# NEW ZEALAND DATA SHEET

# RISPERON®

## 1. Product Name

Risperon, 1 mg/mL, oral solution.

## 2. Qualitative and Quantitative Composition

1 mL of solution contains 1 mg of risperidone.

Excipient with known effect: contains benzoic acid.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

Risperon is a clear, colourless solution.

## 4. Clinical Particulars

### *4.1 Therapeutic indications*

Risperidone is indicated for the treatment of schizophrenia and other psychotic disorders. These include first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech) are prominent.

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

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

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

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

for patients with disruptive behaviour disorders should be initiated only in consultation with a specialist, including child and adolescent psychiatrists, paediatric neurologists, developmental paediatricians, or other physicians conversant in the diagnosis and treatment of conduct and other disruptive behaviour disorders.

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

## *4.2 Dose and method of administration*

### Schizophrenia

#### *Switching from other antipsychotics*

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

#### *Adults*

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

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

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

#### *Elderly*

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

Risperidone is well tolerated in the elderly.

#### *Children*

Experience is lacking in children aged less than 15 years.

### Bipolar mania

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

### Behavioural disturbances in patients with dementia

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

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

## Conduct and other disruptive behaviour disorders

### For Subjects ≥ 50 kg

A starting dose of 0.5 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, which 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, although some patients 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 risperidone must be evaluated and justified on an on-going basis.

## Autism

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

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

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

**Doses of Risperidone in Paediatric Patients with Autistic Disorder**

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

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

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

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

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

### Special populations

#### *Renal and hepatic impairment*

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

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

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

## *4.3 Contraindications*

Risperidone is contraindicated in patients with a known hypersensitivity to any ingredient in the product (see section 6.1).

## *4.4 Special warnings and precautions for use*

## *Warnings*

### 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 medicines, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% (40/1009) for risperidone treated patients compared to 3.1% (22/712) for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

#### *Concomitant use with furosemide*

In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3% [15/206]; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1% [25/803]; mean age 84 years, range 70-96) or furosemide alone (4.1% [5/121]; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been clearly identified to explain this finding, and no consistent pattern for cause of death was observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased mortality among patients taking other diuretics concomitantly with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

#### *Cerebrovascular adverse events*

In placebo-controlled trials in elderly patients with dementia, there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient

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

## *Precautions*

### Alpha blocking activity

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see section 4.2). A dose reduction should be considered if hypotension occurs. Special care should be taken in patients taking medications to lower blood pressure.

### Tardive dyskinesia / extrapyramidal symptoms (TD/EPS)

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

#### *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).

### 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

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

### Parkinson’s disease and dementia with Lewy bodies

Physicians should weigh the risks versus benefits when prescribing antipsychotics including risperidone 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 risperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

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

## Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including risperidone. 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 risperidone 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 risperidone and have their WBC followed until recovery.

## Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic agents. 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 risperidone and preventative measures undertaken.

## Priapism

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

## Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing risperidone 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 medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

## Seizures

As with other antipsychotic medicines, risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower seizure threshold.

## Intraoperative floppy iris syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha$_1$-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha$_1$ blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

## Weight gain

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

## QT interval

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

## Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medication use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone and other antipsychotic medications should be used cautiously in patients at risk for aspiration pneumonia.

## Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy. Prescriptions for risperidone should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

## Special populations

### *Use in the elderly*

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

### *Use in renal impairment*

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

***Use in hepatic impairment***

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

***Paediatric use***

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

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

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

Experience of risperidone treatment in children with schizophrenia aged less than 15 years is lacking. Experience is lacking in children with conduct and other disruptive behaviour disorders aged less than 5 years. Experience is lacking in children with autism aged less than 5 years. However, in a toxicity study with juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Long bone growth was not affected at a dose similar to the maximum human dose in adolescents (6 mg/day); effects were observed at a dose 4-fold (on an AUC basis) or 7-fold (on a mg/m$^2$ basis) the maximum human dose in adolescents.

## *4.5 Interaction with other medicines and other forms of interaction*

### Pharmacodynamic-related interactions

***Centrally-acting drugs and alcohol***

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

***Levodopa and dopamine agonists***

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

***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).

***Drugs with hypotensive effects***

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

***Drugs known to prolong the QT interval***

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

### Pharmacokinetic-related interactions

Food does not affect the absorption of Risperon.

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

### *CYP3A4 and/or P-gp inhibitors*

Co-administration of Risperon 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 Risperon.

### *CYP3A4 and/or P-gp inducers*

Coadministration of Risperon 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 Risperon.

### *Highly protein-bound drugs*

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

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

### *Paediatric population*

Interaction studies have only been performed in adults. The relevance of the results from these studies in 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 plasma concentrations of the active antipsychotic fraction.

### *Anticholinesterases*

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

### *Antiepileptics*

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone.

- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

***Antifungals***

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

***Antipsychotics***

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

***Antivirals***

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

***Beta blockers***

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

***Calcium channel blockers***

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

***Digitalis glycosides***

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

***Diuretics***

- Furosemide: See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide and oral risperidone.

