RISPERDAL®

risperidone

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

RISPERDAL® 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg film-coated tablets

RISPERDAL® 1 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperdal film-coated tablets

Each film-coated tablet contains 0.5 mg, 1mg, 2 mg, 3 mg or 4 mg of risperidone.

Excipients with known effect:

Sugars as lactose. Each 0.5 mg, 1mg, 2 mg, 3 mg or 4 mg film-coated tablet contains 91 mg, 131 mg, 130 mg, 195 mg or 260 mg lactose monohydrate, respectively.

For the full list of excipients, see **section 6.1**.

Risperdal oral solution

1 ml oral solution contains 1 mg of risperidone

Excipients with known effect:

Benzoates.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets

0.5 mg: brownish-red, film-coated, biconvex, half-scored oblong tablets
(marked on the scored side with “Ris 0.5” and “JANSSEN” on the other side)

1 mg: white, film-coated, biconvex, half-scored, oblong tablets
(marked on the scored side with "Ris 1")

2 mg: orange, film-coated, biconvex, half-scored, oblong tablets
(marked on the scored side with "Ris 2")

3 mg: yellow, film-coated, biconvex, half-scored, oblong tablets
(marked on the scored side with "Ris 3")

4 mg: green, film-coated, biconvex, half-scored, oblong tablets
(marked on the scored side with "Ris 4")

Oral solution

1mg/mL: clear colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RISPERDAL is indicated for the treatment of schizophrenia and other psychotic disorders. These include 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 effect, emotional and social withdrawal, poverty of speech) are prominent.

RISPERDAL is also indicated for the treatment and long term control of mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self esteem, decreased need for sleep, pressured speech, racing thoughts, distractability, or poor judgement, including disruptive or aggressive behaviours.

RISPERDAL also alleviates affective symptoms (such as depression, guilt-feelings, anxiety) associated with schizophrenia. In addition, RISPERDAL also appears effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial response to treatment with this agent.

RISPERDAL is indicated for the treatment (up to 12 weeks) of agitation, aggression or psychotic symptoms in patients with moderate to severe dementia of the Alzheimer type.

RISPERDAL is also indicated for the treatment of conduct and other disruptive behaviour disorders in children (over 5 years), adolescents and adults with subaverage intellectual functioning or mental retardation, or average IQ, in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent. RISPERDAL is also effective in maintaining the clinical improvement during continuation therapy in children and adolescents who have shown an initial treatment response. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. Treatment with RISPERDAL for patients with disruptive behaviour disorders should be initiated only in consultation with a specialist, including child and adolescent psychiatrists, paediatric neurologists, developmental paediatricians, or other physicians conversant in the diagnosis and treatment of conduct and other disruptive behaviour disorders.

RISPERDAL is indicated for the treatment of autism in children and adolescents.

4.2 Dose and method of administration

RISPERDAL may be given as tablets or oral solution.

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 dose may be increased on the second day to 4 mg. From then on the dosage can be maintained unchanged, or further individualised, 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

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 - 2 mg twice daily.

RISPERDAL is well tolerated in the elderly.

Children

Experience is lacking in children aged less than 15 years.

Bipolar Mania

RISPERDAL should be administered on a once daily schedule, starting with 2mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1mg per day. A dosing range between 2 and 6mg per day is recommended. As with all symptomatic treatments, the continued use of RISPERDAL must be evaluated and justified on an ongoing basis.

Behavioural Disturbances in Patients with Dementia

A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

Once patients have reached their target dose, a once daily dosing regimen can be considered. As with all symptomatic treatments, the continued use of RISPERDAL must be evaluated and justified on an on-going basis.

Conduct and other disruptive behaviour disorders

For Subjects ≥ 50kg

A starting dose of 0.5mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5mg once daily not more frequently than every other day, if needed. The optimum dose is 1mg once daily for most patients. Some patients, however, may benefit from 0.5mg once daily while others may require 1.5mg once daily.

