ROZIDAL TABLETS
(Risperidone Tablets 1/2/3 mg)

COMPOSITION

ROZIDAL TABLETS 1 mg
Each tablet contains
Risperidone ……1 mg

ROZIDAL TABLETS 2 mg
Each tablet contains
Risperidone ……2 mg

ROZIDAL TABLETS 3 mg
Each tablet contains
Risperidone ……3 mg

Excipients: Lactose Monohydrate, Pregelatinised Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry II 31G58920 White, Opadry II 31G53291 Orange, Opadry II 31G52247 Yellow, Purified Water

PRODUCT DESCRIPTION

ROZIDAL TABLETS 1 mg
White capsule shaped, biconvex film coated tablets debossed with 'RA85' on one side and plain on the other side.

ROZIDAL TABLETS 2 mg
Orange coloured, capsule shaped, biconvex film coated tablets debossed with 'RA86' on one side and plain on the other side.

ROZIDAL TABLETS 3 mg
Yellow coloured, capsule shaped, biconvex film coated tablets debossed with 'RA87' on one side and plain on the other side.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

- **Mechanism of Action**

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2-receptors. Risperidone binds also to α_1-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and α_2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2-antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

- **Pharmacokinetics**

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1-2 hrs. The absorption is not affected by food and thus, it can be given with or without meals.

Dose proportinality

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.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In the plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein-binding of risperidone is 88%; that of 9-hydroxy-risperidone is 77%. It was reported that one week after administration, 70% of the dose is excreted in the urine and 14% in the feces. In urine, risperidone plus 9-hydroxy-risperidone represent 35 - 45% of the dose. The remainder is inactive metabolites.

Metabolism

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

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 the active antipsychotic fraction is 24 hours.

Special populations

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

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

INDICATIONS

Risperidone is indicated for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

For Risperidone with 1 mg strength: Risperidone is also indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

DOSE AND METHOD OF ADMINISTRATION

ROZIDAL TABLETS are available as 1 mg, 2 mg & 3 mg strength which may not be suitable for all dosage recommendations given below. In such cases, other suitable approved dosage forms of risperidone (such as oral solution) or suitable strengths (such as 0.5 mg film-coated) should be used.

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

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

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

Elderly (65 years of age and older)
A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

Children
Risperidone is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.

Manic episodes in bipolar disorder

Adults
Risperidone should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimise each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes. As with all symptomatic treatments, the continued use Risperidone must be evaluated and justified on an ongoing basis.

Elderly
A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.

Paediatric population
Risperidone is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy

Conduct disorder

Children and adolescents from 5 to 18 years of age
For subjects ≥ 50 kg, a starting dose of 0.5 mg of oral solution 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 oral solution is the recommended pharmaceutical form to administer 0.5 mg. 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 of oral solution once daily is recommended. The oral solution is the recommended pharmaceutical form to administer 0.25 mg. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients.

Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg of oral solution once daily. The oral solution is the recommended pharmaceutical form to administer 0.75 mg.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis. Risperidone is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

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

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

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

Pregnancy and Lactation

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 the 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.

Neonates exposed to antipsychotic drugs (including Risperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while is some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Risperidone should only be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It was reported through animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breast feed.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Elderly Patients with Dementia

Overall mortality
Increased mortality has been reported in elderly patients with dementia treated with atypical antipsychotic drugs, including risperidone. The incidence of mortality has been reported to be 4.0% for risperidone-treated patients. The mean age (range) of patients who died was 86 years (range 67 - 100).

Concomitant Use with Furosemide
A higher incidence of mortality has been reported in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or furosemide alone.

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

Cerebrovascular adverse events (CAE)
In placebo-controlled trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, (cerebrovascular accidents and transient ischemic attacks), including fatalities, in patients treated with Rozidal Tablets compared to patients receiving placebo (mean age 85 years; range 73 – 97).

