AUSTRALIAN PRODUCT INFORMATION – NOUMED RISPERIDONE TABLETS

(Risperidone)

1. NAME OF THE MEDICINE

Risperidone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NOUMED RISPERIDONE tablets contain 0.5 mg, 1 mg, 2 mg, 3 mg or 4 mg of risperidone.

List of excipients with known effect: sugars (as lactose).

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

3. PHARMACEUTICAL FORM

NOUMED RISPERIDONE 0.5mg tablets - Red, oval shaped tablets with a breaking notch.

NOUMED RISPERIDONE 1mg tablets - White coated, oval, scored tablets, coded “1” on one side.

NOUMED RISPERIDONE 2mg tablets - Apricot coated, oval, scored tablets, coded “2” on one side.

NOUMED RISPERIDONE 3mg tablets - Yellow coated, oval, scored tablets, coded “3” on one side.

NOUMED RISPERIDONE 4mg tablets - Green coated, oval, scored tablets, coded “4” on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of schizophrenia and related psychoses.

Short-term treatment of acute mania associated with bipolar I disorder.

Treatment of behavioural disturbances in dementia.

Treatment of conduct and other disruptive 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 for maintenance data*).

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

Schizophrenia

Studies on the efficacy and safety of risperidone have been performed, predominantly in patients with schizophrenia. The pivotal studies lasted up to eight 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 NOUMED RISPERIDONE therapy is initiated. In the case of depot injections, it is recommended that NOUMED RISPERIDONE not be administered until the next scheduled injection.

Alterations in requirements of antiparkinson therapy may be required in patients switching to NOUMED RISPERIDONE. These requirements should be evaluated periodically.

Adults

NOUMED RISPERIDONE may be given once or twice daily.

Patients, whether acute or chronic, may start with NOUMED RISPERIDONE 1mg twice daily. The dosage may be increased on the second day to 2mg 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, NOUMED RISPERIDONE may be given once daily or twice daily, with a recommended daily dose between 4 and 6mg. However, some patients may benefit from higher doses.

Doses above 5mg 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 NOUMED RISPERIDONE 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 to 2 mg twice daily.

Use in children

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

Use in patients with hepatic and/or renal impairment

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

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

Compatibility to meals

The absorption is not affected by food and thus risperidone can be given with or without meals (see *Section 5.2 Pharmacokinetic Properties*).

Bipolar mania

NOUMED RISPERIDONE 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/day.

A dosing range of between 2 and 6mg/day is recommended.

Behavioural disturbances in dementia

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

Conduct and other disruptive behaviour disorders

Subjects ≥ 50kg

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

Subjects < 50kg

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 NOUMED RISPERIDONE must be evaluated and justified on an ongoing basis.

Experience is lacking in children aged less than 5 years.

Behavioural Disorders Associated with Autism

NOUMED RISPERIDONE can be administered once or twice daily.

NOUMED RISPERIDONE should be administered based on bodyweight. Dosing should begin at 0.25mg or 0.5mg/day based upon weight (see Table 1 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 ≥ two 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 Table 1.

Table 1: Doses of risperidone 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
< 20kg	0.25mg	0.5mg	+ 0.25mg at ≥ 2 week intervals	0.5 - 1.5mg
≥ 20kg	0.5mg	1.0mg	+ 0.5mg at ≥ 2 week intervals	1.0 - 2.5mg*
For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided *Doses of risperidone in paediatric patients with autistic disorder (by mg/kg/day)*				
All	0.01mg/kg/day	0.02mg/kg/day	+0.01mg/kg/day at ≥ 2 week intervals	0.02mg/kg/day - 0.06mg/kg/day

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

4.3 CONTRAINDICATIONS

Known hypersensitivity to the medicine or any of its excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 risperidone. In placebo controlled trials with risperidone in this population, the incidence of mortality was 4.0% (40/1,009) for risperidone treated patients and 3.1% (22/712) for placebo treated patients. The mean age (range) of patients who died was 86 years (range 67 to 100).

Concomitant use with frusemide

In the risperidone placebo controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3% (15/206); mean age 89 years, range 75 to 97)

compared to treatment with risperidone alone (3.1% (25/803); mean age 84 years, range 70 to 96) or frusemide alone (4.1% (5/121); mean age 80 years, range 67 to 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 (CVAE)

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 to 97) treated with risperidone 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 nonserious 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).

