RISPERDAL®

DESCRIPTION

Tablets:

Each tablet contains 1 mg or 2 mg of risperidone.

Oral Solution:

The oral solution contains 1 mg/ml risperidone.

Excipients

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Tablets:

Film-coated tablets for oral use:

- 1 mg risperidone as white half-scored oblong biconvex tablets;

- 2 mg risperidone as orange half-scored oblong biconvex tablets;

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Oral Solution:

The oral solution contains 1 mg/ml risperidone.

CLINICAL PARTICULARS

Therapeutic Indications

RISPERDAL® TABLET (1MG & 2MG) AND RISPERDAL® ORAL SOLUTION 1MG/ML

RISPERDAL® is indicated for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. RISPERDAL® alleviates affective symptoms (such as depression, guilt

feelings, anxiety) associated with schizophrenia. RISPERDAL® is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

RISPERDAL® is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

RISPERDAL® TABLETS (1MG) AND RISPERDAL® ORAL SOLUTION 1MG/ML

RISPERDAL® is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

DOSAGE AND ADMINISTRATION

Schizophrenia

Switching from other antipsychotics.

When medically appropriate, gradual discontinuation of the previous treatment while RISPERDAL® therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medications should be re-evaluated periodically.

Adults

RISPERDAL® may be given once daily or twice daily.

Patients should start with 2 mg/day RISPERDAL®. The dosage may be increased on the second day to 4 mg. From then on, the dosage can be maintained unchanged, or further individualized, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms. Since the safety of doses above 16 mg/day has not been evaluated, doses above this level should not be used.

A benzodiazepine may be added to RISPERDAL® when additional sedation is required.

Elderly (65 years of age and older)

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

Children

Risperidone is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.

Manic episodes in bipolar disorder

Adults

RISPERDAL® should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimise each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.

As with all symptomatic treatments, the continued use of RISPERDAL® must be evaluated and justified on an ongoing basis.

Elderly

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.

Paediatric population

Risperidone is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.

Conduct disorder

Children and adolescents from 5 to 18 years of age

For subjects ≥ 50 kg, a starting dose of 0.5 mg of oral solution once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The oral solution is the recommended pharmaceutical form to administer 0.5 mg. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily. For subjects < 50 kg, a starting dose of 0.25 mg of oral solution once daily is recommended. The oral solution is the recommended pharmaceutical form to administer 0.25 mg. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients.

Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg of oral solution once daily. The oral solution is the recommended pharmaceutical form to administer 0.75 mg.

As with all symptomatic treatments, the continued use of RISPERDAL® must be evaluated and justified on an ongoing basis.

RISPERDAL® is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

RISPERDAL® should be used with caution in these groups of patients.

CONTRAINDICATIONS

RISPERDAL® is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS AND PRECAUTIONS

Elderly patients with dementia

Overall mortality

Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including RISPERDAL®. In 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. The mean age (range) of patients who died was 86 years (range 67 - 100).

Concomitant use with furosemide

In the RISPERDAL® 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) or furosemide alone (4.1%; mean age 80 years, range 67 - 90). 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 (CAE)

In placebo-controlled trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, (cerebrovascular accidents and transient ischemic attacks), including fatalities, in patients treated with RISPERDAL® compared to patients receiving placebo (mean age 85 years; range 73 - 97).

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. RISPERDAL® should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see Dosage and Administration). A dose reduction should be considered if hypotension occurs.

Leucopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including RISPERDAL®. Agranulocytosis has been reported very rarely (< 1/10000 patients) during post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored 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 < 1 x 10^9/L) should discontinue RISPERDAL® and have their WBC followed until recovery.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for

VTE should be identified before and during treatment with RISPERDAL® and preventive measures undertaken.

Tardive dyskinesia/extrapyramidal symptoms (TD/ EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because RISPERDAL® has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

Extrapyramidal symptoms and psychostimulants - Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered (see Interactions).

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotic drugs, including RISPERDAL®, should be discontinued.

