AUSTRALIAN PRODUCT INFORMATION

RISPERDAL®

Risperidone

Film coated tablets

Oral Solution

1 NAME OF THE MEDICINE

Risperidone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RISPERDAL contains risperidone as the active ingredient, and is available as 0.5, 1, 2, 3 and 4 mg oral film-coated tablets or as a 1 mg/mL oral solution.

Excipients of known effect:

Tablets: Sugars as lactose

Oral solution: Benzoates.

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

3 PHARMACEUTICAL FORM

RISPERDAL Tablets:

0.5 mg brownish-red, film-coated, biconvex, half-scored oblong tablets, “Ris 0.5” on the scored side and “JANSSEN” on the other side.

1 mg white, film-coated, half-scored oblong tablets, "Ris 1" on the scored side.

2 mg orange, film-coated, half-scored oblong tablets, "Ris 2" on the scored side.

3 mg yellow, film-coated, half-scored oblong tablets, "Ris 3" on the scored side.

4 mg green, film-coated, half-scored oblong tablets, "Ris 4" on the scored side.

RISPERDAL Oral Solution:

1mg/mL clear, colourless oral solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RISPERDAL is indicated for the treatment of schizophrenia and related psychoses.

RISPERDAL is indicated for the short term treatment of acute mania associated with bipolar 1 disorder. (See **section 4.2 DOSE AND METHOD OF ADMINISTRATION: Bipolar mania**).

RISPERDAL is indicated for the treatment (up to 12 weeks) of psychotic symptoms, or persistent agitation or aggression unresponsive to non-pharmacological approaches in patients with moderate to severe dementia of the Alzheimer type. (See **section 4.2 DOSE AND METHOD OF ADMINISTRATION: Behavioural Disturbances in Dementia**)

RISPERDAL is indicated in the treatment of conduct and other disruptive behaviour disorders in children (over 5 years), adolescents and adults with sub-average intellectual functioning or mental retardation in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent. (See **section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical Trials**).

RISPERDAL is indicated for the treatment of behavioural disorders associated with autism in children and adolescents (see **section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical Trials**).

4.2 DOSE AND METHOD OF ADMINISTRATION

RISPERDAL may be given as tablets or oral solution.

Schizophrenia

Studies on the efficacy and safety of RISPERDAL have been performed predominantly in patients with schizophrenia. The pivotal studies lasted up to 8 weeks, but more than 600 patients have been treated for at least 12 months.

Switching from Other Antipsychotics

When medically appropriate, gradual discontinuation of the previous treatment is recommended while RISPERDAL therapy is initiated. In the case of depot injections, it is recommended that RISPERDAL not be administered until the next scheduled injection.

Alterations in requirements of anti-Parkinson therapy may be required in patients switching to RISPERDAL. These requirements should be evaluated periodically.

Adults:

RISPERDAL may be given once or twice daily.

Patients, whether acute or chronic, may start with 1 mg RISPERDAL twice daily. The dosage may be increased on the second day to 2 mg twice daily. From then on the dosage can be maintained unchanged, or further individualised, if needed. In some patients a slower titration phase and lower starting and maintenance dose may be appropriate. Patients should be titrated gradually in view of the risk of first dose orthostatic hypotension.

In stable patients, RISPERDAL may be given once daily or twice daily, with a recommended daily dose between 4 and 6 mg. However, some patients may benefit from higher doses.

Doses above 5 mg twice daily have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms.

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

Elderly:

A starting dose of 0.5 mg twice daily is recommended in view of the increased risk of first dose orthostatic hypotension. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 - 2 mg twice daily.

Renal and hepatic impairment:

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.

RISPERDAL should be used with caution in this group of patients until further experience is gained.

Children:

Experience is lacking in children with schizophrenia aged less than 15 years.

Bipolar mania

RISPERDAL should be administered on a once daily basis, starting with 2mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increment of 1mg per day.

A dosing range of between 2 – 6mg per day is recommended.

Behavioural Disturbances in 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.

There is no data to support treatment beyond 12 weeks in patients with moderate to severe dementia of the Alzheimer type with agitation, aggression or psychotic symptoms.

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 $\geq$ 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 < 50 Kg

A starting dose of 0.25mg once daily is recommended. This dosage 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. Some patients however 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.

Experience is lacking in children aged less than 5 years.

Behavioural Disorders Associated with Autism

RISPERDAL can be administered once or twice daily.

RISPERDAL should be administered based on body weight. Dosing should begin at 0.25mg or 0.5mg/day based upon weight (see the table for relative weight categories). On day 4 of

treatment the dose may be increased up to 0.5 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 0.25mg for patients <20kg or 0.5mg for patients ≥20kg. In clinical studies the maximum dose studied did not exceed a total daily dose of 1.5mg in patients <20kg, 2.5mg in patients ≥20kg or 3.5mg in patients >45kg. In a clinical study**,** doses of 0.175 mg/day in children ≥45kg and 0.125 mg/day in children 20 to <45kg were not effective.

Doses by total mg/day and by mg/kg/day for starting doses and incremental increases are shown in the Table 1.

Table 1 Doses of RISPERDAL in Paediatric Patients with Autistic Disorder (by total mg/day)

Weight Categories	Days 1 – 3	Days 4 – 14+	Increments if dose increases are needed	Dose Range
< 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*

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

For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided:

Table 2 Doses of RISPERDAL in Paediatric Patients with Autistic Disorder (by mg/kg/day)

Weight Categories	Days 1 – 3	Days 4 – 14+	Increments if dose increases are needed	Dose Range
All	0.01 mg/kg/day	0.02 mg/kg/day	+0.01 mg/kg/day at ≥ 2 week intervals	0.02 mg/kg/day – 0.06 mg/kg/day

Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime or twice daily.

