Risperiget™

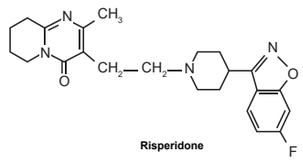
رسپیریگیٹ

(R i s p e r i d o n e)

1mg, 2mg, 3mg and 4mg Film-coated Tablets

DESCRIPTION

Risperiget is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. Chemically it is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl] -6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and the structural formula is:



Risperidone

QUALITATIVE AND QUANTITATIVE COMPOSITION

Risperiget (Risperidone) is available for oral administration as:

Risperiget Tablets 1mg
Each film-coated tablet contains:
Risperidone USP…1mg

Risperiget Tablets 2mg
Each film-coated tablet contains:
Risperidone USP…2mg

Risperiget Tablets 3mg
Each film-coated tablet contains:
Risperidone USP…3mg

Risperiget Tablets 4mg
Each film-coated tablet contains:
Risperidone USP…4mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Risperidone is a selective monoaminergic antagonist having a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and with lower affinity, to H_1-histamine and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy risperidone. Risperidone, as a potent D_2 antagonist, improves the positive symptoms of schizophrenia but causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacokinetics

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 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. Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1mg to 16mg daily (0.5mg to 8mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in *extensive* metabolizers). Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Effect of Food

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha$_1$-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.
Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

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 represent 35-45% of the dose. The remainder is inactive metabolites. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Overall mean elimination half-life is about 20 hours.

Special Population

Elderly

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

Renal Impairment

In adults with moderate renal disease the clearance of the active moiety was ~48% of the clearance in young healthy adults. In adults with severe renal disease the clearance of the active moiety was ~31% of the clearance in young 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%.

Hepatic Impairment

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.

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.

THERAPEUTIC INDICATIONS

Risperiget (Risperidone) is indicated for the treatment of:

1. Schizophrenia and other psychotic disorders. These include first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech) are prominent. Risperiget (Risperidone) also alleviates affective symptoms (such as depression, guilt-feelings, anxiety) associated with schizophrenia. In addition, Risperiget (Risperidone) also appears effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial response to treatment with this agent.
2. Long term control of mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self esteem, decreased need for sleep, pressured speech, racing thoughts, distractability, or poor judgement, including disruptive or aggressive behaviours.
3. Agitation (upto 12 weeks), aggression or psychotic symptoms in patients with moderate to severe dementia of the Alzheimer type.
4. Conduct and other disruptive behaviour disorders in children (over 5 years), adolescents and adults with subaverage intellectual functioning or mental retardation, or average IQ, in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent. Risperiget (Risperidone) is also effective in maintaining the clinical improvement during continuation therapy in children and adolescents who have shown an initial treatment response. Treatment with Risperiget (Risperidone) for patients with disruptive behaviour disorders should be initiated only in consultation with a specialist, including child and adolescent psychiatrists, paediatric neurologists, developmental paediatricians, or other physicians conversant in the diagnosis and treatment of conduct and other disruptive behaviour disorders.
5. Behavioural disorders associated with autism in children and adolescents.

DOSAGE & ADMINISTRATION

Schizophrenia

Switching from Other Antipsychotics

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

Adults

Risperiget (Risperidone) may be given once daily or twice daily. Patients should start with 2mg/day Risperiget (Risperidone). The dose may be increased on the second day to 4mg. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4mg and 6mg. In some patients a slower titration phase and a lower starting and maintenance dose may be appropriate. Doses above 10mg/day have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms. Since the safety of doses above 16mg/day has not been evaluated, doses above this level should not be used. A benzodiazepine may be added to Risperiget (Risperidone) when additional sedation is required.

Elderly

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

Pediatric population

Risperiget (Risperidone) is not recommended for use in children below age 15 years with schizophrenia due to a lack of data on efficacy.

Bipolar manic

Adults

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

Elderly

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

Renal and hepatic impairment

A starting dose of 0.5mg twice daily is recommended. This dosage can be individually adjusted with 0.5mg twice daily increments to 1mg to 2mg twice daily. Risperiget (Risperidone) should be used with caution in this group of patients until further experience is gained.

Pediatric population

Risperiget (Risperidone) is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.

Patients with moderate to severe Alzheimer's 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 Risperiget (Risperidone) must be evaluated and justified on an on-going basis.

Conduct and other disruptive behaviour disorders

For subjects ≥ 50 kg, a starting dose of 0.5mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5mg once daily not more frequently than every other day, if needed. The optimum dose is 1mg once daily for most patients. Some patients, however, may benefit from 0.5mg once daily while others may require 1.5mg once daily.
For subjects <50 kg, a starting dose of 0.25mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5mg once daily for most patients. Some patients, however, may benefit from 0.25mg once daily while others may require 0.75mg once daily.
As with all symptomatic treatments, the continued use of Risperiget (Risperidone) must be evaluated and justified on an ongoing basis.