Parkinson's Disease and Dementia with Lewy Bodies

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, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycemia and diabetes mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. 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 events in patients treated with the atypical antipsychotics, Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

Weight gain

Significant weight gain has been reported. Monitoring weight gain is advisable when RISPERDAL® is being used.

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.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with RISPERDAL® during postmarketing surveillance (see Adverse Reactions).

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing RISPERDAL® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Seizures

As with other antipsychotic drugs, RISPERDAL® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including RISPERDAL® (see Adverse Reactions).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Other

See Dosage and Administration – Schizophrenia - Elderly for specific posology recommendations for elderly patients, Dosage and Administration – Conduct and other disruptive behavior disorders for pediatric patients with conduct and other disruptive behavior disorders, and Dosage and Administration – Renal and Hepatic Impairment for patients with renal or hepatic impairment.

INTERACTIONS

Pharmacodynamic-related interactions

Centrally-acting drugs and alcohol
Given the primary CNS effects of RISPERDAL®, it should be used with caution in combination with other centrally acting drugs or alcohol.

Levodopa and dopamine agonists
RISPERDAL® may antagonize the effect of levodopa and other dopamine agonists.

Psychostimulants
The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see Warnings and Precautions).

Drugs with hypotensive effects
Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

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

Pharmacokinetic-related interactions

Food does not affect the absorption of RISPERDAL®.

Risperidone is mainly metabolized through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors
Co-administration of RISPERDAL® with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). When concomitant paroxetine or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®.

CYP3A4 and/or P-gp inhibitors
Coadministration of RISPERDAL® with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®.

CYP3A4 and/or P-gp inducers
Co-administration of RISPERDAL® with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®.

Highly protein-bound drugs
When RISPERDAL® is taken together with highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosages.

Pediatric population
Interaction studies have only been performed in adults. The relevance of the results from these studies in pediatric patients is unknown.

Examples
Examples of drugs that may potentially interact or that were shown not to interact with risperidone are listed below:

Antibacterials:
- Erythromycin, a moderate CYP3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.
- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

- Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics:

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxy-risperidone.

Antipsychotics:

- Phenothiazines, may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.
- Aripiprazole, a CYP2D6 and CYP3A4 substrate: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Antivirals:

- Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Beta-Blockers:

- Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium Channel Blockers:

- Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active antipsychotic fraction.

Digitalis Glycosides:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Diuretics:

- Furosemide: See section Warnings and Precautions regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Gastrointestinal Drugs:

- H_2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

Lithium:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

SSRIs and Tricyclic Antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.
- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

PREGNANCY AND BREAST-FEEDING

Pregnancy and Lactation

The safety of risperidone for use during human pregnancy has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non-clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed.

Neonates exposed to antipsychotic drugs (including RISPERDAL®) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while is some cases symptoms

have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

RISPERDAL® should only be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

RISPERDAL® may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of risperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with risperidone cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of RISPERDAL® was evaluated from a clinical trial database consisting of 9803 patients exposed to one or more doses of RISPERDAL® for the treatment of various psychiatric disorders in adults, elderly patients with dementia, and pediatrics. Of these 9803 patients, 2687 were patients who received RISPERDAL® while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with RISPERDAL® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures.

The majority of all adverse reactions were mild to moderate in severity.

Double-blind, placebo-controlled data – Adult patients

Adverse reactions reported by ≥ 1% of RISPERDAL®-treated adult patients in nine 3- to 8-week double-blind, placebo-controlled trials are shown in Table 1.