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. NOUMED RISPERIDONE should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia or cerebrovascular disease. The dosage should be gradually titrated as recommended (see *section 4.2 Dose and Method of Administration*). Special care should be taken to avoid hypotension in patients with a history of cerebrovascular insufficiency or cardiovascular disorders, and in patients taking medications to lower blood pressure. In case of hypotension a dose decrease should be considered.

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.

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 NOUMED RISPERIDONE 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 NOUMED RISPERIDONE 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 NOUMED RISPERIDONE 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, risperidone should be used with caution in patients with known cardiovascular disease (e.g.

congenital long QTc syndrome, heart failure, myocardial infarction, conduction abnormalities and arrhythmia) and other conditions (such as dehydration, hypokalaemia and hypovolaemia).

Tardive dyskinesia

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements, 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 risperidone than with haloperidol. In the optimal clinical dose range, the difference between risperidone and haloperidol was significant. Therefore, the risk of developing TD may be less with risperidone. 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, risperidone should be prescribed in a manner that is most likely to minimise the risk of TD. As with any antipsychotic medicine, risperidone 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.

Neuroleptic malignant syndrome

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

The 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) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary CNS pathology.

The management of NMS should include the immediate discontinuation of all antipsychotic medicines and other medicines not essential to current therapy; intensive symptomatic treatment and medical monitoring; and 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.

Parkinson’s disease/ dementia with Lewy bodies

Doctors should weigh the risks versus benefits when prescribing antipsychotics, including NOUMED RISPERIDONE, to patients with Parkinson's disease or dementia with Lewy bodies (DLB) since both groups may be at increased risk of NMS 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.

Seizures

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

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

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.

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 NOUMED RISPERIDONE 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 risperidone 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 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 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 NOUMED RISPERIDONE 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 NOUMED RISPERIDONE (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 alpha 1 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-oestrogenic bone loss.

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

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.

Patients with psycho-organic disturbances have an increased risk of undesirable effects.

Paradoxically, antipsychotic medicinal products can increase symptoms like excitation, agitation and aggressiveness. When these symptoms occur, a dose reduction of risperidone or stopping of treatment can be necessary, just like with the other antipsychotic medicinal products.

Special caution should be exercised in patients with hyperprolactinaemia, prolactin-dependent tumors (e.g. hypophysal prolactinoma) and possibly prolactin dependent tumors (e.g. breast cancer). Risperidone may lead to dose-related elevation of prolactin levels. Possible associated manifestations are galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and even absence of menstruation (amenorrhoea) (see also *Section 4.8 Adverse Effects (Undesirable Effects)*). In addition tissue culture studies indicate that cell growth in human breast tumors may be stimulated by prolactin. Although no clear connection between administration of antipsychotics and breast cancer has so far been demonstrated in clinical or epidemiological studies, caution is advisable if there is relevant previous history.

Withdrawal symptoms

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the mergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Use in hepatic impairment

Since clinical experience is lacking in this patient population, risperidone 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 hepatic disease, it is advised to monitor the hepatic function.

Use in renal impairment

Since clinical experience is lacking in this patient population, NOUMED RISPERIDONE 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 elderly patients. The frequency of dizziness, bradycardia and injuries caused by a tendency to fall down seems to be higher in elderly than in younger patients.

Paediatric use

Experience is lacking in children with schizophrenia aged less than 15 years. There are also insufficient preclinical 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 (6mg/day); exposure at the no-effect dose was similar to human exposure.

Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands. The sedative effect of risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents. Risperidone was associated with mean increases in body weight and body mass index (BMI).

Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects. During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.For information on the use of NOUMED RISPERIDONE in children 5 years and older in the treatment of conduct disorder (see *section 5.1 Pharmacodynamic Properties: Clinical Trials*).

Effects on laboratory tests

Refer to *section 4.8 Adverse Effects (Undesirable Effects)*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The risks of using NOUMED RISPERIDONE in combination with other medicines have not been systematically evaluated. Given the primary central nervous system effects of risperidone, it should be used with caution in combination with other centrally acting medicines. Risperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Tricyclic antidepressants may potentiate the postural hypotensive effect of risperidone. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

Verapamil, an inhibitor of CYP3A4 and P-gp, increases the plasma concentration of risperidone. Concomitant treatment with other antipsychotics, lithium, antidepressants, anti-parkinsonian medicines, and medicines with a central anticholinergic effect increases the risk of tardive dyskinesia.