For Subjects <50kg

A starting dose of 0.25mg once daily is recommended, which can be individually adjusted by increments of 0.25mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5mg once daily for most patients, although some patients may benefit from 0.25mg once daily while others may require 0.75mg once daily.

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

Autism

RISPERDAL can be administered once or twice daily. Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime, or twice daily.

RISPERDAL should be administered based on body weight. Dosing should begin at 0.25 mg or 0.5 mg/day based upon weight (see table below for relative weight categories). On Day 4 of treatment, the dose may be increased up to 0.5 mg or 1.0mg/day. This dose should be maintained and response assessed at approximately day 14. Only in patients not achieving sufficient clinical response should additional dose increases be considered. Dose increases may proceed at ≥2-week intervals in increments of 0.25 mg for patients <20 kg or 0.5 mg for patients ≥20 kg. Based upon current studies, the maximum dose studied did not exceed a total daily dose of 1.5 mg in patients <20 kg, 2.5 mg in patients ≥20 kg and 3.5 mg in patients >45 kg. Doses below 0.25 mg/day were not effective in clinical studies.

The table of the maximum daily doses provides a reference for titration and dosing by weight based upon current studies, and may serve as a guide according to clinical need:

Doses of RISPERDAL in Paediatric Patients with Autistic Disorder				
Weight Categories	**Days 1 – 3**	**Days 4 – 14+**	**Increments if dose increases are needed**	**Dose Range**
			Dose by Weight in mg/day	
< 20 kg	0.25 mg	0.5 mg	+0.25 mg at ≥2 week intervals	0.5 mg-1.5 mg
≥ 20 kg	0.5 mg	1.0 mg	+0.5 mg at ≥2 week intervals	1.0 mg-2.5 mg*
			Dose Range in mg/kg/day	
			Increments if dose increases are needed	Dose Range
All	0.01 mg/kg/d	0.02 mg/kg/d	+0.01 mg/kg/day at ≥2 week intervals	0.02 mg/kg/d-0.06 mg/kg/d

* Subjects weighing >45 kg may require higher doses: maximum dose studied was 3.5 mg/day

Once sufficient response has been achieved and maintained consideration may be given to gradually lowering the dose to achieve optimum balance of effectiveness and tolerance.

Clinical experience was limited in autistic adolescents and in autistic children with an IQ>84 as not many of these patients were included in the trials.

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

Special populations

Renal and Hepatic Impairment

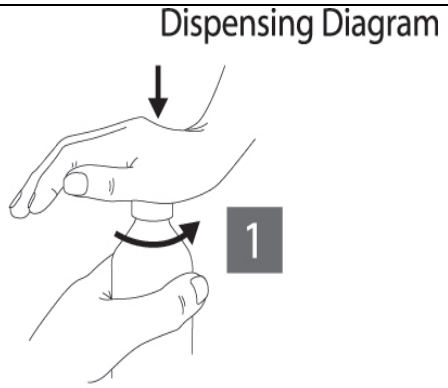
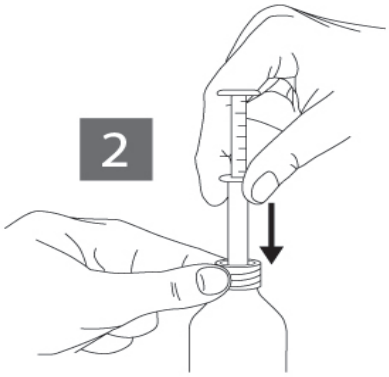
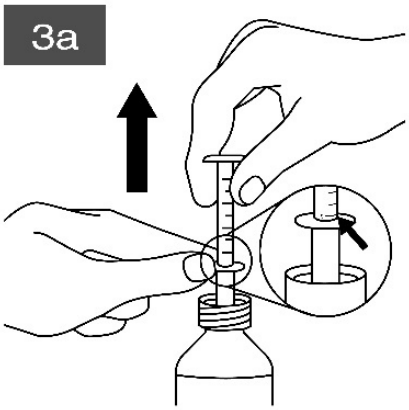
Patients with renal impairment have less ability to eliminate risperidone plus 9-hydroxy risperidone than normal adults. Patients with impaired hepatic function have increases in plasma concentration of unbound risperidone.