Once sufficient response has been achieved and maintained, consideration may be given to gradually lowering the dose to achieve the optimum balance of efficacy and safety. There is insufficient evidence from controlled trials to indicate how long the patient with Autistic Disorder should be treated with RISPERDAL.

DIRECTIONS FOR OPENING THE BOTTLE AND USING THE PIPETTE FOR THE ORAL SOLUTION:

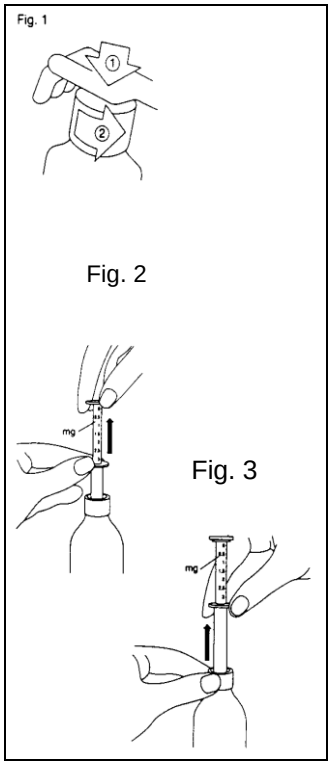
1. Push the plastic screw cap down while turning it anti-clockwise. Remove the unscrewed cap (Figure 1).

2. Use the pipette from the container. While holding the bottom ring, pull the top ring up to the level that corresponds with the dosage required for administration (Figure 2).

3. Holding the bottom ring, remove the entire pipette from the bottle (Figure 3).

4. 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.

5. Close the bottle. Rinse the pipette with some cold water after use, 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 medicine or any of its excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 **section 4.2 DOSE AND METHOD OF ADMINISTRATION**). A dose reduction should be considered if hypotension occurs. Special care should be taken in patients taking medications to lower blood pressure.

Leukopenia, Neutropenia and Agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including RISPERDAL. Agranulocytosis has been reported very rarely (<1/10,000 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 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 preventative measures undertaken.

Use in Patients with Concomitant Illness

Patients with a history of clinically significant cardiac disorders were excluded from clinical trials. As clinical experience is limited, RISPERDAL should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities) and other conditions (such as dehydration, hypokalaemia and hypovolaemia).

Tardive Dyskinesia/Extrapyramidal Symptoms

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic, rhythmical movements, including those of the tongue and/or face, may develop in patients treated with conventional neuroleptics. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD.

It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD. In clinical studies, the observed incidence of drug-induced Parkinsonism was lower with RISPERDAL than with haloperidol. In the optimal clinical dose-range, the difference between RISPERDAL and haloperidol was significant. Therefore the risk of developing tardive dyskinesia may be less with RISPERDAL. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for an established case of TD. The syndrome may remit partially or completely if antipsychotic medicine treatment is withdrawn.

Antipsychotic medicine treatment itself, however, may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, RISPERDAL should be prescribed in a manner that is most likely to minimise the risk of TD. As with any antipsychotic medicine, RISPERDAL should be reserved for patients who appear to be obtaining substantial benefit from the medicine. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient on antipsychotics, medicine discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

Extrapyramidal symptoms and psychostimulants

Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered (see **section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

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.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including risperidone.

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

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of all antipsychotic medicines and other medicines not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic medicine treatment after recovery from NMS, the potential reintroduction of this therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Seizures

Classical neuroleptics are known to lower the seizure threshold. RISPERDAL has not been studied in patients who also have epilepsy. In clinical trials, seizures have occurred in a few RISPERDAL-treated patients. 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.

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 anti-diabetic treatment despite discontinuation of the suspect medicine.

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 post-marketing 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.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, 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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

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

Other Precautions

Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventive therapy to avoid hypo-estrogenic bone loss.

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.

For the conduct disorder indication, effects on sexual maturation and gonadal function in children and adolescents have not been evaluated beyond 12 months in relation to long-term treatment.

Safety data beyond 12 months is lacking in relation to the effect of long-term treatment for the conduct disorder indication.

Use in hepatic impairment

Since clinical experience is lacking in this patient population, RISPERDAL should be used with caution until further experience is gained. For hepatically-impaired schizophrenic patients, it is recommended to halve both the starting dose and the subsequent dose increments in patients with hepatic insufficiency. In patients with known liver disease, it is advised to monitor the liver function.

Use in renal impairment

Since clinical experience is lacking in this patient population, RISPERDAL should be used with caution until further experience is gained. For renally-impaired schizophrenic patients, it is recommended to halve both the starting dose and the subsequent dose increments in patients with renal insufficiency.

Use in the elderly

For elderly schizophrenic patients, it is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients.

Elderly Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic medicines 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 and 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) compared to treatment 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 Odds Ratio (95% exact confidence interval) was 1.82 (0.65, 5.14). The increase in mortality 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 treat, 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 to patients treated with placebo. The pooled data from six placebo-controlled trials 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).

Paediatric use

Experience is lacking in children with schizophrenia aged less than 15 years. There are also insufficient nonclinical data to adequately define the safety of risperidone in young children. A 39-day oral toxicity study with juvenile rats noted increased pup mortality, a delay in physical development and, in a small proportion of animals, impairment of auditory startle, at exposures (plasma AUC) less than that at the maximum recommended oral paediatric dose (6 mg/day). The clinical relevance of these findings for children of 5 years and above is uncertain, given the relative immaturity of the rat pups upon commencement of treatment. A 40-week oral toxicity study with juvenile dogs noted delayed sexual maturation, probably secondary to hormonal changes. Long bone growth was slightly reduced at exposures (plasma AUC) of 3 fold and greater those at the maximum dose in children and adolescents (6 mg/day); exposure at the no-effect dose was similar to human exposure.

