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INSTRUCTION
for medical use

ROSEMIDE® ODT

Composition:
active substance: risperidone;
each tablet contains risperidone 1 mg or 2 mg, or 4 mg;
excipients: mannitol (E 421), croscarmellose sodium, ferric oxide red (E 172), aspartame (E 951), masking flavor (Powder 599399TP0951), Powdarome peppermint premium, calcium stearate.

Pharmaceutical form. Orodispersible tablets.
Main physicochemical properties:
1 mg and 2 mg tablets: pink, round, flat beveled edged, mottled tablets, debossed with "K"on one side and plain on the other side.
4 mg tablets: pink, round, biconvex, mottled tablets, plain on both sides.

Pharmacotherapeutic group. Other antipsychotics. ATC code: N05A X08.

Pharmacological properties.
Pharmacodynamics.
Risperidone is a selective monoaminergic antagonist with unique properties. It shows a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and alpha$_2$-adrenergic receptors. Risperidone shows 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 antipsychotics. 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.
Risperidone orodispersible tablets and oral solution are bio-equivalent to film-coated tablets.
Risperidone is metabolized to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone.
Absorption.

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours, in elderly patients – within 2–3 hours. The absolute oral bioavailability of risperidone is 70% (CV = 25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV = 10%) compared with a solution. The absorption is not affected by food, and thus risperidone can be given with or without meals. Absolute bioavailability is 66% for rapid metabolizers and 82% for slow metabolizers.

Distribution.

Risperidone is rapidly distributed in the body. The volume of distribution is 1–2 l/kg. In plasma, risperidone is bound to albumin and alpha$_1$-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%. Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4–5 days.

Biotransformation and elimination.

Risperidone is metabolized by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP2D6 is subject to genetic polymorphism. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolizers of CYP2D6.

Another metabolic pathway of risperidone is N-dealkylation. *In vitro* studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. 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. 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, and 34 hours in elderly patients.

Linearity.

Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Elderly, hepatic and renal impairment.

A single-dose PK-study with oral risperidone showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly.

In adults with moderate renal disease the clearance of the active moiety was ~48% of the clearance in healthy adults. In adults with severe renal disease the clearance of the active moiety was ~31% of the clearance in healthy adults. The half-life of the active moiety was 16.7 h in young adults, 24.9 h in adults with moderate renal disease (or ~1.5 times as long as in young adults), and 28.8 h in those with severe renal disease (or ~1.7 times as long as in young adults). Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by 37.1%.

The oral clearance and the elimination half-life of risperidone and of the active moiety in adults with moderate and severe liver impairment were not significantly different from those parameters in young healthy adults.

Pediatric population.

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

Gender, race and smoking habits.

A population pharmacokinetic analysis revealed no apparent effect of gender, race, or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction.

Clinical characteristics.

Indications.

- Treatment of schizophrenia;
- treatment of moderate to severe manic episodes associated with bipolar disorders;
- short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others (see "Administration and dosage" and "Special warnings and precautions for use" sections);
- 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.

Contraindications.

Hypersensitivity to the active ingredient or to any of the excipients.
Dementia and symptoms of Parkinson's disease (rigidity, bradykinesia and Parkinsonian posture disorders).
Dementia and suspected dementia with Lewy bodies (in addition to dementia symptoms, at least two of the following symptoms: parkinsonism, visual hallucinations, gait instability).

Interaction with other medicinal products and other forms of interaction.

Pharmacodynamic-related interactions.

Drugs known to prolong the QT interval.

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, such as antiarrhythmics (e.g., quinidine, dysopiramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalemia, hypomagnesaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally-acting drugs and alcohol.

Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists.

Risperidone may antagonize 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.

Drugs with hypotensive effect.

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

Psychostimulants.

Administration of psychostimulants (e.g., methylphenidate) and risperidone concomitantly may cause extrapyramidal symptoms when adjusting one or both medications (see "Special warnings and precautions for use" section).