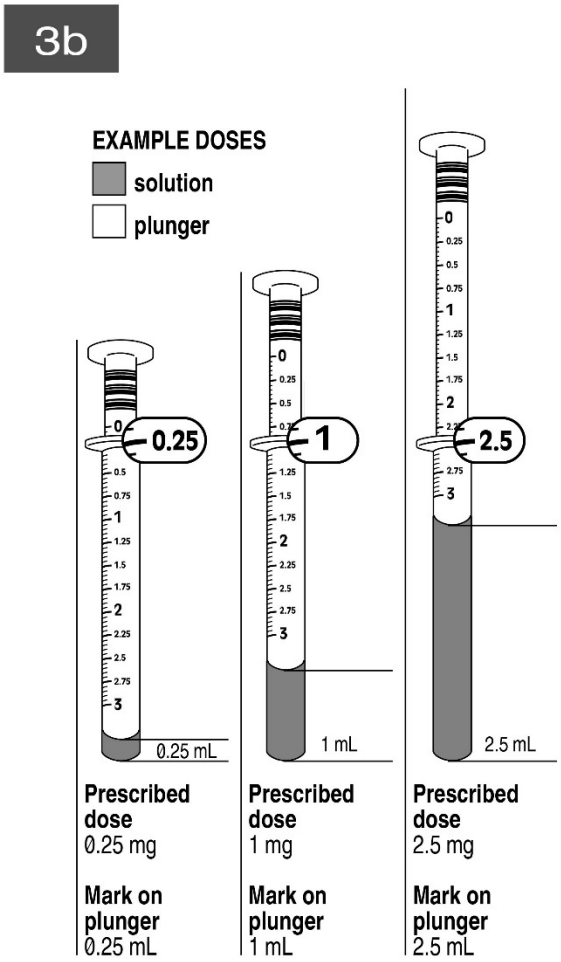
Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

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

Directions for opening the bottle and using the pipette for the oral solution:

The solution comes with a syringe (pipette). Use only the pipette that comes with RISPERDAL oral solution for measuring the dose prescribed. 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 millilitre); for 0.5 mg, measure 0.5 mL (half a millilitre).

Figure 1: The bottle comes with a child-resistant cap, and should be opened as follows: - Push the plastic screw cap down while turning it anti-clockwise. - Remove the unscrewed cap.	
Figure 2: Insert the pipette into the bottle.	
Figure 3: While holding the bottom ring (Figure 3a), pull the top ring up to the mark that corresponds to the number of millimetres or milligrams you need to give (See examples Figure 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 millilitre); for 0.5 mg, measure 0.5 mL (half a millilitre). 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. Figure 3b shows **examples** of prescribed doses and corresponding marks on the plunger.	
Figure 4: Holding the bottom ring, remove the entire pipette from the bottle. Empty the pipette into a non-alcoholic drink by sliding the upper ring down. Mineral water, orange juice, coffee and milk are suitable. Do not use tea. Close the bottle. Rinse the pipette with some cold water after use, let it air dry and store it in its case. Use of detergents or extensive rubbing with a cloth may increase the risk of fading or disappearing print.	

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings

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% (40/1009) for RISPERDAL treated patients compared to 3.1% (22/712) 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% [15/206]; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3,1% [25/803]; mean age 84 years, range 70-96) or furosemide alone (4.1% [5/121]; 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 clearly identified to explain this finding, and no consistent pattern for cause of death was 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 mortality among patients taking other diuretics concomitantly 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

In placebo-controlled trials in elderly patients with dementia, there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient ischaemic attacks in patients (mean age 85 years, range 73-97) treated with RISPERDAL compared with patients treated with placebo. The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular adverse events (serious and non-serious combined) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Precautions

Alpha blocking activity

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 (eg. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see **section 4.2**). A dose reduction should be considered if hypotension occurs. Special care should be taken in patients taking medications to lower blood pressure.