Table 1: Adverse Reactions Reported by ≥ 1% of RISPERDAL®-Treated Adult Patients in Double-Blind Placebo-Controlled Studies

System/Organ Class Adverse Reaction	**RISPERDAL® ≤ 8 mg/day (N = 853) %**	**RISPERDAL® > 8 - 16 mg/day (N = 198) %**	**PLACEBO (N = 687) %**
Infections and Infestations			
Nasopharyngitis	2.1	4.0	1.7
Upper respiratory tract infection	1.5	2.5	1.5
Sinusitis	0.7	1.5	0.6
Urinary tract infection	0.5	2.5	0.1
Blood and Lymphatic System Disorders			
Anemia	0.1	1.0	0.1
Immune System Disorders			
Hypersensitivity	0.1	1.0	0.1
Psychiatric Disorders			
Insomnia	16.2	25.3	13.2
Anxiety	7.7	11.1	4.4
Nervousness	0.5	1.0	0.1
Nervous System Disorders			
Parkinsonism*	19.3	17.2	7.9
Akathisia*	9.8	10.1	2.7
Somnolence	6.8	1.5	2.0
Dizziness	6.3	3.5	3.9
Sedation	4.6	3.0	1.3
Tremor*	4.2	2.5	2.5
Dystonia*	3.8	3.5	1.0
Lethargy	2.6	0	1.3
Dizziness postural	1.2	0	0.1
Dyskinesia*	1.2	2.0	0.9
Syncope	0.4	1.0	0
Eye Disorders			
Vision blurred	2.1	1.0	0.7
Ear and Labyrinth Disorders			
Ear pain	0.1	1.0	0.3
Cardiac Disorders			
Tachycardia	1.1	2.5	0.1
Vascular Disorders			
Orthostatic hypotension	1.3	0.5	0.1
Hypotension	0.2	1.0	0.3
Respiratory, Thoracic and Mediastinal Disorders			
Nasal congestion	2.0	6.1	1.3
Dyspnea	0.8	2.0	0
Epistaxis	0.5	1.5	0.1
Sinus congestion	0.5	1.0	0.6
Gastrointestinal Disorders			
Nausea	6.4	4.0	2.6
Constipation	4.6	9.1	3.6
Dyspepsia	4.3	6.1	2.6

Vomiting	3.9	4.5	3.8
Diarrhea	2.3	0.5	1.9
Salivary hypersecretion	2.3	1.0	0.4
Dry mouth	2.1	0	1.0
Abdominal discomfort	1.5	1.0	0.9
Abdominal pain	1.1	0.5	0.7
Stomach discomfort	1.1	1.0	0.6
Abdominal pain upper	0.7	1.0	0.1
Skin and Subcutaneous Tissue Disorders			
Rash	0.8	3.5	0.9
Dry skin	0.5	2.5	0.3
Dandruff	0.2	1.0	0
Seborrheic dermatitis	0.2	1.0	0
Hyperkeratosis	0	1.0	0.3
Musculoskeletal and Connective Tissue Disorders			
Back pain	2.5	1.0	1.6
Arthralgia	1.5	2.5	0.6
Pain in extremity	1.2	1.0	2.2
Renal and Urinary Disorders			
Urinary incontinence	0.2	1.0	0.3
Reproductive System and Breast Disorders			
Ejaculation failure	0.4	1.0	0
General Disorders			
Fatigue	2.3	1.0	1.0
Asthenia	1.3	0.5	0.6
Pyrexia	1.3	1.0	0.7
Chest pain	0.8	1.5	0.4
Investigations			
Blood creatine phosphokinase increased	0.4	1.5	0.1
Heart rate increased	0.2	1.5	0.1

* Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, Parkinsonism, cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson's disease. Akathisia includes akathisia and restlessness. Dystonia includes dystonia, muscle spasms, muscle contractions involuntary, muscle contracture, oculogyration, tongue paralysis. Tremor includes tremor and Parkinsonian rest tremor. Dyskinesia includes dyskinesia, muscle twitching, chorea, and choreoathetosis.

Double-blind, Placebo-controlled data – Elderly patients with dementia

Adverse reactions reported by ≥ 1% of RISPERDAL®-treated elderly patients with dementia in six 4- to 12-week double-blind, placebo-controlled trials are shown in Table 2. Table 2 includes only those adverse reactions that are either not listed in Table 1 or those adverse reactions that occurred at ≥ 2 times the frequency of the adverse reactions listed in Table 1.