For information on the use of RISPERDAL in children 5 years and older in the treatment of conduct disorder, see **section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical Trials**.

Effects on laboratory tests

No data available

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 RISPERDAL, it should be used with caution in combination with other centrally acting medicines or alcohol.

Levodopa and Dopamine Agonists

RISPERDAL may antagonise the effect of levodopa and other dopamine-agonists

Psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see **section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)

Drugs with Hypotensive Effects

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

Drugs Known to Prolong the QT interval

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

Pharmacokinetic-related interactions

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 or fluoxetine). See also Section ***SSRIs and Tricyclic antidepressants***.

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.

A formal drug-drug interaction study to investigate the effect of risperidone on carbamazepine was not performed; however the effect of carbamazepine as adjunctive treatment to risperidone was investigated in a pharmacokinetic study. In this study, patients were stabilized on a risperidone dose of 3 mg twice daily, and carbamazepine was administered from 3 weeks (Days 22 to 42) at a dose that was adjusted for the therapeutic concentration (5 to 12 µg/mL, average dose 573 ± 168 mg/day). Carbamazepine serum concentrations were determined at the beginning and at the end of the period of coadministration of the 2 compounds. The results showed that coadministration of risperidone with carbamazepine did

not affect the serum concentrations of carbamazepine during the observation period of 3 weeks. The values were all within the therapeutic range of 5 to 12 µg/mL. Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction.

Highly Protein-bound Drugs

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

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 paediatric 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 risperidone active antipsychotic fraction C_{max} by 41% and AUC_{last} by 45%, following a single dose of risperidone 1mg.

Anticholinesterases:

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

Antiepileptics:

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

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 risperidone AUC by 67%, and decreased the 9-hydroxyrisperidone AUC by 49%, following a single dose of risperidone 2mg. However, maximal CYP3A4 inhibition may not have been achieved in this study.

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; Protease inhibitors are moderate to strong CYP3A4 inhibitors; ritonavir is also a weak CYP2D6 inhibitor and tipranavir is also a strong CYP2D6 inhibitor. Protease inhibitors therefore may 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, at a dose of 240mg/day, increased the risperidone Cmax and AUC by 1.8-fold, and the active antipsychotic fraction Cmax by 1.3-fold and AUC by 1.4-fold, following a single dose of risperidone 1mg.

Digitalis Glycosides:

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

Diuretics:

- Furosemide: See **section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Gastrointestinal Drugs:

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

- In volunteer studies, a single 1mg risperidone dose was administered with cimetidine 400mg twice daily or ranitidine 150mg twice daily. Cimetidine produced a relative increase in $AUC_{0\text{-}Inf}$ of 1.95 ± 0.78, 1.01 ± 0.25 and 1.15 ± 0.28 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. Relative C_{max} increases were 1.90 ± 0.95, 0.95 ± 0.21 and 1.24 ± 0.27. Co-administration of ranitidine produced a relative increase of 1.35 ± 0.32, 1.23 ± 0.44 and 1.25 ± 0.39 in $AUC_{0\text{-}Inf}$ and of C_{max} of 1.45 ± 0.61, 1.28 ± 0.37 and 1.36 ± 0.35. Dose modification is not considered to be necessary.

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. Co-administration of fluoxetine produced relative increases of 1.63 ± 0.43, 1.54 ± 0.54 and 1.40 ± 0.24 in C_{min}, C_{max} and $AUC_{0\text{-}12hr}$ of risperidone plus 9-hydroxy risperidone. Administration of paroxetine 20mg/day for 4 weeks to patients stabilised on 4 - 8mg risperidone/day produced a relative increase of 1.51±0.34 in C_{min} of risperidone plus 9-hydroxy risperidone.

- Paroxetine is a strong CYP2D6 inhibitor. At paroxetine doses of 10mg/day the plasma concentration of risperidone increased by 4-fold, without a significant increase in the active antipsychotic fraction (1.3-fold). Dosages of paroxetine of 20mg/day resulted in a 7-fold increase in the concentration of risperidone, and a non-significant increase in the active antipsychotic fraction (1.6-fold). Paroxetine 40mg/day resulted in a significant increase in the concentrations of both risperidone (10-fold) and the active antipsychotic fraction (1.8- fold). Doses of risperidone of 4mg/day were used in this study.

- When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of RISPERDAL.

- 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, the concentrations of the active antipsychotic fraction increased by 42% in 2 patients treated with sertraline 150mg/day, and by 26% in 5 patients treated with fluvoxamine 200mg/day. Doses of risperidone used were 4-6mg/day in the sertraline study and 3-6mg/day in the fluvoxamine study.

- 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.

In patients with schizophrenia receiving risperidone 3mg twice daily for 28 days, the addition of amitriptyline initially at 50mg twice daily, increasing to 100mg twice daily for the last 6 days of the study produced relative increases in the 0 – 12 hr AUC of 1.21 ± 0.35, 1.15 ± 0.36 and 1.16 ± 0.34 and C_{max} of 1.17 ± 0.33, 1.11 ± 0.43 and 1.11 ± 0.38 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. These modest increases do not necessitate dose modification.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Risperidone impaired mating, but not fertility, in Wistar rats at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis. The effect appeared to be in females since impaired mating behaviour was not noted when males only were treated. In repeat dose toxicity studies in Beagle dogs, risperidone at dose of 1 to 17 times the maximum human dose on a mg/m^2 basis was associated with adverse effects on the male reproductive system

(inhibited ejaculation, incomplete spermatogenesis, reduced sperm motility and concentration, reduced gonadal and prostatic weight, prostatic immaturity, decreased serum testosterone). Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No-effect doses were not determined in either rat or dog

Use in pregnancy

Category C

The safety of risperidone 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.

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.