Tardive Dyskinesia

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised 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 classic neuroleptics, it should have a reduced risk of inducing tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic medicines should be considered.

Neuroleptic Malignant Syndrome

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

Parkinson's Disease and Dementia with Lewy Bodies

Physicians should weigh the risks versus 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.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycaemia 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 hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Leukopenia, Neutropenia, and Agranulocytosis

Events of leucopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including RISPERDAL. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during postmarketing 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.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with RISPERDAL during postmarketing surveillance.

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 tumour.

Seizures

As with other antipsychotic drugs, RISPERDAL should be used cautiously in patients with a history of seizures or other conditions that potentially lower 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 **section 4.8**).

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.

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.

Dysphagia

Oesophageal 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.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy. Prescriptions for RISPERDAL should

be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Akathisia

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Special Populations

Use in the elderly

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients.

Use in renal impairment

It is recommended to halve both the starting dose and the subsequent dose increments in patients with renal insufficiency.

Use in hepatic impairment

It is recommended to halve both the starting dose and the subsequent dose increments in patients with hepatic insufficiency.

Paediatric Use

RISPERDAL had no adverse effects on cognitive function in paediatric patients. In combined, long-term, open-label trials, mean changes in cognitive function tests were small and did not increase or decrease over time.

A mean increase of 7.5 kg after 12 months of RISPERDAL treatment was observed, somewhat higher than the expected weight gain (approximately 3 to 3.5 kg per year) for children predominantly between 5 and 12 years of age.

RISPERDAL treatment for up to 3 years showed no adverse effects on growth and sexual maturation. No differences were observed between risperidone and placebo groups in measurements of sexual maturation, using the Tanner scale, and no adverse events suggestive of delayed pubertal maturation were reported. The mean change in height after 1 year of treatment with risperidone was within the expected growth range in this population.

Experience of risperidone treatment in children with schizophrenia aged less than 15 years is lacking. Experience is lacking in children with conduct and other disruptive behaviour disorders aged less than 5 years. Experience is lacking in children with autism aged less than 5 years. However, 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.

4.5 Interactions with other medicines and other forms of interactions

Pharmacodynamic-related Interactions

Centrally-acting Drugs and Alcohol

Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally-acting medicines or alcohol.

Levodopa and Dopamine Agonists

Risperidone may antagonise the effects of levodopa and other dopamine agonists.

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

As with other antipsychotics, caution should be exercised when RISPERDAL is prescribed in combination with other medicines thought to prolong the QT interval or medicines known to cause electrolyte imbalance.

Pharmacokinetic-related Interactions

Food does not affect the absorption of RISPERDAL.

Risperidone is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxyrisperidone 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.

Paediatric 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 concentrations 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-hydroxyrisperidone.

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 4.4** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide and oral RISPERDAL.

Gastrointestinal Drugs:

- H2-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.

Sodium Channel Blockers:

- Quinidine may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

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.
- 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.
- 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 (see **section 5.2**).

4.6 Fertility, 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.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including RISPERDAL) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeling disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases neonates have required additional medical treatment or monitoring.

RISPERDAL should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 drug reactions (ADRs) 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 Drug 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			
Anaemia	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

System/Organ Class Adverse Reaction	RISPERDAL ≤8 mg/day (N=853) %	RISPERDAL >8-16 mg/day (N=198) %	PLACEBO (N=687) %
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
Dyspnoea	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
Diarrhoea	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
Seborrhoeic 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			

System/Organ Class Adverse Reaction	RISPERDAL ≤8 mg/day (N=853) %	RISPERDAL >8-16 mg/day (N=198) %	PLACEBO (N=687) %
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 drug reactions (ADRs) 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 ADRs that are either not listed in **Table 1** or those ADRs that occurred at ≥ 2 times the frequency of the ADRs listed in **Table 1**.