Table 2: Adverse Reactions Reported by ≥ 1% of RISPERDAL®-Treated Elderly Patients with Dementia in Double-Blind Placebo-Controlled Studies: Adverse Reactions Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of Adverse Reactions Listed in Table 1.		
System/Organ Class Adverse Reaction	**RISPERDAL®** **(N = 1009)** **%**	**PLACEBO** **(N = 712)** **%**
Infections and Infestations		
Urinary tract infection	12.9	10.3
Pneumonia	3.1	2.4
Cellulitis	1.1	1.3
Metabolism and Nutrition Disorders		
Decreased appetite	2.3	1.4
Psychiatric Disorders		
Confusional state	2.7	0.1
Nervous System Disorders		
Lethargy	7.6	2.2
Transient ischemic attack	1.6	0.6
Depressed level of consciousness	1.3	0.3
Drooling	1.3	0
Cerebrovascular accident	1.1	0.4
Eye Disorders		
Conjunctivitis	2.7	1.1
Vascular Disorders		
Hypotension	2.2	1.4
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4.6	3.1
Rhinorrhea	1.5	0.8
Gastrointestinal Disorders		
Dysphagia	1.5	1.3
Fecaloma	1.1	0.4
Skin and Subcutaneous Tissue Disorders		
Erythema	4.0	4.6
Musculoskeletal and Connective Tissue Disorders		
Posture abnormal	1.8	0.8
Joint swelling	1.5	0.3
General Disorders		
Edema peripheral	7.7	3.9
Pyrexia	4.0	1.8
Gait disturbance	3.5	1.5
Pitting edema	1.5	0.3
Investigations		
Body temperature increased	2.6	0.8

Double-blind, placebo-controlled data – Pediatric patients

Adverse reactions reported by ≥ 1% of RISPERDAL®-treated pediatric patients in eight 3- to 8-week double-blind, placebo-controlled trials are shown in Table 3. Table 3 includes only those adverse reactions

that are either not listed in Table 1 or those adverse reactions that occurred at ≥ 2 times the frequency of the adverse reactions listed in Table 1.

Table 3: Adverse Reactions Reported by ≥ 1% of RISPERDAL®-Treated Pediatric Patients in Double-Blind Placebo-Controlled Studies: Adverse Reactions Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of Adverse Reactions Listed in Table 1.			
System/Organ Class Adverse Reaction	**RISPERDAL® ≤ 3 mg/day (N = 344) %**	**RISPERDAL® > 3 - 6 mg/day (N = 95) %**	**PLACEBO (N = 349) %**
Infections and Infestations			
Upper respiratory tract infection	5.2	2.1	3.4
Rhinitis	3.5	1.1	3.2
Influenza	1.7	0	1.7
Metabolism and Nutrition Disorders			
Increased appetite	17.2	3.2	7.2
Psychiatric Disorders			
Middle insomnia	1.7	0	0.9
Listless	0.9	1.1	0
Nervous System Disorders			
Somnolence	26.5	15.8	7.7
Headache	22.4	21.1	14.9
Sedation	20.1	14.7	4.0
Dizziness	8.1	13.7	2.3
Tremor	6.1	8.4	1.1
Drooling	4.9	2.1	1.1
Dysarthria	1.5	1.1	0
Disturbance in attention	0.9	1.1	0.6
Balance disorder	0.9	1.1	0
Hypersomnia	0.6	1.1	0.9
Cardiac Disorders			
Palpitations	0.6	2.1	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	8.7	3.2	6.6
Rhinorrhea	4.9	2.1	3.4
Epistaxis	3.8	4.2	1.7
Pharyngolaryngeal pain	3.8	2.1	1.7
Pulmonary congestion	0.3	1.1	0.3
Gastrointestinal Disorders			
Vomiting	13.7	8.4	9.2
Abdominal pain upper	8.4	6.3	4.6
Diarrhea	6.7	2.1	6.0
Salivary hypersecretion	3.5	6.3	0.9
Stomach discomfort	2.9	0	1.4
Abdominal pain	2.3	2.1	0.6
Skin and Subcutaneous Tissue Disorders			
Pruritus	1.2	0	0