Use in lactation

Risperidone and 9-hydroxyrisperidone are excreted in human breast milk. Women receiving RISPERDAL should not breast feed.

In rats oral administration of risperidone during late gestation and lactation was associated with an increase in pup deaths during the first 4 days of lactation at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis (a no-effect dose was not determined) and with reduced pup weight gain at doses 5 fold or greater than the maximum recommended human dose on a mg/m^2 basis. It is not known whether these effects resulted from a direct effect on the foetuses and pups and/or to an effect on the dams. There were also increases in stillborn rat pups at an oral dose 2.5 - 5 times the maximum human dose on a mg/m^2 basis.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 paediatrics. 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 3:

Table 3. 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
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 4. Table 4 includes only those ADRs that are either not listed in Table 3 or those ADRs that occurred at ≥ 2 times the frequency of the ADRs listed in Table 3.

Table 4 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 3 or Reported at ≥ 2 Times the Frequency of ADRs Listed in Table 3.

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 – Paediatric Patients

Adverse drug reactions (ADRs) reported by ≥ 1% of RISPERDAL-treated paediatric patients in eight 3- to 8-week double-blind, placebo-controlled trials are shown in Table 5. Table 5 includes only those ADRs that are either not listed in Table 3 or those ADRs that occurred at ≥ 2 times the frequency of the ADRs listed in Table 3.

Table 5 Adverse Drug Reactions (ADRs) Reported by ≥ 1% of RISPERDAL-Treated Paediatric Patients in Double-Blind Placebo-Controlled Studies: ADRs Not Listed in Table 3 or Reported at ≥ 2 Times the Frequency of ADRs Listed in Table 3.

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

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 6.

Table 6 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 7.

Table 7 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, Peripheral coldness, Thirst
Injury, poisoning and procedural complications
Procedural pain

*__Convulsion includes__: Grand mal convulsion; __Menstrual disorder includes__: Menstruation irregular, Oligomenorrhea

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 8.

Table 8 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 Tables 9. 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
Not known	cannot be estimated from the available data

In Table 9, ADRs are presented by frequency category based on spontaneous reporting rate.

Table 9 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	Catatonia, Mania, Somnambulism, 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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms:

In general, reported signs and symptoms have been those resulting from an exaggeration of the medicine's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms.

In overdose, QT prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL and paroxetine.

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

Treatment:

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

RISPERDAL (risperidone) is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Mechanism of Action

Risperidone is a selective monoaminergic antagonist with 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. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy risperidone.

Central dopamine D_2 receptor antagonism is considered to be the mechanism of action by which conventional neuroleptics improve the positive symptoms of schizophrenia, but also induce extrapyramidal symptoms and release of prolactin.

Although risperidone antagonises dopamine D_2 receptors and causes release of prolactin, it is less potent than classical neuroleptics for depression of motor activity and for induction of catalepsy in animals.

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.

Due to the alpha-blocking activity of RISPERDAL, orthostatic hypotension can occur, especially during the initial dose-titration period. This alpha-blocking activity may also induce nasal mucosal swelling, which is probably related to the observed incidence of rhinitis associated with the use of RISPERDAL.

Antagonism of serotoninergic and histaminergic receptors may induce body weight gain.

In controlled clinical trials, RISPERDAL was found to improve positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), as well as negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech). RISPERDAL may also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Clinical trials

Schizophrenia

Clinical trials have shown that RISPERDAL is indicated for the treatment of schizophrenia including first episode psychoses, acute schizophrenic exacerbations and chronic schizophrenia. RISPERDAL is also indicated as long term therapy for the prevention of relapse (acute exacerbations) in chronic schizophrenic patients.

First episode psychosis. In a 6-week double blind, parallel group, active controlled study in first admission, newly diagnosed schizophrenic patients (N=183, risperidone=99, haloperidol=84) risperidone (1-8 mg twice daily, mean daily dose 6.1 mg) was as effective as haloperidol (1-8 mg twice daily, mean daily dose 5.6 mg) in controlling psychotic symptoms. The average patient age was 26 years (range 15-50) and 31% of the patients were women. There were statistically significant ($p<0.001$) reductions in total PANSS, positive, negative and general psychological symptom scores and in derived BRPS scores in both groups.

Acute exacerbations of chronic schizophrenia. Two new studies were conducted to establish the efficacy of risperidone in the treatment of acute exacerbations of schizophrenia. A third study investigated the efficacy of risperidone in the treatment of resistant schizophrenics.

The first was a double blind, parallel group, actively controlled study of 6 weeks duration in 98 patients (risperidone=48, zuclopenthixol=50), 48% of who were male. The dosage was risperidone 2 mg bid and zuclopenthixol 10 mg bid increasing by one tablet a day until adequate control was achieved. The mean daily dose at end point for risperidone was 8 mg and for zuclopenthixol 38 mg. The median age was in the mid 30's (range 18-65). The overall severity of symptoms during the study was lower for risperidone ($p=0.06$) and the clinical response (58% vs 42%; $p=0.11$) was higher for risperidone.

Two dosages of risperidone 4 mg bid and 8 mg od, were studied in the treatment of acute exacerbations of schizophrenia in chronic or subchronic schizophrenics. The study was a double blind parallel-group study of 6 weeks duration with a patient population of 211 patients (67% males) aged 18-64 (median 34) years. Efficacy was comparable for the two groups although the trough plasma drug concentrations were lower and concentrations in the first 8 hours post dose were higher (statistically not significant) for the 8 mg od dosage. According to basic pharmacokinetic principles, these findings are expected because a once daily dosage regimen will result in higher peaks and lower troughs than after the same daily dose given over two intakes.