As with other antipsychotics, caution is advised when prescribing risperidone to patients currently using medications known to:

- prolong QT interval - these medications include other antipsychotics, antiarrhythmics class IA or III, arsenic trioxide, levomethadyl acetate, dolasetron, cisapride, antibiotics (e.g. erythromycin), medicines used to treat/prevent malaria, antihistamines, antidepressants
- cause hypokalemia or hypomagnesemia (certain diuretics)
- increase the excretion of water, sodium and sometimes chlorides to a large extent (diuretics like frusemide and chlorothiazide)
- inhibit the hepatic metabolism of risperidone.

The anti-α_1-adrenergic effect can increase the blood pressure lowering effect of phenoxybenzamine, labetalol and other α-blocking sympathomimetic active substances, methyldopa, reserpine and other centrally acting antihypertensive active substances. Tricyclic antidepressants may potentiate the postural hypotensive effect of risperidone.

A study on interactions between antipsychotic and antihypertensive drugs identified that older antipsychotics, such as chlorpromazine, haloperidol and thiothixene may block the antihypertensive effects of guanethidine. Therefore, caution is advised when newer antipsychotics, such as risperidone, are used in combination with guanethidine.

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 stabilised on a risperidone dose of 3mg twice daily, and carbamazepine was

administered from three weeks (days 22 to 42) at a dose that was adjusted for the therapeutic concentration (5 to 12microgram/mL, average dose 573 +/- 168mg/day). Carbamazepine serum concentrations were determined at the beginning and at the end of the period of coadministration of the two compounds. The results showed that coadministration of risperidone with carbamazepine did not affect the serum concentrations of carbamazepine during the observation period of three weeks. The values were all within the therapeutic range of 5 to 12microgram/mL.

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic risperidone plus 9-hydroxyrisperidone of risperidone. Similar effects may be observed with other hepatic enzyme inducers, for example rifampicin, phenytoin, barbiturates and St. John's Wort (Hypericum perforatum). On initiation or discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of NOUMED RISPERIDONE should be re-evaluated and, if necessary, reduced.

Fluoxetine, paroxetine, terbinafine and other strong inhibitors of CYP2D6 may increase the plasma concentrations of the active moiety (risperidone plus 9-hydroxyrisperidone).

Paroxetine and fluoxetine are potent CYP2D6 inhibitors. Coadministration 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 to 12 hour of risperidone plus 9-hydroxyrisperidone. Administration of paroxetine 20mg/day for four weeks to patients stabilised on risperidone 4 to 8mg/day produced a relative increase of 1.51 +/- 0.34 in C_{min} of risperidone plus 9-hydroxyrisperidone.

Therefore, the risperidone dose should be re-evaluated during initiated and cessation of concomitant treatment with strong inhibitors of CYP2D6.

Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic risperidone plus 9-hydroxyrisperidone.

Quinidine, phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but the antipsychotic risperidone plus 9-hydroxyrisperidone stays lower than usual (see *section 5.2 Pharmacokinetic Properties*). Therefore, the total effect of the active moiety has not changed to a clinically relevant extent.

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 six days of the study, produced relative increases in the 0 to 12 hour 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-hydroxyrisperidone respectively. These modest increases do not necessitate dose modification.

In volunteer studies, a single risperidone 1mg dose was administered with cimetidine 400mg twice daily or ranitidine 150mg twice daily. Cimetidine produced a relative increase in AUC 0-infinity of 1.95 +/- 0,78, 1.01 +/- 0.25 and 1.15 +/- 0.28 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxyrisperidone respectively. Relative C_{max} increases were 1.90 +/- 0.95, 0.95 +/- 0.21 and 1.24 +/- 0.27. Coadministration of ranitidine produced a relative increase of 1.35 +/- 0.32, 1.23 +/- 0.44 and 1.25 +/- 0.39 in AUC 0-infinity 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.

Antacids may reduce the oral absorption of antipsychotic medicines.

Erythromycin, a CYP3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic risperidone plus 9-hydroxyrisperidone. The cholinesterase inhibitors galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic risperidone plus 9-hydroxyrisperidone.

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

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 risperidone or for any of the medicines tested.

See *section 4.4 Special Warnings and Precautions for Use - Elderly patients with dementia*, regarding increased mortality due to interaction of risperidone and concomitant frusemide.