Paliperidone.

Concomitant use of oral risperidone with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

Pharmacokinetic-related interactions.

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). It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant paroxetine, quinidine, 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.

Co-administration 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. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

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 dosage.

Pediatric population.

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

The combined use of psychostimulants (e.g., methylphenidate) with risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.

Effect of other medicinal products on the pharmacokinetics of risperidone.

Antibacterials:

- erythromycin, a moderate CYP3A4 inhibitor and P-gp 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 concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g., phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein;
- 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.

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.

Antivirals:

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

Beta-blockers:

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

Calcium channel blockers:

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

Gastrointestinal drugs:

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

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.

Effect of risperidone on the pharmacokinetics of other medicinal products.

Antiepileptics:

- risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:

- 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.

Digitalis glycosides:

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

Lithium:

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

Concomitant use of risperidone with furosemide.

See "Special warnings and precautions for use" section regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Special warnings and precautions for use.

Elderly patients with dementia.

Increased mortality.

In a meta-analysis of 17 controlled trials of atypical antipsychotics, including risperidone, elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4.0% for risperidone-treated patients compared to 3.1% for placebo-treated patients. The diagnostic odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67–100).

Data from two large observational studies showed that elderly people with dementia who are treated with conventional (typical) antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Concomitant use with furosemide.

In the placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75–97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70–96) or furosemide alone (4.1%; mean age 80 years, range 67–90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics in patients was not associated with similar findings.

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 or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment 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 (CVAE).

In placebo-controlled clinical trials, patients with dementia treated with risperidone had higher rates (approximately 3-fold) of cerebrovascular side effects (strokes and transient ischemic

attacks) with a fatal outcome compared with those receiving placebo (mean age 85 years; range 73–97 years).
The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio for risperidone and placebo groups (odds ratio; 95% confidence interval) was 2.96 (1.34; 7.50); The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Risperidone should be used with caution in patients with risk factors for stroke.
The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with risperidone.
Physicians are advised to assess the risks and benefits of the use of risperidone in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.
Risperidone should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.
Patients should be reassessed regularly, and the need for continuing treatment reassessed.
Orthostatic hypotension.
Due to the alpha$_1$-lytic activity of risperidone, orthostatic hypotension can occur, especially during the initial treatment period. Clinically significant hypotension has been observed postmarketing 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 (see "Administration and dosage" section). A dose reduction should be considered if hypotension occurs.
Leukopenia, neutropenia, and agranulocytosis.
Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including risperidone. Agranulocytosis has been reported very rarely (<1/10,000 patients) during postmarketing surveillance.
Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be closely monitored during the first few months of therapy and discontinuation of risperidone should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1\times10^9$/L) should discontinue risperidone and have their WBC followed until recovery.
Tardive dyskinesia / extrapyramidal symptoms (TD/EPS).
Medicines 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. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.
Caution should be exercised when co-administering psychostimulants (e.g., methylphenidate) and risperidone, as extrapyramidal symptoms may occur when adjusting one or both medications.

Gradual discontinuation of psychostimulants is recommended (see "Interaction with other medicinal products and other forms of interaction" section).

Neuroleptic malignant syndrome (NMS).

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with classic antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In case of neuroleptic malignant syndrome, all antipsychotics, including risperidone, should be discontinued.

Parkinson's disease and dementia with Lewy bodies.

Physicians should weigh the risks versus the benefits when using antipsychotics, including risperidone, to patients with Parkinson's disease or dementia with Lewy bodies (DLB) (see "Contraindications" section). Parkinson's disease may worsen with risperidone. Patients with any of the above diseases may be at increased risk of neuroleptic malignant syndrome as well as having an increased sensitivity to antipsychotic medicinal products (e.g., confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms).

Hyperglycaemia and diabetes mellitus.

Hyperglycaemia, diabetes mellitus and exacerbation of pre-existing diabetes have been reported during treatment with risperidone.