The efficacy and tolerability of risperidone (1-6 mg twice daily) compared to clozapine (50-300 mg twice daily) in treatment resistant schizophrenic patients was studied in an 8 week multicentre, double-blind, parallel group study in 86 patients (risperidone=43, clozapine=43). In both groups of patients, there was a significant reduction in total PANSS scores in the positive, negative and psychopathology subscales and in the PANSS-derived BPRS scores. The percentage of patients showing a clinical response at endpoint on the PANSS and BPRS (at least 20% reduction in base score) was comparable (68%) for both treatment groups.

Long term therapy for the prevention of relapse (acute exacerbations) in chronic schizophrenic patients. The long term efficacy and tolerability of risperidone was established at the time of marketing in open long term studies involving 402 patients of whom 282 had been treated with risperidone for 6 months, 221 for 12 months and 30 patients for between 12 and 40 months. Additional long-term data are available from an actively controlled study and a study compared to the patient's usual neuroleptic treatment. The total number of patients treated with risperidone in these two studies was 285, while 306 patients were treated with haloperidol or other neuroleptics. In another three long-term open studies, 758 patients were treated with risperidone.

In a multicentre, double blind, randomised, parallel group trial of 1 year duration risperidone (91 patients, 63% male) was compared to haloperidol (99 patients, 59% male) to evaluate the incidence of relapse in chronic schizophrenic patients. The mean daily dose at endpoint was 9 mg risperidone and 8.9 mg haloperidol. The incidence of relapse was 14% for risperidone and 16% for haloperidol and the time to withdrawal from the study because of an adverse event and/or psychotic relapse was longer for risperidone (day 99) compared to day 42 under haloperidol (p=0.023). At endpoint response on the total PANSS score defined as a 50% score reduction versus baseline was observed in 43% of patients receiving risperidone compared to 30% of patients receiving haloperidol (p=0.035). The total BPRS score at endpoint, defined as at least a 50% reduction in baseline score value, was 47% of patients receiving risperidone compared with 34% patients receiving haloperidol (p=0.043). The instrumental role functioning on the Quality of Life Scale scored significantly better under risperidone (p=0.037). The Clinical Global Impression scores showed no significant difference between the two treatment groups. The results of the trial show that risperidone is as efficacious and safe as haloperidol.

Mania in Bipolar Disorder

Monotherapy: The efficacy of RISPERDAL in the treatment of acute mania was established in three double-blind placebo-controlled studies of 3-week duration in patients who met the DSM-IV criteria for bipolar 1 disorder. These studies included patients with or without psychotic features.

The primary efficacy variable in all studies was the Young Mania Rating Scale (YMRS), an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behaviour, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance and insight). Secondary efficacy measures included the Clinical Global Impression Scale of Severity and the Global Assessment Scale. In order to capture treatment effects on depressive symptomatology the Montgomery Asberg Depression Scale or the Hamilton Rating Scale for Depression was used. Psychosis and general psychopathology were measured using the PANSS or BPRS.

All studies used a flexible once daily dose of risperidone in the range of 1-6mg/day.

In studies 1 and 2 (n=246 and n=286) risperidone was superior to placebo in the reduction of YMRS total score regardless of baseline disease severity and the presence or absence of psychosis at baseline. Significant treatment differences were evident at week 1 and increased during the 3-week treatment period. Risperidone also showed significant differences in secondary efficacy measures.

Study 3 (n=438) also included an active comparator arm using haloperidol. Risperidone was superior to placebo and similar to haloperidol in its effects on both primary and secondary efficacy measures. The maintenance phase of this study involved a 9-week double blind treatment of risperidone or haloperidol or a 9-week open label treatment on risperidone. Efficacy was maintained throughout the treatment period, although change from baseline in the MADRS were not as clearly maintained.

In open label extension studies, change from baseline in total YMRS showed continued improvement.

Adjunctive therapy: The efficacy of RISPERDAL in the treatment of acute mania in combination with mood stabilisers was demonstrated in two 3-week double-blind studies in patients who met the DSM-IV criteria for bipolar 1 disorder.

One study (n=148) was in patients on lithium or valproate therapy with inadequately controlled symptoms randomised to receive risperidone, haloperidol or placebo in combination with their original therapy. Risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

The second study (n=142) was in patients on lithium, valproate or carbamazepine therapy with inadequately controlled symptoms randomised to receive risperidone or placebo in combination with their original therapy. A failure to demonstrate a significant advantage appeared to be due to carbamazepine induction of the metabolism of risperidone reducing risperidone plus 9-hydroxy risperidone plasma concentration. When the carbamazepine group was excluded in post hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Behavioural disturbances in dementia

The efficacy of risperidone in the treatment of behavioural disturbances, such as aggressiveness (verbal outburst, physical violence), activity disturbances (agitation, wandering) and psychotic symptoms (paranoid and delusional ideation, hallucinations), in patients with dementia was demonstrated in two double blind, placebo-controlled clinical studies. One study was a randomised, parallel group, multicentre design involving 617 patients that examined the efficacy of three doses of risperidone (0.5, 1 or 2 mg/day) over a twelve-week period. The other involved 344 patients assigned to either placebo, risperidone or haloperidol for a 12-week period. The two studies were pooled and the results from this analysis are presented in the Table 10 below. The primary outcome parameter was the percentage of responders, defined as a reduction at endpoint of at least 30% on the Behave-AD total score. Several important aspects of efficacy were assessed by the secondary endpoints that examined the effect on individual disturbances (e.g. aggressiveness). Aggressive symptoms were the major problem at entry in the two trials.