Concomitant use of risperidone and alcohol should be avoided, because risperidone increases the effect of alcohol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

As with other drugs that antagonize dopamine D_2-receptors, risperidone elevates prolactin level. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. There were no relevant effects observed in the non-clinical studies.

Use in pregnancy

Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The safety of NOUMED RISPERIDONE during human pregnancy has not been established. Although in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin and CNS mediated effects were observed. No teratogenic effect was noted in rats and rabbits following oral administration of risperidone during the period of organogenesis at doses up to nine times the human dose on a mg/m^2 basis. The use of neuroleptic medicines during the last trimester of pregnancy has resulted in long term but reversible neurological disturbances of extrapyramidal nature in the infant

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (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, respiration distress and feeding 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.

NOUMED RISPERIDONE should only be used during pregnancy 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 NOUMED RISPERIDONE should not breastfeed.

In rats oral administration of risperidone during late gestation and lactation was associated with an increase in pup deaths during the first four 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 fivefold 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 to 5 times the maximum human dose on a mg/m^2 basis.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

NOUMED 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The safety of risperidone was evaluated from a clinical trial database consisting of 9712 patients exposed to one or more doses of risperidone for the treatment of various psychiatric disorders in adults, elderly patients with dementia, and pediatrics. Of these 9712 patients, 2626 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 2.

Table 2: Adverse Dr**ug Reactions Reported by ≥ 1% of Risperidone**-Treated Adult Patients in Double-Blind Placebo-Controlled Studies

System/Organ Class 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

System/Organ Class Adverse Reaction	Risperidone **≤ 8 mg/day** (N=853) %	Risperidone > 8-16 mg/day (N=198) %	Placebo (N=687) %
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 3. Table 3 includes only those ADRs that are either not listed in Table 2 or those ADRs that occurred at ≥ 2 times the frequency of the ADRs listed in Table 2.

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

System/Organ Class Adverse Reaction	Risperidone (N=1009) %	Placebo (N=712) %
Infections and Infestations		
Urinary tract infection	12.9	10.3
Pneumonia	3.1	2.4
Cellulitis	1.1	1.3
Metabolism and Nutrition Disorders		
Decreased appetite	2.3	1.4
Psychiatric Disorders		
Confusional state	2.7	0.1
Nervous System Disorders		
Lethargy	7.6	2.2
Transient ischaemic attack	1.6	0.6
Depressed level of consciousness	1.3	0.3
Drooling	1.3	0
Cerebrovascular accident	1.1	0.4
Eye Disorders		
Conjunctivitis	2.7	1.1
Vascular Disorders		
Hypotension	2.2	1.4
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4.6	3.1
Rhinorrhoea	1.5	0.8
Gastrointestinal Disorders		
Dysphagia	1.5	1.3
Faecaloma	1.1	0.4
Skin and Subcutaneous Tissue Disorders		
Erythema	4.0	4.6
Musculoskeletal and Connective Tissue Disorders		
Posture abnormal	1.8	0.8
Joint swelling	1.5	0.3
General Disorders		
Oedema peripheral	7.7	3.9
Pyrexia	4.0	1.8
Gait disturbance	3.5	1.5
Pitting oedema	1.5	0.3
Investigations		
Body temperature increased	2.6	0.8

Double-Blind, Placebo-Controlled Data – Pediatric Patients

Adverse drug reactions (ADRs) reported by ≥ 1% of risperidone-treated pediatric patients in eight 3- to 8-week double-blind, placebo-controlled trials are shown in Table 4. Table 4 includes only those ADRs that are either not listed in Table 2 or those ADRs that occurred at ≥ 2 times the frequency of the ADRs listed in Table 2.

Table 4: Adverse Drug Reactions (ADRs) Reported by **≥ 1% of risper**idone-Treated Pediatric Patients Double-Blind Placebo-Controlled Studies: ADRs Not Listed in Table 2 or Reported at ≥ 2 Times the Frequency of ADRs Listed in Table 2