Orthostatic hypotension
Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed 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, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Leukopenia, Neutropenia, and Agranulocytosis
Class Effect: Events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently 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 <1000/mm^3) should discontinue 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 risperidone and preventative measures undertaken.

Tardive dyskinesia/extrapyramidal symptoms (TD/ EPS)

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

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.

Neuroleptic Malignant Syndrome (NMS)

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

Parkinson's Disease and Dementia with Lewy Bodies

Physicians should weigh the risks versus the 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.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. 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 this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological data suggest an increased risk of treatment-emergent hyperglycemia-related events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-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 hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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 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 postmarketing surveillance (see **UNDESIRABLE EFFECTS**).

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. 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 treatment with anticholinergic activity, or being subject to dehydration.

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

Seizures
As with other antipsychotic drugs, Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the 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 **UNDESIRABLE EFFECTS**).

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

Other
See Dosage and Administration – Schizophrenia – Elderly for specific posology recommendations for elderly patients, Dosage and Administration – Conduct and other disruptive behavior disorders for pediatric patients with conduct and other disruptive behavior disorders, and Dosage and Administration – Renal and Hepatic Impairment for patients with renal or hepatic impairment.

DRUG 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 drugs and alcohol.

Levodopa and dopamine agonists
Risperidone may antagonise the effect of levodopa and other dopamine-agonists.

Psychostimulants
The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments.

Drugs with hypotensive effects

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

Drugs known to prolong the QT interval
caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval.

Food does not affect the absorption of risperidone.

Risperidone is mainly metabolized through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone 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 risperidone 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 risperidone.

CYP3A4 and/or P-gp inhibitors
Coadministration of risperidone 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 risperidone.

CYP3A4 and/or P-gp inducers
Co-administration of risperidone 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 risperidone.

Highly protein-bound drugs
When risperidone 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.

Pediatric population
Interaction studies have only been performed in adults. The relevance of the results from these studies in pediatric patients is unknown.

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-hydroxy-risperidone.
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 Blocker	• 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 Warnings and Precautions regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide
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.
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. • 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. • 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.

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.

UNDESIRABLE EFFECTS

Adverse reactions reported with risperidone.

Immune system disorders
Anaphylactic reaction

Metabolism and nutrition disorders
Hyperinsulinemia

Psychiatric disorders
Anorgasmia

Nervous system disorders
Head titubation, Neuroleptic malignant syndrome

Eye disorders
Eye movement disorder, Photophobia

Cardiac disorders
Postural orthostatic tachycardia syndrome

Gastrointestinal disorders
Intestinal obstruction

Skin and subcutaneous tissue disorders
Drug eruption, Urticaria

Reproductive system and breast disorders
Breast discomfort, Breast engorgement, Breast enlargement, Menstruation delayed

General disorders and administration site conditions
Induration
Postmarketing data
Adverse events first identified as adverse reactions during postmarketing experience with risperidone and/or paliperidone are included in Table 7. In the table, 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
Unknown	Cannot be estimated from the available data

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, Hypoglycemia, Water intoxication

Psychiatric Disorders
Very rare: Catatonia, Mania, Somnambulism, Sleep-related eating disorder

Nervous System Disorders
Very rare: Dysgeusia, Restless legs syndrome

Eye Disorders
Not known: 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 apnea syndrome[a]

[a]Atypical antipsychotic drugs, such as Risperidone, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Rozidal Tablets should be prescribed with caution.

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

OVERDOSE

Symptoms
In general, reported signs and symptoms have been those resulting from an exaggeration of risperidone known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of 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. 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 case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

STORAGE AND HANDLING INSTRUCTIONS
Store below 30°C, protect from moisture.

PACKAGING

ROZIDAL TABLETS
Carton having 10 blister and 6 blister of 10 tablets each

Product Registration Holder / Manufactured by:
RANBAXY (MALAYSIA) SDN.BHD. (A Sun Pharma company)
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah.
Malaysia

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