Table 10

Parameter	**Treatment**			
	Placebo	**RIS <0.75 mg**	**RIS 0.75 - <1.5 mg**	**RIS ≥1.5 mg**
	n = 275	n = 193	n = 203	n = 175
BEHAVE-AD, % Responders	50	52	58	65*
BEHAVE-AD, Total score % Improvement	25	30	36**	40**
BEHAVE-AD, Aggression cluster % Improvement	18	28	36**	45**
BEHAVE-AD, Psychosis cluster % Improvement	32	33	44*	40
CMAI, Physical Aggressive % Improvement	9	18	39**	47**
CMAI, Verbal Aggressive % Improvement	10	31*	30**	41**
CMAI, Total Aggressive % Improvement	9	24	36**	47**

* p≤0.05 vs placebo ** p<0.01 vs placebo

The rate of discontinuation from the pooled studies was similar for patients receiving placebo (30.2%), risperidone (33.5%) and haloperidol (29.6%). In the combined analysis, risperidone, at a daily dose above 0.75 mg, effectively reduces the severity (measured by means of the Behave-AD) and frequency (measured by the CMAI) of aggressiveness symptoms in this patient population. Reductions in Behave-AD aggressiveness scores and on each of the aggressive clusters of the CMAI were significantly greater with risperidone (doses above 0.75 mg/day) than placebo at endpoint in both studies and in the combined analysis. Reductions in CMAI total aggressive scores declined throughout the studies in the risperidone patients but changed minimally after week 2 in patients receiving haloperidol or placebo.

Conduct Disorder

Children and Adolescents. Two double blind placebo controlled randomised parallel group studies of 6 weeks duration were conducted in children and adolescents 5 to 12 years with borderline intellectual functioning or mild to moderate mental retardation. The studies, of identical design, involved a combined population of 120 patients receiving placebo and 105 patients receiving risperidone at 0.02-0.06mg/kg/day. Twenty six per cent of the patients receiving risperidone had conduct disorder with attention deficit hyperactivity disorder (ADHD), 39% had oppositional defiant disorder with ADHD and 6% had disruptive behavioural disorder with ADHD. A decrease in the primary efficacy parameter of the Conduct Problem Subscale of the Nisonger Child Behaviour Rating Form (N-CBRF) of -6.5±1.02 was observed in placebo treated patients compared to –15.6±1.04 for risperidone. The improvement for risperidone compared to placebo was statistically significant ($p<0.001$). A statistically significant difference between risperidone and placebo was apparent at Week 1 and continued throughout treatment. A subanalysis of patients with ADHD indicated risperidone was effective for the primary and secondary efficacy parameters whether psychostimulants were or were not being taken.

A 6-month, double-blind, placebo-controlled, relapse prevention study in children and adolescents with disruptive behaviour disorders who responded to 12 weeks of treatment with risperidone (6 weeks of open-label treatment followed by 6 weeks of single-blind treatment) was performed. The subjects enrolled had either average IQ, borderline intellectual functioning, or mild mental retardation/learning disorder; subjects with moderate or severe mental retardation/learning disorder were excluded. The study consisted of 3 phases: a 6-week, open-label acute treatment phase with risperidone (phase 1); a 6-week single-blind continuation phase with risperidone (phase 2); and a 6-month, double-blind, withdrawal phase during which subjects were randomly assigned to treatment with placebo or continued risperidone (phase 3). The total study duration was 36 weeks. This relapse prevention study used a flexible dose range of risperidone based on body weight categories, with 0.25 to 0.75 mg/day administered to subjects <50 kg and 0.5 to 1.5 mg/day given to subjects $\geq$50 kg. A total of 306 children and adolescents aged 5 to 17 years with disruptive behaviour disorders and an IQ of at least 55 (63% had normal intellectual functioning) were maintained on risperidone therapy or switched to placebo. The primary efficacy parameter was the time from initiation of double-blind treatment to discontinuation resulting from relapse, based on predefined criteria. Results of the study demonstrated that children and adolescents with disruptive behaviour disorders who continued treatment with risperidone experienced relapse significantly later than subjects who were switched to placebo ($p< 0.001$). The time to when 25% of subjects relapsed was 91 days in the risperidone group compared with 32 days in the placebo group. Safety results of this study demonstrated that the overall adverse event rate was similar to that seen in the acute disruptive behaviour disorders trials and consistent with the adverse event profile seen in adults with psychotic disorders.

Adults. A double blind placebo controlled, randomised parallel group study was conducted in adults with borderline intellectual function or mild to moderate mental retardation and conduct or other disruptive behaviour disorders. Thirty nine patients received 1.0-4.0mg/day of risperidone (modal dose 1.64mg/day) and 38 patients received placebo for 4 weeks. The

change in the Aberrant Behaviour Checklist (ABC) score from baseline to endpoint, the primary efficacy parameter, was –27.3 in the risperidone group compared to –14.9 in the placebo group ($p<0.05$). Significantly greater reduction in the ABC total score was noted at week 2 in patients receiving risperidone and was maintained throughout the double blind period.

Long term studies. Three open label long term studies, two in children and adolescents and one in adults, were conducted. One study in children and adolescents (N=107) of 48 weeks duration was an extension of a primary clinical study. A statistically significant improvement from the double blind ($p<0.001$) and open label ($p<0.01$) baselines was observed. In the other long term study in children (N=319) of 52 weeks duration the mean change in N-CBRF from baseline to endpoint was highly statistically significant. ($p<0.001$). The mean modal dose for the long term studies in children was 1.67±0.039mg/day 9range 0.2 to 4.0). The one year long term study in adults (N=58) was a continuation of the 6-week double blind study. The mean ABC score at open label baseline was 31.2. At endpoint the mean decrease from OL baseline was 9.0 ($p=0.012$). The overall mean modal dose in adults during long term treatment was 1.81±0.125mg.day (range 1 to 4mg.day). The safety profile of risperidone in children, adolescents and adults with conduct disorder and other disruptive disorders is comparable to that seen in other populations (e.g. schizophrenia).

The growth observed in children and adolescents after one year of treatment with risperidone was 6.9cm. On the basis of growth curves in children of the same age, growth is as expected.