System/Organ Class 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

System/Organ Class Adverse Reaction	Risperidone **≤ 3 mg/day** (N=344) %	Risperidone > 3-6 mg/day (N=95) %	Placebo (N=349) %
Renal and Urinary Disorders			
Enuresis	6.4	1.1	5.2
Urinary incontinence	2.0	0	1.4
Pollakiuria	1.5	1.1	0.3
Reproductive System and Breast Disorders			
Galactorrhea	0.6	2.1	0
General Disorders			
Fatigue	19.2	18.9	4.9
Pyrexia	8.4	3.2	6.3
Feeling abnormal	1.2	0	0
Sluggishness	0.9	1.1	0
Chest discomfort	0.3	1.1	0
Investigations			
Weight increased	4.9	2.1	0.9
Blood prolactin increased	3.8	0	0.3

Other Clinical Trial Data

Adverse drug reactions (ADRs) reported in double-blind placebo-controlled clinical trials by < 1% of risperidone-treated adult or pediatric patients, or elderly patients with dementia, or at any rate by risperidone-treated patients in other studies, including double-blind, active-controlled and open-label studies are shown in Table 5.

Table 5: Adverse Drug Reactions Reported in Double-Blind Placebo-Controlled Clinical Trials by < 1% of Risperidone-Treated Adult or Pediatric Patients, or Elderly Patients with Dementia, or at Any Rate by Risperidone-Treated Patients in Other Studies, Including Double-Blind, Active-Controlled and Open-Label Studies
Infections and Infestations Ear infection, Viral infection, Pharyngitis, Tonsillitis, Bronchitis, Eye infection, Localised infection, Cystitis, Otitis media, Onychomycosis, Acarodermatitis, Bronchopneumonia, Respiratory tract infection, Tracheobronchitis, Otitis media chronic
Blood and Lymphatic System Disorders Granulocytopenia Immune System Disorders Drug hypersensitivity Endocrine Disorders Hyperprolactinemia Metabolism and Nutrition Disorders Polydipsia, Anorexia Psychiatric Disorders Agitation, Blunted affect, Sleep disorder, Libido decreased, Anorgasmia Nervous System Disorders Unresponsive to stimuli, Coordination abnormal, Loss of consciousness, Speech disorder, Hypoesthesia, Movement disorder, Tardive dyskinesia, Cerebral ischemia, Cerebrovascular disorder, Neuroleptic malignant syndrome, Diabetic coma, Head titubation Eye Disorders Ocular hyperemia, Eye discharge, Eye rolling, Eyelid oedema, Eye swelling, Eyelid margin crusting, Dry eye, Lacrimation increased, Photophobia, Glaucoma, Visual acuity reduced

Ear and Labyrinth Disorders Tinnitus Cardiac Disorders Sinus bradycardia, Sinus tachycardia, Palpitations, Atrioventricular block first degree, Bundle branch block left, Bundle branch block right, Atrioventricular block Vascular Disorders Flushing Respiratory, Thoracic, and Mediastinal Disorders Wheezing, Pneumonia aspiration, Dysphonia, Productive cough, Respiratory tract congestion, Rales, Respiratory disorder, Nasal oedema, Hyperventilation Gastrointestinal Disorders Fecal incontinence, Gastritis, Lip swelling, Cheilitis, Aptyalism
Skin and Subcutaneous Tissue Disorders Skin discoloration, Skin lesion, Skin disorder, Rash erythematous, Rash papular, Rash generalised, Rash maculo-papular Musculoskeletal and Connective Tissue Disorders Musculoskeletal chest pain, Joint stiffness, Muscular weakness, Rhabdomyolysis Renal and Urinary Disorders Dysuria Reproductive System and Breast Disorders Menstruation irregular, Amenorrhea, Gynecomastia, Vaginal discharge, Erectile dysfunction, Ejaculation disorder, Menstrual disorder, Breast enlargement, Sexual dysfunction, Retrograde ejaculation General Disorders Thirst, Influenza-like illness, Oedema, Malaise, Face oedema, Discomfort, Generalised oedema, Chills, Peripheral coldness, Drug withdrawal syndrome, Adverse drug reaction Investigations Alanine aminotransferase increased, Electrocardiogram abnormal, Eosinophil count increased, Aspartate aminotransferase increased, White blood cell count decreased, Blood glucose increased, Hemoglobin decreased, Hematocrit decreased, Body temperature decreased, Blood pressure decreased, Transaminases increased

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

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

Blood and Lymphatic Disorders: Neutropenia

Metabolism and nutrition disorders: Hyperglycaemia

Psychiatric Disorders: Depression, Initial insomnia

Nervous System Disorders: Paresthesia, Convulsion

Eye Disorders: Blepharospasm

Ear and Labyrinth Disorders: Vertigo

Cardiac Disorders: Bradycardia

Vascular Disorders: Hypertension

Gastrointestinal Disorders: Toothache, Tongue spasm

Skin and Subcutaneous Tissue Disorders: Eczema

Musculoskeletal, Connective Tissue, and Bone Disorders: Buttock pain

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

General Disorders and Administration Site Conditions: Pain, Gait abnormal

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

Injury and Poisoning: Fall

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with risperidone are included in Table 6. The frequencies are provided according to the following convention:

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

In Table 6, ADRs are presented by frequency category based on spontaneous reporting rate.