In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely, and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including risperidone should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain.

Significant weight gain has been reported with risperidone use. Weight should be monitored regularly.

Hyperprolactinemia.

Hyperprolactinemia is a common side effect of treatment with risperidone. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side effects (e.g., gynecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhea).

Tissue culture studies suggest that cell growth in human breast tumors may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinemia and in patients with prolactin-dependent tumours, such as pituitary prolactinoma, or possible prolactin-dependent, such as epithelial tumors of the breast.

QT interval prolongation.

In clinical trials, QT prolongation was not associated with risperidone. QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, bradycardia, electrolyte disturbances (hypokalemia, hypomagnesaemia) or family history of QT prolongation as it may increase the risk of arrhythmogenic effects. Caution should also be exercised in concomitant use with medicines known to prolong the QT interval.

Seizures.

Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism.

Priapism may occur with risperidone treatment due to its alpha-adrenergic blocking 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 may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.
Renal and hepatic impairment.
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone (see "Administration and dosage" section).
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.
Intraoperative floppy iris syndrome (IFIS).
Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha$_1$-adrenergic antagonist effect, including risperidone.
IFIS may increase the risk of eye complications during and after the operation. Current or past use of antipsychotic drugs 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.
Pediatric population.
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). Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height have not been adequately studied.
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.
Results from a small postmarketing observational study showed that risperidone-exposed subjects between the ages of 8–16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical antipsychotic medications. This study was not adequate to determine whether exposure to risperidone had any impact on final adult height, or whether the result was due to a direct effect of risperidone on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying disease with resulting increase in linear growth.
During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in pediatric population see "Administration and dosage" section.
The drug contains aspartame (E951), a derivative of phenylalanine, which may be harmful for people with phenylketonuria.

Use during pregnancy and lactation.
Pregnancy.
Controlled studies involving pregnant women have not been performed. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen. The potential risk for humans is unknown.
Neonates whose mothers used antipsychotics (including risperidone) during the third trimester of pregnancy are at risk of reversible extrapyramidal and/or withdrawal symptoms. These symptoms include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. These complications can be of varying severity. Consequently newborns should be monitored carefully.
Risperidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.
Breast-feeding.
In animal studies, risperidone and 9-hydroxy-risperidone were excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk.
There are no data available on adverse reactions in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.
Fertility.
As with other drugs that antagonise dopamine D2 receptors, risperidone elevates prolactin level.
Hyperprolactinaemia may suppress hypothalamic gonadotropin-releasing hormone, 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.

Effects on ability to drive and use machines.
Risperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see "Adverse effects" section). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Administration and dosage.
Risperidone should be administered orally with or without food.
As the tablets are orodispersible, they should be carefully removed with dry hands from the blister immediately before use, placed under the tongue and, if necessary, washed down with water.
Common dose
Risperidone can be used once or twice a day. Doses greater than 8 mg should be divided into two divided doses (morning and evening). Food does not affect the absorption of risperidone.
Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia, and dyskinesia) has been reported.
Schizophrenia and other mental disorders
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. Subsequently, 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 demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated.
Elderly patients (aged 65 years and above).
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.
Pediatric population.
The drug is not recommended for use in children below age 18.
Manic episodes in bipolar disorder
Adults.
The recommended starting dose of risperidone is 2 mg once daily in the evening. Individual dosage adjustments should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. The recommended dose range is from 1 to 6 mg per day. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.
As with all symptomatic treatments, with long-term use of risperidone, it is necessary to periodically review the doses and adjust them throughout therapy.
Elderly patients (aged 65 years and above).
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, if needed. Since clinical experience in elderly is limited, caution should be exercised.
Pediatric population.
The drug is not recommended for use in children below age 18.
Short-term treatment of persistent aggression in patients with Alzheimer's dementia
A starting dose of 0.25* mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25* mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5* mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily. Risperidone should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. As with all symptomatic treatments, it is necessary to periodically review the risperidone doses and adjust them throughout therapy.
* In case of prescribing doses of 0.25 mg and 0.5 mg, risperidone preparations with the possibility of such dosing should be used.
Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder
Children and adolescents from 5 to 18 years of age
For subjects ≥50 kg
A starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5* mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5* mg once daily while others may require 1.5* mg once daily.
For subjects <50 kg
A starting dose of 0.25* mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25* mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5* mg once daily for most patients. Some patients, however, may benefit from 0.25* mg once daily while others may require 0.75* mg once daily.
As with all symptomatic treatments, with long-term use of risperidone, it is necessary to periodically review the doses and adjust them throughout therapy.
* In case of prescribing doses of 0.25 mg, 0.5 mg, 0.75 mg and 1.5 mg, risperidone preparations with the possibility of such dosing should be used.