Autism

The efficacy of RISPERDAL in the treatment of behavioural disorders associated with autism was established in two 8 week, double blind, parallel group, placebo controlled trials in patients who met the DSM IV criteria for Autism Disorder.

Efficacy was evaluated using two primary assessment scales: the Aberrant Behaviour Checklist (ABC) and the Clinical Global Impression-Change (CGI-C) scale. The ABC scale, which was completed by the parent or caregiver, is a validated instrument composed of five subscales to assess Irritability, Lethargy/Social Withdrawal, Stereotypic Behaviour, Hyperactivity/Noncompliance and Inappropriate Speech. The CGI-C scale, which was completed by a clinician, reflects the impression of a skilled observer, fully familiar with the symptoms of autism, about the overall clinical disposition of the patient.

In Study 1 (N=101) patients aged 5-17 years received twice daily doses of placebo or RISPERDAL 0.5-3.5mg/day on a weight-adjusted basis. RISPERDAL titrated to clinical response (mean modal dose of 1.9mg/day, equivalent to 0.06mg/kg/day) significantly improved scores on the ABC Irritability subscale and on the CGI-C scale compared to placebo. RISPERDAL was also superior to placebo in improving scores on the ABC subscales of Lethargy/Social Withdrawal, Stereotypic Behaviour, Hyperactivity/Noncompliance and Inappropriate Speech.

Table 11 Analysis of 5 ABC Subscales at End Point by study, for the Autistic Disorder subset of RIS-CAN-23 and for the Pooled Autistic Disorder Subset (RIS-USA-150 Part 1 +RIS-CAN-23)

	Lethargy/Social Withdrawal	Stereotypic Behaviour	Inappropriate Speech	Irritability	Hyperactivity/ Noncompliance
RIS-USA-150 Part 1					
N (RIS:Placebo)	101 (49:52)	101 (49:52)	101 (49:52)	101 (49:52)	101 (49:52)
Diff LS Means Change	-3.2	-2.5	-1.8	-10.6	-10.4
(95% CI)	(-5.6, -0.8)	(-3.9, -1.1)	(-2.7, -0.9)	(-13.8, -7.5)	(-13.8, -7.1)
p-value	0.009	<0.001	<0.001	<0.001	<0.001
RIS-CAN-23					

N (RIS:Placebo)	77 (39:38)	76 (38:38)	77 (39:38)	75 (37:38)	75 (37:38)
Diff LS Means Change	-3.3	-1.9	-1.3	-6.3	-8.1
(95% CI)	(-5.8, -0.8)	(-3.6, -0.2)	(-2.3, -0.2)	(-9.4, -3.2)	(-12.0, -4.2)
p value	0.010	0.030	0.016	<0.001	<0.001
RIS-CAN-23 Autistic Disorder Subset					
N (RIS:Placebo)	54 (26:28)	53 (25:28)	54 (26:28)	52 (24:28)	52 (24:28)
Diff LS Means Change	-3.9	-2.2	-1.3	-5.8	-8.8
(95% CI)	(-7.1, -0.6)	(-4.4, 0.0)	(-2.6, 0.0)	(-9.5, -2.2)	(-13.8, -3.9)
p value	0.020	0.053	0.058	0.002	<0.001
Pooled Autistic Disorder Subset					
N (RIS:Placebo)	155 (75:80)	154 (74:80)	155 (75:80)	153 (73:80)	153 (74:79)
Diff LS Means Change	-3.4	-2.5	-1.6	-9.4	-10.4
(95% CI)	(-5.2, -1.5)	(-3.7, -1.3)	(-2.4, -0.9)	(-11.8, -6.9)	(-13.2, -7.6)
p value	<0.001	<0.001	<0.001	<0.001	<0.001

Diff LS Means Change = LS Means change in risperidone group minus LS means change in placebo group based on ANCOVA model.

95%CI = 95% confidence interval for between treatment group difference based on ANCOVA model.

p value: comparison with placebo based on ANCOVA model with treatment, investigator (or study for pooled) as factors, and baseline value as a covariate

Following completion of Study 1, 63 patients entered an open-label extension for up to 4 additional months. Thirty nine patients who were clinically stable and who showed a positive response to risperidone after 6 months were then randomised to receive RISPERDAL or placebo during an 8-week, double blind withdrawal period. The relapse rate was 11/16 and 2/16 in placebo and RISPERDAL treated patients respectively (Odds Ratio 15.4, 95% confidence limits 2.50, 95.05)

In Study 2 (N=55) patients aged 5-12 years received once or twice daily doses of placebo or RISPERDAL 0.02-0.06mg/kg/day. RISPERDAL titrated to clinical response (mean modal dose of 1.4mg/day equivalent to 0.04mg/kg/day) significantly improved scores on the ABC Irritability subscale compared to placebo. RISPERDAL was also superior to placebo in improving scores on the CGI-C scale and on the ABC subscales of Lethargy/ Social Withdrawal and Hyperactivity/Noncompliance.

Table 12 CGI-C Responders at End Point by study for the Autistic Disorder Subset of RIS-CAN-23, and for the Pooled Autistic Disorder Subset (RIS-USA-150 Part I +RIS-CAN-23)

Study Treatment	Total N	Responders N (%)	Comparison with placebo Trt Diff in % (95% CI)	p value*
RIS-USA-150 Part 1				
Placebo	52	6 (11.5)	--	--
Risperidone	49	37 (75.5)	64.0 (49.1, 78.8)	<0.001
RIS-CAN-23				
Placebo	38	7 (18.4)	--	--
Risperidone	39	21 (53.8)	35.4 (15.5, 55.3)	0.001
RIS-CAN-23 Autistic Disorder Subset				

Placebo	28	6 (21.4)	--	--
Risperidone	26	14 (53.8)	32.4 (8.0, 56.9)	0.015
RIS-USA-150 +RIS-CAN-23 Autistic Disorder Subset				
Placebo	80	12 (15.0)	--	--
Risperidone	75	51 (68.0)	53.0 (39.9, 66.1)	<0.001

*p value:CMH test for association between risperidone treatment and CGI-C response controlling for investigator (or study for pooled)

As few autistic children with an IQ>84 are seen, there is limited clinical experience with RISPERDAL in such children. Experience in autistic adolescents is also limited.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone in children is similar to that in adults.