Table 6: Adverse Drug Reactions Identified During Postmarketing Experience with Risperidone by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and Lymphatic Disorders	
Very rare	Agranulocytosis
Endocrine Disorders	
Very rare	Inappropriate antidiuretic hormone secretion
Very rare	Thrombocytopenia[a]
Metabolism and Nutrition Disorders	
Very rare	Diabetic ketoacidosis, Diabetes mellitus, Hyperglycaemia
Very rare	Water intoxication
Psychiatric Disorders	
Very rare	Mania
Nervous System Disorders	
Very rare	Dysgeusia
Eye Disorders	
Very rare	Floppy iris syndrome (intraoperative)
Rare	Ventricular arrhythmias (VF or VT)
Very rare	Cardiac arrest, torsades de pointes and sudden unexplained deaths
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal Disorders	
Very rare	Intestinal obstruction
Very rare	Pancreatitis, Ileus
Hepatobiliary Disorders	
Very rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Angioedema[b]
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
Investigations *Very rare*	Electrocardiogram QT prolonged[c]

[a] Search terms included Thrombocytopenia, Platelet count decreased, Plateletcrit decreased, Platelet production decreased

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

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

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

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

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the medicine's known pharmacological effects. These include drowsiness, sedation, tachycardia, hypotension and extrapyramidal symptoms. Torsade de pointes has been reported in association with combined overdose of NOUMED RISPERIDONE and paroxetine.

Overdosages of up to 360mg have been reported in the years since the international launch of risperidone. Cases of QT prolongation and convulsions have been reported, some in association with confounding factors such as hypokalaemia.

Treatment

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

There is no specific antidote to 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 the case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Risperidone is a selective monoaminergic antagonist with a high affinity for serotoninergic $5HT_2$-receptors 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 risperidone, 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 risperidone.

Antagonism of serotoninergic and histaminergic receptors may induce bodyweight gain.

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

Clinical trials

Schizophrenia

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

First episode psychosis

In a six week double blind parallel group actively controlled study in first admission, newly diagnosed schizophrenic patients (n = 183, risperidone = 99, haloperidol = 84), risperidone (1 to 8mg twice daily, mean daily dose 6.1mg) was as effective as haloperidol (1 to 8mg twice daily, mean daily dose 5.6mg) in controlling psychotic symptoms. The average patient age was 26 years (range 15 to 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 BPRS 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 six weeks duration in 98 patients (risperidone = 48, zuclopenthixol = 50), 48% of whom were male. The dosage was risperidone 2mg twice daily and zuclopenthixol 10mg twice daily increasing by one tablet a day until adequate control was achieved. The mean daily dose at endpoint for risperidone was 8mg and for zuclopenthixol 38mg. The median age was in the mid 30s (range 18 to 65). The overall severity of symptoms during the study was lower for risperidone ($p = 0.06$) and the clinical response (58% versus 42%; $p = 0.11$) was higher for risperidone.

Two dosages of risperidone, 4mg twice daily and 8mg once daily, 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 six weeks duration with a patient population of 211 patients (67% males) aged 18 to 64 (median 34) years. Efficacy was comparable for the two groups, although the trough plasma drug concentrations were lower and concentrations in the first eight hours post dose were higher (statistically not significant) for the 8mg once daily 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 to 6mg twice daily) compared to clozapine (50 to 300mg twice daily) in treatment resistant schizophrenic patients was studied in an eight 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 six months, 221 for 12 months and 30 patients for 12 to 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 one 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 risperidone 9mg and haloperidol 8.9mg. 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% of 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 risperidone in the treatment of acute mania was established in three double blind placebo controlled studies of three week duration in patients who met the DSM-IV criteria for bipolar I 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 eleven 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 to 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 three 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 nine week double blind treatment of risperidone or haloperidol or a nine week open label treatment on risperidone. Efficacy was maintained throughout the treatment period, although change from baseline in the MADRS was not as clearly maintained.