Acne	0.9	1.1	0
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1.2	1.1	0.9
Neck pain	0.3	1.1	0.3
Renal and Urinary Disorders			
Enuresis	6.4	1.1	5.2
Urinary incontinence	2.0	0	1.4
Pollakiuria	1.5	1.1	0.3
Reproductive System and Breast Disorders			
Galactorrhea	0.6	2.1	0
General Disorders			
Fatigue	19.2	18.9	4.9
Pyrexia	8.4	3.2	6.3
Feeling abnormal	1.2	0	0
Sluggishness	0.9	1.1	0
Chest discomfort	0.3	1.1	0
Investigations			
Weight increased	4.9	2.1	0.9
Blood prolactin increased	3.8	0	0.3

Other clinical trial data

Paliperidone is the active metabolite of risperidone, therefore the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. This subsection includes additional adverse reactions reported with risperidone and/or paliperidone in clinical trials. Adverse reactions reported with risperidone and/or paliperidone by ≥ 1% of RISPERDAL®-treated subjects in a pooled dataset of 23 double-blind, placebo-controlled pivotal studies (9 in adults, 6 in elderly patients with dementia, and 8 in pediatric patients) are shown in Table 4.

Table 4: Adverse Reactions Reported with Risperidone and/or Paliperidone by ≥1% of RISPERDAL® -treated Subjects in a Pooled Dataset of the 23 Double-blind, Placebo-controlled Pivotal Studies- 9 in Adults, 6 in Elderly Patients with Dementia, and 8 in Paediatric patients (The Terms within each System Organ Class are Sorted Alphabetically)

System/Organ Class
Adverse Reaction
Psychiatric disorders
Agitation, Insomnia*
Nervous system disorders
Akathisia*, Dyskinesia*, Dystonia*, Parkinsonism*
Vascular disorders
Hypertension
Musculoskeletal and connective tissue disorders
Musculoskeletal pain

Table 4: Adverse Reactions Reported with Risperidone and/or Paliperidone by ≥1% of RISPERDAL® -treated Subjects in a Pooled Dataset of the 23 Double-blind, Placebo-controlled Pivotal Studies- 9 in Adults, 6 in Elderly Patients with Dementia, and 8 in Paediatric patients (The Terms within each System Organ Class are Sorted Alphabetically)

System/Organ Class
Adverse Reaction
General disorders and administration site conditions
Gait abnormal, Edema*, Pain
Injury, poisoning and procedural complications
Fall

* **Insomnia includes:** initial insomnia, middle insomnia; **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; **Dystonia includes**: blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Parkinsonism includes:** akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness; **Edema includes:** generalised edema, edema peripheral, pitting edema.

Adverse reactions reported with risperidone and/or paliperidone by < 1% of RISPERDAL®-treated subjects in a pooled dataset of 23 double-blind, placebo-controlled pivotal studies (9 in adults, 6 in elderly patients with dementia, and 8 in paediatric patients) are shown in Table 5.

Table 5: Adverse Reactions Reported with Risperidone and/or Paliperidone by < 1% of RISPERDAL®-treated Subjects in a Pooled Dataset of 23 Double-blind, Placebo-controlled Pivotal Studies -9 in Adults, 6 in Elderly Patients with Dementia, and 8 in Paediatric patients. (The Terms within each System Organ Class are Sorted Alphabetically).

