

DATA SHEET

NAME OF MEDICINE

RISPERDAL®

Risperidone

0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets

0.5 mg, 1 mg, 2 mg, 3 mg[^], 4 mg[^] Quicklet™ orally-disintegrating tablets

1 mg/mL oral solution

PRESENTATION

RISPERDAL is available as oral, film-coated tablets of the following strengths:

- | | |
|---------------------|---|
| 0.5 mg risperidone: | brownish-red, film-coated biconvex, half-scored oblong tablets
(marked on the grooved side with "Ris 0.5" and "JANSSEN" on the other side) |
| 1 mg risperidone: | white, film-coated, half-scored, oblong tablets
(marked on the grooved side with "Ris 1") |
| 2 mg risperidone: | orange, film-coated, half-scored, oblong tablets
(marked on the grooved side with "Ris 2") |
| 3 mg risperidone: | yellow, film-coated, half-scored, oblong tablets
(marked on the grooved side with "Ris 3") |
| 4 mg risperidone: | green, film-coated, half-scored, oblong tablets
(marked on the grooved side with "Ris 4") |

RISPERDAL is also available as a 1 mg/mL oral solution

RISPERDAL Quicklet is available as orally-disintegrating tablets of the following strengths:

- | | |
|--------------------------------|--|
| 0.5 mg risperidone: | round, light coral, biconvex, etched on one side with "R0.5" |
| 1 mg risperidone: | square, light coral, biconvex, etched on one side with "R1" |
| 2 mg risperidone: | Square, coral, biconvex, etched on one side with "R2" |
| 3 mg [^] risperidone: | Round, coral, biconvex, etched on one side with "R3" |
| 4 mg [^] risperidone: | Round, coral, biconvex, etched on one side with "R4" |

[^] indicates not marketed presentations.

USES

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 serotonergic 5-HT₂ and dopaminergic D₂ receptors. Risperidone binds also to alpha₁-adrenergic receptors and, with lower affinity, to H₁-histamine and alpha₂-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 D₂ 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.

Pharmacokinetics

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 alpha₁-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%.

Risperidone Quicklet tablets are bioequivalent to conventional risperidone tablets.

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 affect, 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, distractibility, 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 also indicated for the treatment of behavioural and psychological symptoms of dementia such as aggressiveness (verbal outburst, physical violence), activity disturbance (agitation, wandering) or psychotic symptoms.

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.

DOSAGE AND 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 ≥ 50 kg

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.

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.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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 Frusemide

In the RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide 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 frusemide alone (4.1% [5/121]; mean age 80 years, range 67-90). The increase in mortality in patients treated with frusemide 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).

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.

Precautions

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 **DOSAGE AND ADMINISTRATION**). 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. In this event, all antipsychotic medicines, including RISPERDAL, should be discontinued.

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.

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.

Other Precautions

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

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.

Pregnancy and Lactation

The safety of RISPERDAL for use during human pregnancy has not been established. Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed. No teratogenic effect of risperidone was noted in any study.

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.

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/m² basis) the maximum human dose in adolescents.

ADVERSE EFFECTS

Clinical Trial Data

The safety of RISPERDAL was evaluated from a clinical trial database consisting of 9712 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 9712 patients, 2626 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 $\geq 1\%$ of RISPERDAL-treated adult patients in nine 3- to 8-week double-blind, placebo-controlled trials are shown in Table 1.

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
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			
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 $\geq 1\%$ 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 $\geq 1\%$ 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

Table 2. Adverse Drug Reactions (ADRs) Reported by $\geq 1\%$ 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) %
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 $\geq 1\%$ 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 $\geq 1\%$ 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
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

Adverse drug reactions (ADRs) reported in double-blind placebo-controlled clinical trials by < 1% of RISPERDAL-treated adult or pediatric patients, or elderly patients with dementia, or at any rate by RISPERDAL-treated patients in other studies, including double-blind, active-controlled and open-label studies are shown in Table 4.

