NAME OF THE MEDICINAL PRODUCT

Tradename

RISPERDAL®

International Non-Proprietary Name

Risperidone

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1, 2, 3, 4 or 6 mg of risperidone.
The oral solution contains 1 mg/ml risperidone.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Film-coated tablets for oral use:

- 1 mg risperidone as white half-scored oblong tablets (marked RIS 1);
- 2 mg risperidone as orange half-scored oblong tablets (marked RIS 2);
- 3 mg risperidone as yellow half-scored oblong tablets (marked RIS 3);
- 4 mg risperidone as green half-scored oblong tablets (marked RIS 4);
- 6 mg risperidone as yellow circular biconvex tablets (marked RIS 6).

Oral solution 1 mg/ml.

CLINICAL PARTICULARS

Therapeutic Indications

RISPERDAL® is indicated for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. RISPERDAL® alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. RISPERDAL® is also effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response.
RISPERDAL® is indicated for the treatment of manic episodes associated with bipolar disorders. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviors.
RISPERDAL® is indicated for the treatment of behavioral disturbances in patients with dementia in whom symptoms such as aggressiveness (verbal outbursts, physical violence), activity disturbances (agitation, wandering) or psychotic symptoms are prominent.
RISPERDAL® is indicated in the treatment of conduct and other disruptive behavior disorders where aggressive or other disruptive behaviors 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.

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

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

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

Elderly

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

Adolescents

A starting dose of 0.5 mg daily is recommended, administered as a single-daily dose either in the morning or evening. If indicated, this dosage can then be adjusted at intervals not less than 24 hours in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Efficacy has been demonstrated at doses between 1 and 6 mg/day. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Experience in schizophrenia is lacking in children less than 13 years of age.

Bipolar Mania

Adults

RISPERDAL® should be administered on a once daily schedule, starting with 2 or 3 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Efficacy was demonstrated in flexible doses over a range of 1 to 6 mg per day.

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

Children and Adolescents

A starting dose of 0.5mg once daily is recommended, administered as a single-daily dose in either the morning or evening. If indicated, this dosage can then be adjusted at intervals not less than 24 hours in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Efficacy has been demonstrated at doses between 0.5 and 6 mg/day. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

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

Experience is lacking in bipolar mania in children less than 10 years of age.

Behavioral 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 ongoing basis.

Conduct and Other Disruptive Behavior Disorders

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

For subjects < 50 kg, a starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg once daily.

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

Experience is lacking in children less than 5 years of age.

Renal and Hepatic Impairment

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

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

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

Contraindications

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

Special Warnings and Special Precautions for Use

Elderly Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including RISPERDAL®. In placebo-controlled trials with RISPERDAL® in this population, the incidence of mortality was 4.0% for RISPERDAL®-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with Furosemide

In the RISPERDAL® placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients

treated with furosemide plus risperidone was observed in two of the four clinical trials.
No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.
Cerebrovascular Adverse Events (CAE)
In placebo-controlled trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, (cerebrovascular accidents and transient ischemic attacks), including fatalities, in patients treated with RISPERDAL® compared to patients receiving placebo (mean age 85 years; range 73-97).
Orthostatic Hypotension
Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. RISPERDAL® should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see Posology and Method of Administration). A dose reduction should be considered if hypotension occurs.
Leukopenia, Neutropenia, and Agranulocytosis
Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including RISPERDAL®. Agranulocytosis has been reported very rarely (< 1/10000 patients) during post-marketing surveillance.
Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of RISPERDAL® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue RISPERDAL® and have their WBC followed until recovery.
Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with RISPERDAL® and preventive measures undertaken.
Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because RISPERDAL® has a lower potential to induce extrapyramidal symptoms

than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

Neuroleptic Malignant Syndrome (NMS)

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

Parkinson's Disease and Dementia with Lewy Bodies

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

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, diabetes mellitus and, exacerbation of pre-existing diabetes have been reported during treatment with 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 hyperglycemia-related adverse events is not completely understood. Any patient treated with atypical antipsychotics, including RISPERDAL® should be monitored for symptoms of hyperglycemia and diabetes mellitus. (see also Undesirable Effects).

Weight Gain

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

QT Interval

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

Priapism

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

Body Temperature Regulation

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

Antiemetic Effect

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

Seizures

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

Other

See section on Posology for specific posology recommendations for elderly patients, for elderly patients with dementia, for patients with bipolar mania, for pediatric patients with conduct and other disruptive behavior disorders, and for patients with renal or hepatic impairment

Interaction with Other Medicinal Products and Other Forms of Interaction

Given the primary CNS effects of RISPERDAL® it should be used with caution in combination with other centrally acting drugs. RISPERDAL® may antagonize the effect of levodopa and other dopamine-agonists.

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

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

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of 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 the active antipsychotic fraction. 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 the active antipsychotic fraction. 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 the active antipsychotic fraction. Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitors, galantamine and donepezil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

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

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

See section Special Warnings and Special Precautions for Use regarding increased

mortality in elderly patients with dementia concomitantly receiving furosemide.
Food does not affect the absorption of RISPERDAL®.