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

Adjunctive therapy: The efficacy of risperidone in the treatment of acute mania in combination with mood stabilisers was demonstrated in two three 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-hydroxyrisperidone 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 2mg/day) over a 12 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 Table 7. 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. (See Table 7)

Table 7

Parameter	Placebo n = 275	Risperidone < 0.75mg n = 193	Risperidone 0.75 - < 1.5mg n = 203	Risperidone **≥ 1.5mg** 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 0.75mg, 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 0.75mg/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 six 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 to 0.06mg/kg/day. 26% 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 six 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 (six weeks of open label treatment followed by six 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 three phases: a six week, open label acute treatment phase with risperidone (phase 1); a six week single blind continuation phase with risperidone (phase 2); and a six 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 bodyweight categories, with 0.25 to 0.75mg/day administered to subjects < 50kg and 0.5 to 1.5mg/day given to subjects ≥ 50kg. 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. 39 patients received risperidone 1.0 to 4.0mg/day (modal dose 1.64mg/day) and 38 patients received placebo for four 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 (range 0.2 to 4.0). The one year long-term study in adults (n = 58) was a continuation of the six 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 risperidone in the treatment of autism was established in two eight 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/non-compliance 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 to 17 years received twice daily doses of placebo or risperidone 0.5 to 3.5mg/day on a weight adjusted basis. Risperidone 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. Risperidone was also superior to placebo in improving scores on the ABC subscales of lethargy/social withdrawal, stereotypic behaviour, hyperactivity/non-compliance and inappropriate speech. (See Table 8)

Table 8: Analysis of five subscales at endpoint 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/ non compliance
RIS-USA-150 part 1 n (RIS: placebo) Diff LS means change	101 (49 : 52) - 3.2	101 (49 : 52) - 2.5	101 (49 : 52) - 1.8	101 (49 : 52) - 10.6	101 (49 : 52) - 10.4
95 % CI p-value	- 5.6, - 0.8 0.009	- 3.9, - 1.1 < 0.001	- 2.7, - 0.9 < 0.001	- 13.8, - 7.5 < 0.001	- 13.8, - 7.1 < 0.001
RIS-CAN-23 n (RIS: placebo) Diff LS means change	77 (39 : 38) - 3.3	76 (38 : 38) - 1.9	77 (39 : 38) - 1.3	75 (37 : 38) - 6.3	75 (37 : 38) - 8.1
95 % CI p-value	- 5.8, - 0.8 0.010	- 3.6, - 0.2 0.030	- 2.3, - 0.2 0.016	- 9.4, - 3.2 < 0.001	- 12.0, - 4.2 < 0.001
RIS-CAN-23 autistic disorder subset n (RIS: placebo) Diff LS means change	54 (26 : 28) - 3.9	53 (25 : 28) - 2.2	54 (26 : 28) - 1.3	52 (24 : 28) - 5.8	52 (24 : 28) - 8.8
95 % CI p-value	- 7.1, - 0.6 0.020	- 4.4, 0.0 0.053	- 2.6, 0.0 0.058	- 9.5, - 2.2 0.002	- 13.8, -3.9 < 0.001
Pooled autistic disorder subset n (RIS: placebo) Diff LS means change	155 (75 : 80) - 3.4	154 (74 : 80) - 2.5	155 (75 : 80) - 1.6	153 (73 : 80) - 9.4	153 (74 : 79) - 10.4
95 % CI p-value	- 5.2, - 1.5 < 0.001	- 3.7, - 1.3 < 0.001	- 2.4, - 0.9 < 0.001	- 11.8, - 6.9 < 0.001	- 13.2, - 7.6 <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

RIS: Risperidone, ABC: Aberrant Behaviour Checklist

Following completion of Study 1, 63 patients entered an open label extension for up to four additional months. 39 patients who were clinically stable and who showed a positive response to risperidone after six months were then randomised to receive risperidone or placebo during an eight week, double blind withdrawal period. The relapse rate was 11/16 and 2/16 in placebo and risperidone treated patients, respectively (odds ratio 15.4, 95% confidence limits 2.50, 95.05).