System/Organ Class Adverse Reaction
Infections and infestations Acarodermatitis, Bronchitis, Cystitis, Ear infection, Eye infection, Infection, Localised infection, Onychomycosis, Respiratory tract infection, Tonsillitis, Viral infection
Blood and lymphatic system disorders Eosinophil count increased, Hematocrit decreased, Neutropenia, White blood cell count decreased
Endocrine disorders Glucose urine present, Hyperprolactinemia
Metabolism and nutrition disorders Anorexia, Blood cholesterol increased, Blood triglycerides increased, Hyperglycemia, Polydipsia, Weight decreased
Psychiatric disorders Blunted affect, Depression, Libido decreased, Nightmare, Sleep disorder
Nervous system disorders Cerebrovascular disorder, Convulsion*, Coordination abnormal, Diabetic coma, Hypoesthesia, Loss of consciousness, Paresthesia, Psychomotor hyperactivity, Tardive dyskinesia, Unresponsive to stimuli
Eye disorders Dry eye, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperemia
Ear and labyrinth disorders Tinnitus, Vertigo
Cardiac disorders Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Sinus arrhythmia
Vascular disorders Flushing
Respiratory, thoracic and mediastinal disorders Dysphonia, Hyperventilation, Pneumonia aspiration, Rales, Respiratory disorder, Respiratory tract congestion, Wheezing
Gastrointestinal disorders Cheilitis, Fecal incontinence, Flatulence, Gastroenteritis, Swollen tongue, Toothache

Table 5: Adverse Reactions Reported with Risperidone and/or Paliperidone by < 1% of RISPERDAL®-treated Subjects in a Pooled Dataset of 23 Double-blind, Placebo-controlled Pivotal Studies -9 in Adults, 6 in Elderly Patients with Dementia, and 8 in Paediatric patients. (The Terms within each System Organ Class are Sorted Alphabetically).

System/Organ Class Adverse Reaction
Hepatobiliary disorders Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased
Skin and subcutaneous tissue disorders Eczema, Skin discoloration, Skin disorder, Skin lesion
Musculoskeletal and connective tissue disorders Joint stiffness, Muscular weakness, Rhabdomyolysis
Renal and urinary disorders Dysuria
Reproductive system and breast disorders Amenorrhea, Breast discharge, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge
General disorders and administration site conditions Body temperature decreased, Chills, Discomfort, Drug withdrawal syndrome, Face edema, Malaise, Peripheral coldness, Thirst
Injury, poisoning and procedural complications Procedural pain

***Convulsion includes:** Grand mal convulsion; **Menstrual disorder includes:** Menstruation irregular, Oligomenorrhea

Adverse reactions reported with risperidone and/or paliperidone in other clinical trials but not reported by RISPERDAL®-treated subjects in a pooled dataset of 23 double-blind, placebo-controlled pivotal studies are shown in Table 6.

Table 6:	**Adverse Reactions Reported with Risperidone and/or Paliperidone in Other Clinical Trials but Not Reported by RISPERDAL®-treated Subjects in a Pooled Dataset of 23 Double-blind, Placebo-controlled Pivotal Studies. (The Terms within each System Organ Class are Sorted Alphabetically)**
System/Organ Class	Adverse Reaction
Immune system disorders	Anaphylactic reaction
Metabolism and nutrition disorders	Hyperinsulinemia
Psychiatric disorders	Anorgasmia
Nervous system disorders	Head titubation, Neuroleptic malignant syndrome
Eye disorders	Eye movement disorder, Photophobia
Cardiac disorders	Postural orthostatic tachycardia syndrome
Gastrointestinal disorders	Intestinal obstruction
Skin and subcutaneous tissue disorders	Drug eruption, Urticaria
Reproductive system and breast disorders	Breast discomfort, Breast engorgement, Breast enlargement, Menstruation delayed
General disorders and administration site conditions	Induration

Postmarketing data

Adverse events first identified as adverse reactions during postmarketing experience with risperidone and/or paliperidone are included in Table 7. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000 and < 1/1,000
Very rare	< 1/10,000, including isolated reports
Unknown	Cannot be estimated from the available data

In Table 7, adverse reactions are presented by frequency category based on incidence in clinical trials, when known.