Table 4. Adverse Drug Reactions Reported in Double-Blind Placebo-Controlled Clinical Trials by <1% of RISPERDAL-Treated Adult or Pediatric Patients, or Elderly Patients with Dementia, or at Any Rate by RISPERDAL-Treated Patients in Other Studies, Including Double-Blind, Active-Controlled and Open-Label Studies
<p>Infections and Infestations</p> <p>Ear infection, Viral infection, Pharyngitis, Tonsillitis, Bronchitis, Eye infection, Localised infection, Cystitis, Otitis media, Onychomycosis, Acarodermatitis, Bronchopneumonia, Respiratory tract infection , Tracheobronchitis, Otitis media chronic</p> <p>Blood and Lymphatic System Disorders</p> <p>Granulocytopenia, Neutropenia</p> <p>Immune System Disorders</p> <p>Drug hypersensitivity</p> <p>Endocrine Disorders</p> <p>Hyperprolactinemia</p> <p>Metabolism and Nutrition Disorders</p> <p>Polydipsia, Anorexia</p> <p>Psychiatric Disorders</p> <p>Agitation, Blunted affect, Sleep disorder, Libido decreased, Anorgasmia</p> <p>Nervous System Disorders</p> <p>Unresponsive to stimuli, Coordination abnormal, Loss of consciousness, Speech disorder, Hypoesthesia, Movement disorder, Tardive dyskinesia, Cerebral ischemia, Cerebrovascular disorder, Neuroleptic malignant syndrome, Diabetic coma, Head titubation</p> <p>Eye Disorders</p> <p>Ocular hyperemia, Eye discharge, Eye rolling, Eyelid edema, Eye swelling, Eyelid margin crusting, Dry eye, Lacrimation increased, Photophobia, Glaucoma, Visual acuity reduced</p> <p>Ear and Labyrinth Disorders</p> <p>Tinnitus</p> <p>Cardiac Disorders</p> <p>Sinus bradycardia, Sinus tachycardia, Palpitations, Atrioventricular block first degree, Bundle branch block left, Bundle branch block right, Atrioventricular block</p> <p>Vascular Disorders</p> <p>Flushing</p> <p>Respiratory, Thoracic, and Mediastinal Disorders</p> <p>Wheezing, Pneumonia aspiration, Dysphonia, Productive cough, Respiratory tract</p>

congestion, Rales, Respiratory disorder, Nasal edema, Hyperventilation

Gastrointestinal Disorders

Fecal incontinence, Gastritis, Lip swelling, Cheilitis, Aptyalism

Skin and Subcutaneous Tissue Disorders

Skin discoloration, Skin lesion, Skin disorder, Rash erythematous, Rash papular, Rash generalised, Rash maculo-papular

Musculoskeletal and Connective Tissue Disorders

Musculoskeletal chest pain, Joint stiffness, Muscular weakness, Rhabdomyolysis

Renal and Urinary Disorders

Dysuria

Reproductive System and Breast Disorders

Menstruation irregular, Amenorrhea, Gynecomastia, Vaginal discharge, Erectile dysfunction, Ejaculation disorder, Menstrual disorder, Breast enlargement, Sexual dysfunction, Retrograde ejaculation

General Disorders

Thirst, Influenza-like illness, Edema, Malaise, Face edema, Discomfort, Generalised edema, Chills, Peripheral coldness, Drug withdrawal syndrome, Adverse drug reaction

Investigations

Alanine aminotransferase increased, Electrocardiogram abnormal, Eosinophil count increased, Aspartate aminotransferase increased, White blood cell count decreased, Blood glucose increased, Hemoglobin decreased, Hematocrit decreased, Body temperature decreased, Blood pressure decreased, Transaminases increased

The following is a list of additional ADRs associated with risperidone that have been reported with RISPERDAL CONSTA, excluding those associated with the formulation or injection route of administration.

Infections and Infestations: Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess

Metabolism and nutrition disorders: Hyperglycaemia

Psychiatric Disorders: Depression, Initial insomnia

Nervous System Disorders: Paresthesia, Convulsion

Eye Disorders: Blepharospasm

Ear and Labyrinth Disorders: Vertigo

Cardiac Disorders: Bradycardia

Vascular Disorders: Hypertension

Gastrointestinal Disorders: Toothache, Tongue spasm

Skin and Subcutaneous Tissue Disorders: Eczema

Musculoskeletal, Connective Tissue, and Bone Disorders: Buttock pain

Reproductive System and Breast Disorders: Menstruation delayed, Ejaculation delayed
Oligomenorrhea, Breast discomfort

General Disorders: Pain, Gait abnormal

Investigations: Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Glucose urine present