Pediatric population.
The drug is not recommended for use in children below age 18.
Renal and hepatic impairment.
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. 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.
Switching from other antipsychotics.
When medically appropriate, gradual discontinuation of the previous treatment while risperidone therapy is initiated is recommended. Also, when switching patients from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medicines should be re-evaluated periodically.

Pediatric population.
Risperidone should be used to treat persistent aggression in conduct disorder in children over 5 years of age.

Overdose.
Symptoms.
In general, reported signs and symptoms of overdose are known adverse drug reactions in exaggerated form. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT prolongation and convulsions have been reported. Torsades de Pointes has been reported in association with combined overdose of risperidone and paroxetine.
In case of acute overdose, the possibility of multiple drug involvement should be considered.
Treatment.
Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered only when drug intake was less than one hour before. 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. In case of acute overdose, the possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

Adverse reactions.
The most frequently reported adverse drug reactions (ADRs) (incidence ≥10%) are: parkinsonism, sedation/somnolence, headache, and insomnia. The ADRs that appeared to be dose-related included parkinsonism and akathisia.
The following are all the ADRs that were reported in clinical trials and postmarketing experience. The following terms and frequencies are applied: 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), and not known (frequency cannot be estimated from available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Common	pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear infection, influenza
Uncommon	respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis, cellulitis, localized infection, viral infection, acarodermatitis
Rare	infection
Blood and lymphatic system disorders	
Uncommon	neutropenia, white blood cell count decreased, thrombocytopenia, anemia, hematocrit decreased, eosinophil count increased
Rare	agranulocytosis[c]
Immune system disorders	
Uncommon	hypersensitivity
Rare	anaphylactic reaction[c]
Endocrine disorders	
Common	hyperprolactinemia[a]
Rare	inappropriate antidiuretic hormone secretion, glucose urine present
Metabolism and nutrition disorders	
Common	weight increased, increased appetite, decreased appetite
Uncommon	diabetes mellitus[b], hyperglycemia, polydipsia, weight decreased, anorexia, blood cholesterol increased
Rare	water intoxication[c], hypoglycemia, hyperinsulinemia[c], blood triglycerides increased
Very rare	diabetic ketoacidosis
Psychiatric disorders	
Very common	insomnia[d]
Common	sleep disorder, agitation, depression, anxiety
Uncommon	mania, confusional state, libido decreased, nervousness, nightmare
Rare	catatonia, somnambulism, sleep-related eating disorders, blunted affect, anorgasmia
Nervous system disorders	
Very common	sedation/somnolence, parkinsonism[d], headache
Common	akathisia[d], dystonia[d], dizziness, dyskinesia[d], tremor
Uncommon	tardive dyskinesia, cerebral ischemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion[d], syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoesthesia, paresthesia
Rare	neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation
Eye disorders	
Common	vision blurred, conjunctivitis
Uncommon	photophobia, dry eye, lacrimation increased, ocular hyperemia
Rare	glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)[c]
Ear and labyrinth disorders	
Uncommon	vertigo, tinnitus, ear pain
Cardiac disorders	
Common	tachycardia