***Gastrointestinal drugs***

- H2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

***Lithium***

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

***Sodium channel blockers***

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

***SSRIs and tricyclic antidepressants***

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone but less so of the active antipsychotic fraction.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.
- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction (see section 5.2).

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

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

Risperidone 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.

### Breast-feeding

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

### Fertility

*Non-teratogenic class effect:* Neonates exposed to antipsychotic medicines (including risperidone) 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.

## *4.7 Effects on ability to drive and use machines*

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

## *4.8 Undesirable effects*

### Clinical trial data

The safety of risperidone was evaluated from a clinical trial database consisting of 9803 patients exposed to one or more doses of risperidone for the treatment of various psychiatric disorders in adults, elderly patients with dementia, and paediatrics. Of these 9803 patients, 2687 were patients who received risperidone while participating in double-blind, placebo-controlled trials. The conditions and duration of treatment with risperidone 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 risperidone-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 Risperidone -Treated Adult Patients in Double-Blind Placebo-Controlled Studies**

| **System/Organ Class**<br>Adverse reaction | **Risperidone ≤ 8 mg/day (N=853) %** | **Risperidone >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 risperidone-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 Risperidone-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<br>Adverse reaction | Risperidone (N=1009)<br>% | PLACEBO (N=712)<br>% |
|---|---|---|
| **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 Risperidone-treated paediatric 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 Risperidone-Treated Paediatric Patients in Double-Blind Placebo-Controlled Studies: ADRs Not Listed in Table 1 or Reported at ≥ 2 Times the Frequency of ADRs Listed in Table 1.**

| **System/Organ Class**<br>Adverse reaction | **Risperidone ≤ 3 mg/day (N=344) %** | **Risperidone >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 and administration site conditions** | | | |
| Fatigue | 19.2 | 18.9 | 4.9 |
| Pyrexia | 8.4 | 3.2 | 6.3 |
| Feeling abnormal | 1.2 | 0 | 0 |
| Sluggishness | 0.9 | 1.1 | 0 |
| Chest discomfort | 0.3 | 1.1 | 0 |
| **Investigations** | | | |
| Weight increased | 4.9 | 2.1 | 0.9 |
| Blood prolactin increased | 3.8 | 0 | 0.3 |

## Other clinical trial data

Paliperidone is the active metabolite of risperidone, therefore the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. This subsection includes additional adverse drug reactions (ADRs) reported with risperidone and/or paliperidone in clinical trials.

ADRs reported with risperidone and/or paliperidone by ≥ 1% of risperidone-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 Risperidone 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**<br>(The terms within each system organ class are sorted alphabetically) |
|---|
| **System/Organ Class**<br>Adverse reaction |
| **Psychiatric disorders**<br>Agitation, Insomnia* |
| **Nervous system disorders**<br>Akathisia*, Dyskinesia*, Dystonia*, Parkinsonism* |
| **Vascular disorders**<br>Hypertension |
| **Musculoskeletal and connective tissue disorders**<br>Musculoskeletal pain |
| **General disorders and administration site conditions**<br>Gait abnormal, Oedema*, Pain |
| **Injury, poisoning and procedural complications**<br>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 risperidone-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. Adverse Drug Reactions Reported with Risperidone and/or Paliperidone by < 1% of Risperidone-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**.<br>(The terms within each system organ class are sorted alphabetically) |
|---|
| **System/Organ Class**<br>Adverse reaction |
| **Infections and infestations**<br>Acarodermatitis, Bronchitis, Cystitis, Ear infection, Eye infection, Infection, Localised infection, Onychomycosis, Respiratory tract infection, Tonsilitis, Viral infection |
| **Blood and lymphatic system disorders**<br>Eosinophil count increased, Haematocrit decreased, Neutropenia, White blood cell count decreased |
| **Endocrine disorders**<br>Glucose urine present, Hyperprolactinaemia |
| **Metabolism and nutrition disorders**<br>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 discoloration, Skin disorder, Skin lesion

**Musculoskeletal and connective tissue disorders**

Joint stiffness, Muscular weakness, Rhabdomyolysis

**Renal and urinary disorders**

Dysuria

**Reproductive system and breast disorders**

Amenorrhoea, Breast discharge, Ejaculation disorder, Erectile dysfunction, Gynaecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge

**General disorders**

Body temperature decreased, Chills, Discomfort, Drug withdrawal syndrome, Face oedema, Malaise, Peripheral coldness, Thirst

**Injury, poisoning and procedural complications**

Procedural pain

ADRs reported with risperidone and/or paliperidone in other clinical trials but not reported by risperidone-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 Risperidone-treated Subjects in a Pooled Dataset of 23 Double-blind, Placebo-controlled Pivotal Studies**<br>(The terms within each system organ class are sorted alphabetically) |
|---|
| **System/Organ Class**<br>Adverse reaction |
| **Immune system disorders**<br>Anaphylactic reaction |
| **Metabolism and nutrition disorders**<br>Hyperinsulinaemia |
| **Psychiatric disorders**<br>Anorgasmia |
| **Nervous system disorders**<br>Head titubation, Neuroleptic malignant syndrome |
| **Eye disorders**<br>Eye movement disorder, Photophobia |
| **Cardiac disorders**<br>Postural orthostatic tachycardia syndrome |
| **Gastrointestinal disorders**<br>Intestinal obstruction |
| **Skin and subcutaneous tissue disorders**<br>Drug eruption, Urticaria |
| **Reproductive system and breast disorders**<br>Breast discomfort, Breast engorgement, Breast enlargement, Menstruation delayed |
| **General disorders and administration site conditions**<br>Induration |

