, or instances of slurred speech have been seen. If any of these should occur, even for a short period of time, seek medical attention right away.

If you are taking blood pressure medication
Low blood pressure can result from using RISPERDAL® together with medications used to treat high blood pressure. If you need to use both RISPERDAL® and medications used to reduce blood pressure, consult your doctor.

If you may be pregnant
Shaking, muscle stiffness and difficulty in feeding, all of which are reversible, may occur in newborns, if a mother used RISPERDAL® in the last trimester of her pregnancy.

Other cautions
Very rarely, a state of confusion, reduced consciousness, high fever or stiff muscles might occur. If this should happen, contact a doctor right away and tell him or her that you are receiving RISPERDAL®.

During long-term treatment, RISPERDAL® might cause involuntary twitching in the face. Should this happen, consult your doctor.

Since medications of this type may interfere with the ability of the body to adjust to heat, it is best to avoid becoming overheated or dehydrated (for example with vigorous exercise or exposure to extreme heat) while taking RISPERDAL®.

RISPERDAL® should be used with caution, and only after consultation with your doctor, if you have heart problems, particularly irregular heart rhythm, abnormalities in electrical activity of the heart, or if using medications that can change the heart's electrical activity.

Because some people experience drowsiness, you should not drive or operate machinery until you are reasonably certain that RISPERDAL® does not affect your ability to carry out these activities.

It is important for the doctor to have all the above information before prescribing treatment and dosage. This list should be carefully reviewed by you / the caregiver and discussed with the doctor.

INTERACTIONS WITH THIS MEDICATION

Inform all doctors, dentists and pharmacists who are treating you that you are taking RISPERDAL®.

Inform them if you are taking or are planning on taking any other medicine. They will tell you which medicines you can take with RISPERDAL®.

RISPERDAL® can increase the effect of alcohol and drugs that reduce the ability to react (e.g., "tranquillizers", narcotic painkillers, certain antihistamines, certain antidepressants). It is recommended that you DO NOT drink alcohol and only take drugs prescribed by your doctor.

Inform your doctor if you start or stop taking any of the following medications:

- Dopamine agonists, e.g. levodopa (antiparkinsonian agent), as these may decrease the effect of RISPERDAL®.

- Phenothiazines and some heart medications (e.g., medication for high blood pressure, antiarrhythmics, or β-blockers), as these may interact with RISPERDAL® to cause your blood pressure to drop too low.

- RISPERDAL® should be used with caution when taking medications that may change the electrical activity of the heart, such as but not restricted to: medicines for malaria, heart rhythm disorders, allergies, other antipsychotics, antidepressants, water tablets or other medicines affecting body salts (sodium, potassium, magnesium).

- Carbamazepine and topiramate (anticonvulsants), as these may change the effect of RISPERDAL®.

- PROZAC® (fluoxetine), PAXIL® (paroxetine) (antidepressants) and CLOZARIL® (clozapine), as these may increase the level of RISPERDAL® in your blood.

- LASIX® (furosemide): Studies in elderly patients with dementia have shown that taking RISPERDAL® with furosemide, a drug which is sometimes used to treat high blood pressure, some heart problems, or to treat swelling of parts of the body caused by the build-up of too much fluid, is associated with an increased rate of death (see **WARNINGS AND PRECAUTIONS**).

RISPERDAL® oral solution is not compatible with cola or tea.

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take / give RISPERDAL® the way the doctor has prescribed it.
- The doctor has decided on the best dosage for you / the patient you are caring for based on individual needs. Dosage may be increased or decreased depending on the response.
- You may take / give RISPERDAL® together with meals or between meals. Once a regular dose has been established, the total amount can be taken once a day, or divided into two intakes, one in the morning and one in the evening.
- Try to take / give RISPERDAL® at the same time each day.
- **RISPERDAL® tablets** should be swallowed with some water or other liquid.
- Before taking / giving **RISPERDAL® oral solution**, read the "Directions for Use of RISPERDAL® Oral Solution". Be sure to mix the exact dose of RISPERDAL® oral solution that the doctor has prescribed in 100 mL of one of the following beverages: water, coffee, orange juice or low-fat milk; DO NOT MIX it in cola or tea.
- It is important that you keep taking / giving RISPERDAL® even after your / the symptoms have improved or disappeared. Do not change or stop taking / giving RISPERDAL® without consulting the doctor.
- Before taking / giving **RISPERDAL® M-TAB® tablets**, read the "Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets" for opening the blister and handling the tablet.

DO NOT give RISPERDAL® to anyone else. The doctor has prescribed it for you / the patient you are caring for.

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

1. Do not open the blister until ready to administer. Peel open the blister to expose the tablet. Do not push the tablet through the foil because it is fragile and may break. Remove the tablet from the blister with dry hands. Do not break or divide the tablets.
2. Immediately place the tablet on your tongue. The tablet will begin disintegrating within seconds and can then be swallowed. Water may be used if desired.

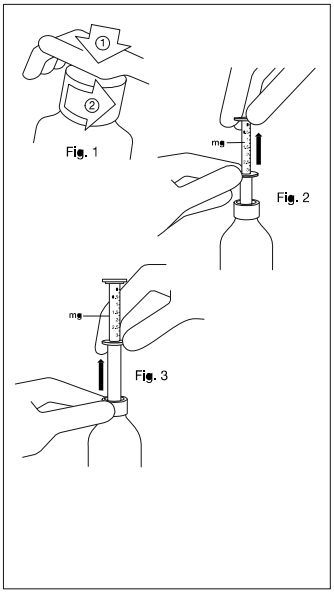
Directions for Use of RISPERDAL® Oral Solution

To open the bottle and use the pipette:

Fig. 1: The bottle comes with a child-proof cap, and should be opened as follows: push the plastic screw cap down while turning it counter-clockwise. Remove the unscrewed cap.