Risperidone oral solution 1mg/mL is bioequivalent to risperidone 1 mg tablet.

Absorption

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

Distribution

Risperidone and 9-hydroxyrisperidone form the pharmacologically active risperidone plus 9-hydroxy risperidone that is similar in extensive and poor metabolisers. Risperidone has an elimination half-life of about 3 hours in extensive metabolisers and 17 hours in poor metabolisers. Clinical studies do not suggest that poor and extensive metabolisers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. The elimination half-life of 9-hydroxyrisperidone and risperidone plus 9-hydroxy risperidone is 24 hours.

Steady state of risperidone is reached within 1 day in most patients. Steady state of 9-hydroxyrisperidone 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% and that of 9-hydroxyrisperidone is 77%. The binding of either product was not affected by the presence of the other.

Metabolism

Risperidone is partly metabolised by CYP 2D6 to 9-hydroxy-risperidone which has two enantiomers with a similar pharmacological activity as risperidone. Another metabolic pathway is oxidative N-dealkylation. 7-hydroxyrisperidone and the metabolite formed by N-dealkylation do not contribute to the activity of risperidone.

In vitro data suggest that drugs that inhibit the metabolism of risperidone to 9-hydroxyrisperidone by inhibition of CYP 2D6 would increase the plasma concentration of risperidone and lower the plasma concentration of 9-hydroxyrisperidone (see **section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). Drugs metabolised by other P450 isoenzymes (1A1, 1A2, 2C9, MP, 3A4) are only weak inhibitors of risperidone metabolism *in vitro*. Although *in vitro* studies suggest that risperidone can inhibit CYP 2D6, substantial inhibition of the clearance of drugs metabolised by this

enzymatic pathway would not be expected at therapeutic risperidone plasma concentrations. However, clinical data to confirm this expectation are not available.

Excretion

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

Special populations

A single-dose study showed higher active plasma concentrations and a slower elimination of 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 was somewhat increased by about 35% due to diminished concentration of both $alpha_1$-acid glycoprotein and albumin.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of genotoxicity was observed in assays for DNA damage, gene mutations or chromosomal damage.

Carcinogenicity

Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times the maximum human dose of 10 mg/day (mice) or 0.6, 2.5 and 10 times the maximum human dose (rats) on a mg/m^2 basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats.

Antipsychotic medicines have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated.

The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these medicines and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, RISPERDAL should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia (see **section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are:

- lactose monohydrate
- maize starch
- microcrystalline cellulose
- hypromellose
- magnesium stearate
- colloidal anhydrous silica
- sodium lauryl sulfate
- propylene glycol
- purified talc (0.5 mg, 2 mg, 3 mg and 4 mg tablets only)
- titanium dioxide (0.5 mg, 2 mg, 3 mg and 4 mg tablets only)
- iron oxide red (0.5 mg tablets only)
- sunset yellow FCF (2 mg tablets only)
- quinoline yellow (3 mg and 4 mg tablets only)
- indigo carmine (4 mg tablets only).

The inactive ingredients for the 1 mg/mL oral solution are

- tartaric acid
- benzoic acid
- sodium hydroxide
- purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

RISPERDAL 0.5 mg tablets – Store below 30ºC. Store in a dry place. Protect from light.

RISPERDAL 1 mg, 2 mg, 3 mg, 4mg tablets – Store below 25°C. Store in a dry place. Protect from light.

RISPERDAL 1 mg/mL oral solution – Store below 30°C. Do not refrigerate.

Keep out of the reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

RISPERDAL 0.5 mg tablets may be supplied in blister packs of 10^ or 20 tablets.

RISPERDAL 1 mg, 2 mg, 3 mg and 4 mg tablets may be supplied in blister packs of 60 tablets.

^Not all pack sizes are marketed.

Risperdal oral solution 1 mg/mL comes in a 30 or 100 mL Glass Type III coloured bottle with a pipette which is calibrated in milligrams (mg) and millilitres (mL). Minimum volume of pipette is 0.25 mL and maximum volume is 3 mL.

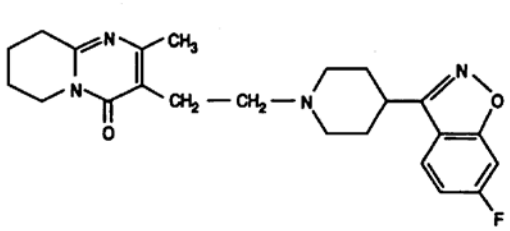
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Risperidone is chemically identified as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Chemical structure



$C_{23}H_{27}FN_4O_2$

MW=410.49

CAS number

CAS-106266-06-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription only medicine

8 SPONSOR

Janssen-Cilag Pty Ltd

1-5 Khartoum Road

Macquarie Park NSW 2113

Telephone: 1800 226 334

NZ Office:

Auckland, NEW ZEALAND

Telephone: 0800 800 806

9 DATE OF FIRST APPROVAL

30 November 1993

10 DATE OF REVISION

11 August 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Excipients with known effect updated
6.1	Reformat excipient information (no actual changes to formulation)
6.4	Updated storage conditions
6.5	Updated pack size details in line with ARTG Added statement that not all pack sizes are marketed