## Class effects

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

## Postmarketing data

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

| | |
|---|---|
| Very common | $\geq$ 1/10 |
| Common | $\geq$ 1/100 to < 1/10 |
| Uncommon | $\geq$ 1/1000 to < 1/100 |
| Rare | $\geq$ 1/10,000 to < 1/1000 |
| Very rare | < 1/10,000, including isolated reports. |

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

| Table 5. Adverse Drug Reactions Identified During Postmarketing Experience with Risperidone and/or Paliperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Risperidone | |
|---|---|
| **Blood and lymphatic disorders** | |
| *Very rare* | Agranulocytosis, Thrombocytopenia |
| **Endocrine disorders** | |
| *Very rare* | Inappropriate antidiuretic hormone secretion |
| **Metabolism and nutrition disorders** | |
| *Very rare* | Diabetes mellitus, Diabetic ketoacidosis, Hypoglycaemia, Water intoxication |
| **Psychiatric disorders** | |
| *Very rare* | Mania, Somnambulism |
| *Not known* | Sleep-related eating disorder |
| **Nervous system disorders** | |
| *Very rare* | Dysgeusia |
| **Eye disorders** | |
| *Very rare* | Floppy iris syndrome (intraoperative) |
| **Cardiac disorders** | |
| *Very rare* | Atrial fibrillation |
| **Vascular disorders** | |
| *Very rare* | Deep vein thrombosis, Pulmonary embolism |
| **Respiratory, thoracic, and mediastinal disorders** | |
| *Very rare* | Sleep apnoea syndrome |
| **Gastrointestinal disorders** | |
| *Very rare* | Pancreatitis, ileus |
| **Hepatobiliary disorders** | |
| *Very rare* | Jaundice |
| **Skin and subcutaneous tissue disorders** | |
| *Very rare* | Alopecia, Angioedema, Stevens-Johnson syndrome/Toxic epidermal necrolysis |
| **Renal and urinary disorders** | |
| *Very rare* | Urinary retention |
| **Pregnancy, puerperium and perinatal conditions** | |
| *Very rare* | Drug withdrawal syndrome neonatal |
| **Reproductive system and breast disorders** | |
| *Very rare* | Priapism |
| **General disorders** | |
| *Very rare* | Hypothermia |

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

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## *4.9 Overdose*

### Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. 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 risperidone 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 risperidone. 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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08

### Mechanism of action

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

Risperidone is a selective monoaminergic antagonist having a high affinity for serotoninergic 5-$HT_2$ and dopaminergic $D_2$ receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to $H_1$-histamine and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy risperidone. Risperidone, as a potent $D_2$ antagonist, improves the positive symptoms of schizophrenia but causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

## *5.2 Pharmacokinetic properties*

### Absorption

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

### Distribution

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

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and $alpha_1$-acid glycoprotein. The plasma protein binding of risperidone is 88%, while that of 9-hydroxy-risperidone is 77%.

### Biotransformation

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

### Elimination

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

One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces.

In urine, risperidone plus 9-hydroxy-risperidone represents 35-45% of the dose.

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

# 6. Pharmaceutical Particulars

## *6.1 List of excipients*

Risperon oral solution also contains:

- Benzoic acid
- Tartaric acid
- Hydrochloric acid
- Purified water.

Contains benzoates.

## *6.2 Incompatibilities*

Not applicable. Incompatible with tea.

## *6.3 Shelf life*

3 years.

Opened: 4 months.

## *6.4 Special precautions for storage*

Stored at or below 30°C.

Do not refrigerate. For storage conditions after first opening of the medicine, see section 6.3.

### *6.5 Nature and contents of container*

Type III amber glass bottle with child resistant cap and pipette. Pack sizes of 30, 60, 100 and 120 mL solution.

Not all pack sizes may be marketed.

### *6.6 Special precautions for disposal*

Not applicable.

## 7. Medicines Schedule

Prescription Medicine

## 8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

## 9. Date of First Approval

11 September 2008

## 10. Date of Revision of the Text

06 March 2023

| Section | Summary of changes |
|---|---|
| Header | Logo updated from Mylan to Viatris |
| 2 | Update to declaration of excipient with known effect, contains benzoic acid. |
| 6.1 | Added statement ‘Contains benzoates.’ |
| 6.2 | Added 'incompatible with tea’. |
| 6.4 | Storage statement updated to ‘Stored at or below 30°C’ to align with TPDR. |
| 8 | Sponsor details updated to Viatris |
| - | Attribution statement included for trade mark |

Risperon® is a Viatris company trade mark.