Table 7: Adverse Reactions Identified During Postmarketing Experience with Risperidone and/or Paliperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Risperidone	
Blood and Lymphatic Disorders	
Very rare	Agranulocytosis, Thrombocytopenia
Endocrine Disorders	
Very rare	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia, Water intoxication
Psychiatric Disorders	
Very rare	Catatonia, Mania, Somnambulism, Sleep-related eating disorder
Nervous System Disorders	
Very rare	Dysgeusia
Eye Disorders	
Not known	Floppy iris syndrome (intraoperative)
Cardiac Disorders	
Very rare	Atrial fibrillation
Vascular Disorders	
Very rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Sleep apnea syndrome[a]
Gastrointestinal Disorders	
Very rare	Pancreatitis, Ileus
Hepatobiliary Disorders	
Very rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Angioedema, Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and Urinary Disorders	
Very rare	Urinary retention
Pregnancy Puerperium and Perinatal Conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
Very rare	Priapism
General Disorders	
Very rare	Hypothermia

[a] Atypical antipsychotic drugs, such as risperidone have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients with who have a history of or are at risk for sleep apnea, Risperdal® should be prescribed with caution.

OVERDOSE

Symptoms and signs

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. 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.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08.

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. 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 than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacodynamic effects

Clinical efficacy

Manic episodes in bipolar disorder

The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in total Young Mania Rating Scale (YMRS) score at week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of ≥ 50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at week 12.

The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Pharmacokinetic Properties

RISPERDAL® oral solution are bio-equivalent to RISPERDAL® oral tablets.

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1 - 2 l/kg. In plasma, risperidone is bound to albumin and alpha$_1$-acid glycoprotein. The plasma protein binding of risperidone is 88%, that of 9-hydroxy-risperidone is 77%.

One week after administration, 70% of the dose is excreted in the urine and 14% in the feces. In urine, risperidone plus 9-hydroxy-risperidone represents 35 - 45% of the dose. The remainder is inactive metabolites.

Metabolism
Risperidone is metabolized by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation.

Elimination
After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Dose proportionality
Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4 - 5 days of dosing. Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Special populations
Renal and hepatic impairment:
A single-dose study showed higher active plasma concentrations and a reduced clearance of the active antipsychotic fraction by 30% in the elderly and 60% in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.

Pediatrics:
The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.

NON-CLINICAL INFORMATION

In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D_2-receptor blocking activity of risperidone. In a toxicity study with juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Long bone growth was not affected at a dose similar to the maximum human dose in adolescents (6 mg/day); effects were observed at a dose 4-fold (on an AUC basis) or 7-fold (on a mg/m^2 basis) the maximum human dose in adolescents.

All other safety data relevant to the prescriber have been included in the appropriate section.

PHARMACEUTICAL PARTICULARS

List of Excipients

Film-coated tablets:

Tablet core

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hypromellose 2910 15 mPa.s
Magnesium stearate
Colloidal anhydrous silica
Sodium lauryl sulfate

Film-coating

Hypromellose 2910 5 mPa.s
Propylene glycol
Titanium dioxide [(a)]
Talc [(a)]
Orange yellow S aluminum lake [(a)]

Oral solution:

Tartaric acid
Benzoic acid
Sodium hydroxide
Purified water

[(a)] Only in 2 mg oral tablets.

Incompatibilities

RISPERDAL® tablets: none.

RISPERDAL® oral solution: incompatible with tea.

Shelf Life

RISPERDAL® oral tablets:
3 years

RISPERDAL® oral solution:
3 years when protected from freezing
Opened container: 3 months when protected from freezing

Special Precautions For Storage

RISPERDAL® oral tablets should be stored below 30°C.

RISPERDAL® oral solution should be stored below 30°C and should be protected from freezing.

Keep out of sight and reach of children.

Nature and Contents of Container

Oral tablets:

PVC-PE-PVDC/Al blister consisting of aluminum foil 20 Tm with a 6 g/m² heat-seal coating and a trilayer foil PVC 200 Tm, LDPE 25 Tm, PVCD 90 g/m².

RISPERDAL® 1 and 2mg tablets are individually packaged in a blister card containing 10 tablets. Blisters are packed in a cardboard box (6 blisters per box).