Table 2. Adverse Drug Reactions (ADRs) Reported by ≥ 1% of RISPERDAL-Treated Elderly Patients with Dementia in Double-Blind Placebo-Controlled Studies: ADRs Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of ADRs 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 ischaemic 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
Rhinorrhoea	1.5	0.8
Gastrointestinal Disorders		
Dysphagia	1.5	1.3
Faecaloma	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

System/Organ Class Adverse Reaction	RISPERDAL (N=1009) %	PLACEBO (N=712) %
Joint swelling	1.5	0.3
General Disorders		
Oedema peripheral	**7.7**	**3.9**
Pyrexia	4.0	1.8
Gait disturbance	3.5	1.5
Pitting oedema	1.5	0.3
Investigations		
Body temperature increased	2.6	0.8

Double-Blind, Placebo-Controlled Data – Pediatric Patients

Adverse drug reactions (ADRs) 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 ADRs that are either not listed in Table 1 or those ADRs that occurred at ≥ 2 times the frequency of the ADRs listed in **Table 1**.

Table 3. Adverse Drug Reactions (ADRs) Reported by ≥ 1% of RISPERDAL-Treated Pediatric Patients in Double-Blind Placebo-Controlled Studies: ADRs Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of ADRs 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
Rhinorrhoea	4.9	2.1	3.4

System/Organ Class Adverse Reaction	RISPERDAL ≤3 mg/day (N=344) %	RISPERDAL >3-6 mg/day (N=95) %	PLACEBO (N=349) %
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
Diarrhoea	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 ADRs reported with risperidone and/or paliperidone in clinical trials.

ADRs 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 4a**.

Table 4a. ADRs 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
General disorders and administration site conditions Gait abnormal, Oedema*, 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; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema.

ADRs 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 4b**.

Table 4b. ADRs 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, Haematocrit decreased, Neutropenia, White blood cell count decreased
Endocrine disorders Glucose urine present, Hyperprolactinaemia
Metabolism and nutrition disorders Anorexia, Blood cholesterol increased, Blood triglycerides increased, Hyperglycaemia, Polydipsia, Weight decreased
Psychiatric disorders Blunted affect, Depression, Libido decreased, Nightmare, Sleep disorder
Nervous system disorders Cerebrovascular disorder, Convulsion*, Coordination abnormal, Diabetic coma, Hypoaesthesia, Loss of consciousness, Paraesthesia, Psychomotor hyperactivity, Tardive dyskinesia, Unresponsive to stimuli
Eye disorders

System/Organ Class Adverse Reaction
Dry eye, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperaemia
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, Faecal incontinence, Flatulence, Gastroenteritis, Swollen tongue, Toothache
Hepatobiliary disorders Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased
Skin and subcutaneous tissue disorders Eczema, Skin discolouration, Skin disorder, Skin lesion
Musculoskeletal and connective tissue disorders Joint stiffness, Muscular weakness, Rhabdomyolysis
Renal and urinary disorders Dysuria
Reproductive system and breast disorders Amenorrhoea, Breast discharge, Ejaculation disorder, Erectile dysfunction, Gynaecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge
General disorders and administration site conditions Body temperature decreased, Chills, Discomfort, Drug withdrawal syndrome, Face oedema, Malaise, Peripheral coldness, Thirst
Injury, poisoning and procedural complications Procedural pain

ADRs 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 4c**.

Table 4c. ADRs 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 Hyperinsulinaemia
Psychiatric disorders Anorgasmia
Nervous system disorders Head titubation, Neuroleptic malignant syndrome

System/Organ Class Adverse Reaction
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

Class effects

QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics.

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with risperidone and/or paliperidone are included in Tables 5. The frequencies are provided according to the following convention:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000, including isolated reports

In **Table 5**, ADRs are presented by frequency category based on spontaneous reporting rate.