Injury and Poisoning: Fall

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 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 by Frequency Category Estimated from Spontaneous Reporting Rates	
Blood and Lymphatic Disorders	
<i>Very rare</i>	Agranulocytosis
<i>Very rare</i>	Thrombocytopenia ^a
Immune System Disorders	
<i>Very rare</i>	Anaphylactic reaction
Endocrine Disorders	
<i>Very rare</i>	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
<i>Very rare</i>	Blood cholesterol increased, Blood triglycerides increased
<i>Very rare</i>	Diabetic ketoacidosis, Diabetes mellitus, Hypoglycaemia
<i>Very rare</i>	Water intoxication
Psychiatric Disorders	
<i>Very rare</i>	Mania
Nervous System Disorders	
<i>Very rare</i>	Dysgeusia
Cardiac Disorders	
<i>Very rare</i>	Atrial fibrillation
Respiratory, Thoracic, and Mediastinal Disorders	
<i>Very rare</i>	Sleep apnea syndrome
Gastrointestinal Disorders	
<i>Very rare</i>	Intestinal obstruction
<i>Very rare</i>	Pancreatitis
Hepatobiliary Disorders	
<i>Very rare</i>	Jaundice
Skin and Subcutaneous Tissue Disorders	

<i>Very rare</i>	Angioedema ^b
<i>Very rare</i>	Alopecia
Renal and Urinary Disorders	
<i>Very rare</i>	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
<i>Very rare</i>	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
<i>Very rare</i>	Priapism
General Disorders	
<i>Very rare</i>	Hypothermia
Investigations	
<i>Very rare</i>	Electrocardiogram QT prolonged ^c

^a Search terms included Thrombocytopenia, Platelet count decreased, Plateletcrit decreased, Platelet production decreased

^b Search terms included Angioneurotic oedema, C1 esterase deficiency acquired, Circumoral oedema, Eyelid edema, Face edema, Hereditary angioedema, Laryngeal oedema, Laryngotracheal oedema, Oculo-respiratory syndrome, Oedema mouth, Periorbital edema, Small bowel angioedema, Tongue oedema

^c Search terms included Electrocardiogram QT corrected interval prolonged, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Long QT syndrome congenital

INTERACTIONS

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

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

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

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.

Inhibitors of hepatic metabolism of risperidone.

Carbamazepine has been shown to decrease the plasma levels of risperidone plus 9-hydroxy risperidone. Similar effects may be observed with other CYP 3A4 hepatic enzyme inducers. When carbamazepine or other CYP 3A4 hepatic enzyme inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL..

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of risperidone plus 9-hydroxy risperidone. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL.

Topiramate modestly reduced the bioavailability of risperidone, but not that of risperidone plus 9-hydroxy risperidone. Therefore, this interaction is unlikely to be of clinical significance.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of risperidone plus 9-hydroxy risperidone. Amitriptyline does not affect the pharmacokinetics of risperidone or risperidone plus 9-hydroxy risperidone. Cimetidine and ranitidine increased the bioavailability of risperidone but only marginally that of risperidone plus 9-hydroxy risperidone.

Erythromycin, a CYP3A4 inhibitor, does not change the pharmacokinetics of risperidone and risperidone plus 9-hydroxy risperidone. The cholinesterase inhibitors galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and risperidone plus 9-hydroxy risperidone. When RISPERDAL is taken together with other highly protein-bound medicines, there is no clinically relevant displacement of either medicine from the plasma proteins.

RISPERDAL does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

See Precautions section (Elderly Patients with Dementia) regarding increased mortality in elderly dementia patients concomitantly receiving frusemide.

Food does not affect the absorption of RISPERDAL.

OVERDOSAGE

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.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

PHARMACEUTICAL PRECAUTIONS

Shelf Life

RISPERDAL 0.5 mg Tablets: 2 years when stored below 30°C.

RISPERDAL 1 mg, 2 mg, 3 mg and 4 mg Tablets: 3 years when stored below 25°C in a dry place and protected from light.

RISPERDAL Quicklet 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets: 2 years when stored below 30°C.

RISPERDAL Oral Solution should be stored below 30°C and should be protected from freezing. Keep out of reach of children.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

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.

RISPERDAL Quicklet 0.5 mg, 1 mg, 2 mg, 3 mg[^] and 4 mg[^] Tablets-blisters in a carton of 28.
RISPERDAL Oral Solution 1 mg/mL - bottle in 30 mL with a pipette of 3 mL, calibrated in mg and mL. Minimum volume is 0.25 mL; maximum volume is 3 mL.

[^] indicates not marketed presentations.

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