Oral solution:

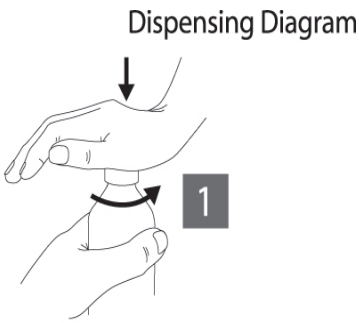
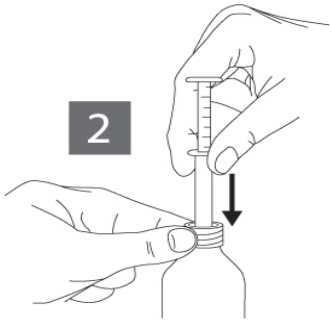
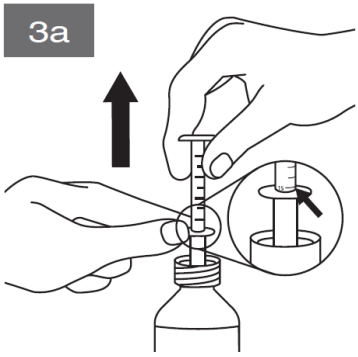
RISPERDAL® Oral Solution is provided in 30 ml and 100 ml amber glass bottles with plastic child resistant closures.

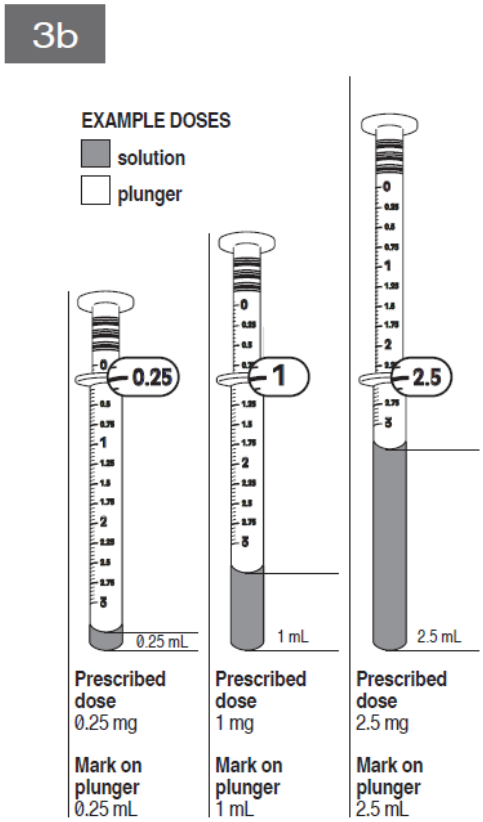
The pipette supplied with the 30 ml and 100 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.

Instructions For Use/Handling

Always take this medicine exactly as your healthcare provider has told you. Check with your healthcare provider if you are not sure.

The solution comes with a syringe (pipette). Use only the syringe (pipette) delivered with this medicine for measuring the dose prescribed by your physician.

Oral Solution Fig. 1: The bottle comes with a child-resistant 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.	
Fig. 3: While holding the bottom ring (Fig. 3a), pull the top ring up to the mark that corresponds to the number of milliliters or milligrams you need to give (See examples Fig. 3b).	

Measure the exact dose of medicine you need. Pay attention when measuring a small dose. For example, for 0.25 mg, measure 0.25 ml (a quarter milliliter); for 0.5 mg, measure 0.5 ml (half a milliliter). 1 ml of RISPERDAL® oral solution contains 1 mg risperidone. The measured volume is printed every 0.25 ml / 0.25 mg on the plunger. Fig. 3b shows **examples** of prescribed doses and corresponding marks on the plunger.	
Fig. 4: Holding the bottom ring, remove the entire pipette from the bottle. Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down. Close the bottle. Rinse the pipette with some water and let it air dry.	

MANUFACTURER

RISPERDAL® tablets:
Janssen-Cilag S.p.A
Via C. Janssen,
Borgo S. Michele, 04100 Latina, Italy

RISPERDAL® oral solution:
Janssen Pharmaceutica N.V.
Turnhoutseweg 30, B-2340 Beerse, Belgium

PRODUCT REGISTRATION HOLDER

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46150, Petaling Jaya, Selangor, Malaysia

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