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.
Neonates exposed to antipsychotic drugs (including RISPERDAL®) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.
RISPERDAL® should only be used during pregnancy if the benefits outweigh the risks.
In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® should not breast feed.

Effects on Ability to Drive and Use Machines

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

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

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
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

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

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 ≥ 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.

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
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.

	RISPERDAL® ≤3 mg/day	RISPERDAL® >3-6 mg/day	PLACEBO

System/Organ Class Adverse Reaction	**N=344)** **%**	**N=95)** **%**	**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

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
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,

System/Organ Class Adverse Reaction
Peripheral coldness, Thirst
Injury, poisoning and procedural complications
Procedural pain

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

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
Eye disorders
Eye movement disorder, Photophobia
Cardiac disorders
Postural orthostatic tachycardia syndrome
Gastrointestinal disorders
Intestinal obstruction
Skin and subcutaneous tissue disorders
Drug eruption, Urticaria
Reproductive system and breast disorders
Breast discomfort, Breast engorgement, Breast enlargement, Menstruation delayed
General disorders and administration site conditions
Induration

Postmarketing Data

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

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports

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

Table 5. Adverse Drug Reactions Identified During Postmarketing Experience with Risperidone and/or Paliperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Risperidone

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
Nervous System Disorders	
Very rare	Dysgeusia
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
Hepatobiliary Disorders	
Very rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Angioedema
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

Overdose

Symptoms

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

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

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

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 risperidone can be given with or without meals.

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

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

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

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

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

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

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

Preclinical Safety Data

In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependant effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D_2-receptor blocking activity of risperidone. In a toxicity study with juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed.

Long bone growth was not affected at a dose similar to the maximum human dose in adolescents (6 mg/day); effects were observed at a dose 4-fold (on an AUC basis) or 7-fold (on a mg/m^2 basis) the maximum human dose in adolescents.
All other safety data relevant to the prescriber have been included in the appropriate section.

PHARMACEUTICAL PARTICULARS

List of Excipients

Film-coated tablets:
Tablet core
Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hypromellose 2910 15 mPa.s[(e)]
Magnesium stearate
Colloidal anhydrous silica
Sodium lauryl sulfate
Film-coating
Hypromellose 2910 5 mPa.s
Propylene glycol
Titanium dioxide [(a)]
Talc [(a)]
Quinoline yellow [(b)]
Indigotindisulfonate aluminum lake [(c)]
Orange yellow S aluminum lake [(d)]
Oral solution:
Tartaric acid
Benzoic acid
Sodium hydroxide
Purified water
[(a)]Only in 2 mg, 3 mg, 4 mg and 6 mg tablets.
[(b)]Only in 3 mg, 4 mg and 6 mg tablets.
[(c)]Only in 4 mg tablets.
[(d)]Only in 2 mg and 6 mg tablets.
[(e)]Only in 1 mg, 2 mg, 3 mg and 4 mg tablets.

Incompatibilities

RISPERDAL® tablets: none.
RISPERDAL® oral solution: incompatible with tea.

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

RISPERDAL® tablets should be stored between 15°C and 30°C.
RISPERDAL® oral solution should be stored between 15°C and 30°C and should be protected from freezing.
Keep out of reach of children.

Nature and Contents of Container

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

RISPERDAL® 1, 2, 3 and 4 mg tablets are individually packaged in a blister card containing 10 tablets. Blisters are packed in a cardboard box (2 or 6 blisters per box).
RISPERDAL® 6 mg tablets are individually packaged in a blister card (calendar pack) containing 7 tablets. Blisters are packed in a cardboard box (4 blisters per box).
Oral solution:
RISPERDAL® oral solution is provided in 30 ml and 100 ml amber glass bottles with plastic child resistant closures.
The pipette supplied with the 30 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.
The pipette supplied with the 100 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.

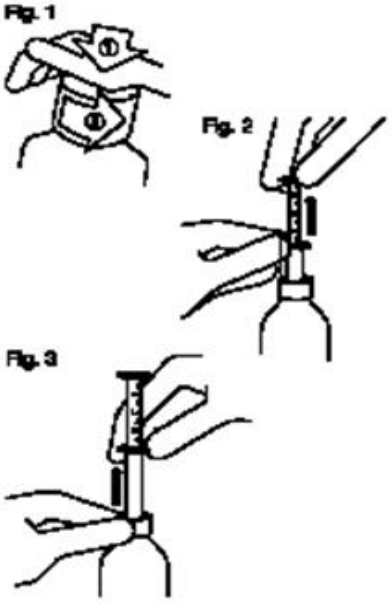
Instructions for Use/Handling and Disposal

Directions for opening the bottle and using the pipette

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

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

Fig 3: Holding the bottom ring, remove the entire pipette from the bottle. Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down. Close the bottle.
Rinse the pipette with some water.



MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
July 2011