Uncommon	atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, palpitations
Rare	sinus arrhythmia
Vascular disorders	
Common	hypertension
Uncommon	hypotension, orthostatic hypotension, flushing
Rare	pulmonary embolism, venous thrombosis
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, pharyngolaryngeal pain, cough, epistaxis, nasal congestion
Uncommon	pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder
Rare	sleep apnea syndrome, hyperventilation
Gastrointestinal disorders	
Common	abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhea, dyspepsia, dry mouth, toothache
Uncommon	fecal incontinence, fecaloma, gastroenteritis, dysphagia, flatulence
Rare	pancreatitis, intestinal obstruction, swollen tongue, cheilitis
Very rare	ileus
Hepatobiliary disorders	
Uncommon	transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased
Rare	jaundice
Skin and subcutaneous tissue disorders	
Common	rash, erythema
Uncommon	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discoloration, acne, seborrheic dermatitis, skin disorder, skin lesion
Rare	drug eruption, dandruff
Very rare	angioedema
Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis[c]
Musculoskeletal and connective tissue disorders	
Common	muscle spasms, musculoskeletal pain, back pain, arthralgia
Uncommon	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain
Rare	rhabdomyolysis
Renal and urinary disorders	
Common	urinary incontinence
Uncommon	pollakiuria, urinary retention, dysuria
Pregnancy, puerperium, and neonatal conditions	
Very rare	extrapyramidal symptoms and/or drug withdrawal syndrome neonatal[c]
Reproductive system and breast disorders	
Uncommon	erectile dysfunction, ejaculation disorder, amenorrhea, menstrual disorder[d], gynecomastia, galactorrhea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge
Rare	priapism[c], menstruation delayed, breast engorgement, breast enlargement, breast discharge
General disorders and administration site conditions	
Common	edema[d], pyrexia, chest pain, asthenia, fatigue, pain

Uncommon	face edema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort
Rare	hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration[c]
Injury, poisoning and procedural complications	
Common	fall
Uncommon	procedural pain

[a] Hyperprolactinemia can in some cases lead to gynecomastia, menstrual disturbances, amenorrhea, anovulation, galactorrhea, fertility disorder, decreased libido, erectile dysfunction.
[b] In placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidone-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all risperidone-treated subjects.
[c] Not observed in risperidone clinical studies but observed in postmarketing environment with risperidone.
[d] Extrapyramidal disorder may occur: **parkinsonism** (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), **akathisia** (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, **dyskinesia** (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia.
Dystonia includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin. **Insomnia** includes initial insomnia, middle insomnia. **Convulsion** includes grand mal convulsion. **Menstrual disorder** includes menstruation irregular, oligomenorrhoea. **Oedema** includes generalized oedema, oedema peripheral, pitting oedema.

Undesirable effects noted with paliperidone formulations
Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, postural orthostatic tachycardia syndrome has been reported with paliperidone and can be expected to occur with risperidone.
Adverse reactions common to antipsychotic drugs
QT interval prolongation
As with other antipsychotics, cases of QT prolongation have been reported postmarketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest, and Torsades de Pointes.
Venous thromboembolism
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs.
Weight gain
The proportions of risperidone and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for risperidone (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥7% at endpoint was comparable in the risperidone (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).
In a population of children and adolescents with conduct disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5–12 years of age is 3 to 5 kg per year. From 12 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.
Additional information on special populations

Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or pediatric patients than in adult populations are described below.
Elderly patients with dementia
Transient ischemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.
Pediatric population
In general, type of adverse reactions in children is expected to be similar to those observed in adults in terms of frequency, type and severity.
The following ADRs were reported with a frequency ≥5% in pediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhea, and enuresis.
The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied (see "Special warnings and precautions for use" section).
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life.
2 years.

Storage conditions.
Store in the original package at a temperature below 25°C.
Keep out of the reach of children.

Package.
10 tablets in a blister; 2 or 6 blisters is in a carton pack.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of its business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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