Table 5. Adverse Drug 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, Hypoglycaemia, Water intoxication
Psychiatric Disorders	
Very rare	Mania, Somnambulism
Not known	Sleep-related eating disorder
Nervous System Disorders	
Very rare	Dysgeusia
Eye Disorders	
Very rare	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 apnoea syndrome
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

There have also been reports of benign pituitary adenoma that were temporally related, but not necessarily causally related, to risperidone therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/**.**

4.9 Overdose

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of RISPERDAL. 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.

As strategies for the management of overdose are continually evolving, it is advisable to contact the Poisons Information Centre to determine the latest recommendations for the management of an overdose.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08

Mechanism of actions

Risperidone is a compound, which belongs to a new class of antipsychotic agents, the benzisoxazole derivatives.

Risperidone is a selective monoaminergic antagonist having 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-histamine and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy risperidone. Risperidone, as a potent D_2 antagonist, improves the positive symptoms of schizophrenia but 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.

5.2 Pharmacokinetic properties

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 RISPERDAL may be given with or without meals.

Risperidone is partly metabolised by CYP2D6 to 9-hydroxyrisperidone, which has similar pharmacological activity to risperidone. Another metabolic pathway is N-dealkylation.

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 risperidone plus 9-hydroxy risperidone is 24 hours.

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.

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%, while that of 9-hydroxy-risperidone is 77%.

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

A single-dose study showed higher active plasma concentrations and a reduced clearance of risperidone plus 9-hydroxy risperidone by 30% in the elderly and 60% in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the unbound risperidone in plasma was increased by about 35%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated Tablets

Colloidal silicon dioxide

Hypromellose

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Propylene glycol

Sodium laurilsulfate

The 0.5 mg tablet contains: purified talc, titanium dioxide and iron oxide red.

The 2 mg tablet contains: purified talc, titanium dioxide and sunset yellow FCF.

The 3 mg tablet contains: purified talc, titanium dioxide and quinoline yellow.

The 4 mg tablet contains: purified talc, titanium dioxide, quinoline yellow and indigo carmine.

Oral Solution

Tartaric acid

Benzoic acid

Sodium hydroxide

Purified water.

6.2 Incompatibilities

RISPERDAL tablets: none.

RISPERDAL oral solution: incompatible with tea.

6.3 Shelf Life

Film-coated Tablets

RISPERDAL 0.5 mg Tablets: 2 years.

RISPERDAL 1 mg, 2 mg, 3 mg and 4 mg Tablets: 3 years.

Oral Solution

RISPERDAL Oral Solution: 3 years.

6.4 Special precautions for storage

Film-coated Tablets

RISPERDAL 0.5 mg Tablets: Stored below 30°C. Store in a dry place. Protect from light.

RISPERDAL 1 mg, 2 mg, 3 mg and 4 mg Tablets: Stored below 25°C. Store in a dry place. Protect from light.

Oral Solution

RISPERDAL Oral Solution: Stored below 30°C. Do not refrigerate.

Keep out of reach of children.

6.5 Nature and contents of container

Film-coated Tablets

RISPERDAL 0.5 mg Tablets - blisters in a carton of 20.

RISPERDAL 1 mg, 2 mg, 3 mg and 4 mg Tablets - blisters in a carton of 60.

Oral Solution

RISPERDAL Oral Solution 1 mg/mL - 30 mL or 100 mL bottle with a pipette of 3 mL, calibrated in mg and mL. Minimum volume is 0.25 mL; maximum volume is 3 mL.

Not all presentations may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: **medinfo@janau.jnj.com**

9. DATE OF FIRST APPROVAL

Film-coated Tablets

RISPERDAL 0.5 mg Tablets – 9 December 1999

RISPERDAL 1 mg, 2 mg, 3 mg and 4 mg Tablets – 11 November 1993

Oral Solution

RISPERDAL Oral Solution 1 mg/mL – 31 October 1996

10. DATE OF REVISION OF THE TEXT

14 April 2025

Summary table of changes

Section changes	Summary of new information
3, 4.4	Minor editorial change
4.2	Additional dosing instructions and diagrams for oral solution
4.8	Change in reporting of suspected adverse reactions information
4.9	Addition of risk assessment wording