In Study 2 (n = 55) patients aged 5 to 12 years received once or twice daily doses of placebo or risperidone 0.02 to 0.06mg/kg/day. Risperidone 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. Risperidone was also superior to placebo in improving scores on the CGI-C scale and on the ABC subscales of lethargy/social withdrawal and hyperactivity/non-compliance. (See Table 9)

Table 9: CGI-C responders at endpoint 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)

Study treatment	Total n	Responders n (%)	Comparison with placebo treatment difference 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 (75.5)	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)*

CGI-C: Clinical Global Impression - Change

As few autistic children with an IQ (intelligence quotient) > 84 are seen, there is limited clinical experience with risperidone in such children. Experience in autistic adolescents is also limited.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

Distribution

Risperidone plasma concentrations are dose proportional within the therapeutic dose range. Risperidone is rapidly distributed. The volume of distribution is 1 to 2L/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 CYP2D6 to 9-hydroxyrisperidone which has two enantiomers with a similar pharmacological activity to 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 CYP2D6 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 CYP2D6, 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.

Risperidone and 9-hydroxyrisperidone form the pharmacologically active risperidone plus 9-hydroxyrisperidone that is similar in extensive and poor metabolisers. Risperidone has an elimination half-life of about three 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 the active risperidone plus 9-hydroxyrisperidone is 24 hours.

Steady state of risperidone is reached within one day in most patients. Steady state of 9-hydroxyrisperidone is reached within four to five days of dosing.

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 to 45% of the dose.

A single dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with hepatic insufficiency, but the unbound risperidone was somewhat increased by about 35% due to diminished concentration of both alpha1-acid glycoprotein and albumin. The pharmacokinetics of risperidone, 9-hydroxyrisperidone and risperidone plus 9-hydroxyrisperidone in children is similar to that in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

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 doses 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.

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 10mg/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 five to sixfold 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, risperidone 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*, NOUMED RISPERIDONE 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

0.5mg tablets: microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, croscarmellose sodium, hypromellose, stearic acid, titanium dioxide, iron oxide red.

1mg tablets: microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, pregelatinised maize starch, hypromellose, macrogol 4000, titanium dioxide.

2mg tablets: microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, pregelatinised maize starch, hypromellose, macrogol 4000, titanium dioxide, iron oxide red, iron oxide yellow.

3mg tablets: microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, pregelatinised maize starch, hypromellose, macrogol 4000, titanium dioxide, quinolone yellow.

4mg tablets: microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, pregelatinised maize starch, hypromellose, macrogol 4000, titanium dioxide, quinolone yellow, indigo carmine aluminium lake.

6.2 INCOMPATIBILITIES

Refer to *Section 4.5 – Interactions with other medicines and other forms of interactions*.

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

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The 0.5 mg tablets are packaged in either PVC/PCTFE (aclar) /Aluminium foil blisters or PVDC/PE/PVC-Aluminium foil blisters. The 1 mg, 2 mg, 3 mg & 4 mg tablets are packaged in either PVC/COC/PVdC/Al (Topas) or PVC/PE/PVDC/Aluminium foil blisters.

Available in blister packs of 60 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

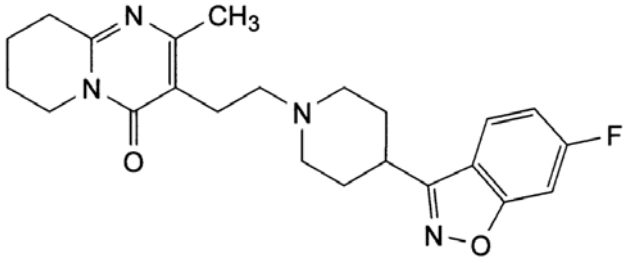
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:

Chemical name: 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9- tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one

Chemical structure: It shows polymorphism.



Empirical formula: $C_{23}H_{27}FN_4O_2$

MW: 410.5

Risperidone is a white or almost white powder.

Risperidone is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96%). It dissolves in dilute acid solutions.

Risperidone is an antipsychotic medicine belonging to the benzisoxazole derivatives.

CAS number:

06266-06-2

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd.

Level 5, 7 Eden Park Drive

Macquarie Park NSW 2113

9. DATE OF FIRST APPROVAL

6 June 2017

10. DATE OF REVISION

29 April 2020

Summary table of changes

Section changed	Summary of new information
All	PI reformat
2, 4.2, 4.4, 6.1 & 6.7	Minor editorial updates
8	Update sponsor details to Avallon Pharmaceuticals Pty Ltd