Fig. 2: Insert the pipette into the bottle. While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of millilitres or milligrams you need to give.

Fig. 3: Holding the bottom ring, remove the entire pipette from the bottle. Empty the pipette into at least 100 mL (3-4 ounces) of any non-alcoholic drink (see list below), by sliding the upper ring down. Stir the mixture thoroughly before consuming.



RISPERDAL® oral solution is compatible with the following beverages: water, coffee, orange juice and low-fat milk. However, it is NOT compatible with cola or tea. Close the bottle and rinse the pipette with some water.

Overdose:

In overdose, one or more of the following signs may occur: reduced consciousness, sleepiness, excessive trembling , excessive muscle stiffness, fast beating heart, dizziness or light-headedness when standing up.

If you take / give too much RISPERDAL®, immediately contact the doctor, regional Poison Control Centre, or go / take the patient to the nearest hospital emergency department. Do this even if there are no signs of discomfort or poisoning.

Make sure to bring your medication bottle with you.

Missed Dose:
If you miss a dose, try not to miss any more. DO NOT TAKE / GIVE TWO DOSES AT ONCE.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, RISPERDAL® can cause some side effects. Some side effects are minor and temporary; however, some may be serious and need medical attention. Many of the side effects are dose related, so it is important not to exceed your prescribed dose. Should you experience these symptoms, please consult your doctor.

In patients with schizophrenia, the most common side effects of RISPERDAL® include the following:

- sleeplessness / sleepiness
- anxiety
- trembling, decreased motor function or activity such as slight muscle stiffness
- a feeling of restlessness (akathisia)
- dizziness
- headache
- runny nose
- constipation
- weight gain
- increased heart rate

In severely demented patients, the most common side effects of RISPERDAL® include the following:

- sleepiness
- trembling, decreased motor function or activity such as slight muscle stiffness
- a feeling of restlessness (akathisia)
- swelling of the ankles
- runny nose
- dizziness, lightheadedness
- difficulty breathing
- increased heart rate

In patients with bipolar disorder, the most common side effects of RISPERDAL® were:

- sleeplessness / sleepiness
- trembling, decreased motor function or activity such as slight muscle stiffness
- dizziness
- headache
- constipation
- anxiety
- weight gain
- nausea
- heartburn
- increased salivation

RISPERDAL® may cause sudden dizziness or lightheadedness (symptoms of postural hypotension). You / the patient you are caring for should not rise rapidly after having been sitting or lying for prolonged periods, especially when you start taking RISPERDAL®.

In addition, the following undesired effects may occur in some cases: agitation, headache, dizziness.

In women, medicines of this type may cause changes in the regularity of their monthly period or leakage of milk from the breast even if they are not pregnant. In some men, after prolonged treatment, there may be some diminished sexual function and breast enlargement may be experienced.

In rare cases, the following may happen: tiredness, concentration difficulties, blurred vision, indigestion, nausea, vomiting, abdominal pain, some loss of urine, and low blood sugar.

High blood sugar, diabetes mellitus and sugar in the urine have been reported. See your doctor if you experience symptoms such as excessive thirst or urination.

Do not be alarmed by this list of possible side effects. You may not experience any of them. If any of these side effects are experienced, they are usually mild and temporary. However, do not hesitate to report any undesired side effects to your doctor.

If you have taken RISPERDAL® in the last three months of your pregnancy and you notice that your newborn baby develops shaking, muscle stiffness and difficulty in feeding, contact your doctor immediately. These symptoms can be reversible.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY OCCUR AND WHAT TO DO ABOUT THEM

Symptom / effect	Call your doctor or pharmacist		Stop taking drug and seek immediate medical emergency help
	Only if severe	In all cases	
Common			
Skin rash on its own		✓	
Uncommon			
Seizure (i.e. loss of consciousness with uncontrollable shaking)			✓
Rare			

Symptoms of allergic reaction, such as itching, skin rash, swelling of the face, lips, or tongue, or shortness of breath.			✓
Very Rare			
A state of confusion, reduced consciousness, high fever, or pronounced muscle stiffness.			✓
Marked changes in body temperature (generally as a result of several factors together including extreme heat or cold).			✓
Long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Muscle twitching or abnormal movements of the face or tongue		✓	
Sudden change in mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, slurred speech or vision problems, even for a short period of time			✓

This is not a complete list of side effects. For any unexpected effects while taking RISPERDAL®, contact your doctor or pharmacist.

HOW TO STORE IT

Store RISPERDAL® in its original package.

RISPERDAL® tablets and RISPERDAL® M-TAB® orally disintegrating tablets should be stored between 15 - 30 °C. Protect from light and moisture.

RISPERDAL® oral solution should be stored between 15 - 30°C. Protect from light and freezing.

Keep RISPERDAL® out of the reach of children.

The expiry date for RISPERDAL® is printed on the package. Do not use the medicine in the package after this date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at:
http://www.janssen.ca
or by contacting the sponsor, Janssen Inc., at:
1-800-567-3331

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