Autism

Risperiget (Risperidone) can be administered once or twice daily. Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime, or twice daily. Risperiget (Risperidone) should be administered based on body weight. Dosing should begin at 0.25mg or 0.5mg/day based upon weight (see table below for relative weight categories). On Day 4 of treatment, the dose may be increased up to 0.5mg or 1.0mg/day. This dose should be maintained and response assessed at approximately day 14. Only in patients not achieving sufficient clinical response should additional dose increases be considered. Dose increases may proceed at ≥2-week intervals in increments of 0.25mg for patients <20 kg or 0.5mg for patients ≥20 kg. Based upon current studies, the maximum dose studied did not exceed a total daily dose of 1.5mg in patients <20 kg, 2.5mg in patients ≥20 kg and 3.5mg in patients >45 kg. Doses below 0.25mg/day were not effective in clinical studies.
The table of the maximum daily doses provides a reference for titration and dosing by weight based upon current studies, and may serve as a guide according to clinical need.

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

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

Once sufficient response has been achieved and maintained consideration may be given to gradually lowering the dose to achieve optimum balance of effectiveness and tolerance. As with all symptomatic treatments, the continued use of Risperiget (Risperidone) in children and adolescents with autism must be evaluated and justified on an ongoing basis.

Method of administration

Food does not affect the absorption of Risperiget (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.

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

ADVERSE REACTIONS

Very common: Insomnia, sedation/somnolence, parkinsonism and headache.

Common: Pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear infection, influenza, hyperprolactinaemia, weight increased, increased appetite, decreased appetite, sleep disorder, agitation, depression, anxiety, akathisia, dystonia, dizziness, dyskinesia, tremor, vision blurred, conjunctivitis, tachycardia, hypertension, dyspnoea, pharyngolaryngeal pain, cough, epistaxis, nasal congestion, abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache, rash, erythema, muscle spasms, musculoskeletal pain, back pain, arthralgia, urinary incontinence, oedema, pyrexia, chest pain, asthenia, fatigue, pain and fall.

Uncommon: Respiratory tract infection, cystitis, eye infection, tonsillitis, nychomycosis, cellulitis localised infection, viral infection, acarodermatitis, neutropenia, white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased, eosinophil count increased, hypersensitivity, diabetes mellitus, hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased, mania, confusional state, libido decreased, nervousness, nightmare, tardive dyskinesia, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion, syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia, photophobia, dry eye, lacrimation increased, ocular hyperaemia, vertigo, tinnitus, ear pain, atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, palpitations, hypotension, orthostatic hypotension, flushing, pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder, faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence, urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrheic dermatitis, skin disorder, skin lesion, blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling, muscular weakness, neck pain, pollakiuria, urinary retention, dysuria, erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder, gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge, face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort, transaminases increased, gamma-glutamyl-transferase increased, hepatic enzyme increased and procedural pain.

Rare: Infection, angranulocytosis, anaphylactic reaction, inappropriate antidiuretic hormone secretion, glucose urine present, water intoxication, hypoglycaemia, hyperinsulinaemiac blood triglycerides increased, catatonia, blunted affect, anorgasmia, neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative), sinus arrhythmia, pulmonary embolism, venous thrombosis, sleep apnoea syndrome, hyperventilation, pancreatitis, intestinal obstruction, swollen tongue, cheilitis, drug eruption, dandruff, rhabdomyolysis, drug withdrawal syndrome neonatal, priapism, menstruation delayed, breast engorgement, breast enlargement, breast discharge, hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome and induration jaundice.

"To report SUSPECTED ADVERSE REACTIOND to Getz Pharma's Pharmacovigilance Section, plese contact at dsafety@getzpharma.com or +92-21-38636363

CONTRAINDICATIONS

Risperidone is contraindicated in patients with hypersensitivity to risperidone and 9-hydroxyrisperidone or to any excipient of the product.

PRECAUTIONS

- Elderly Patients with Dementia

  Overall Mortality

  Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo.

  Concomitant use with Furosemide

  In elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone compared to treatment with risperidone alone. Caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to treat, irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

  Cerebrovascular Adverse Events

  In 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 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.
- 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. 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. Special care should be taken in patients taking medications to lower blood pressure.
- Events of leukopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including risperidone. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of risperidone should be considered at the first sign of 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 should discontinue risperidone and have their WBC followed until recovery.
- 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.
- Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because risperidone has a lower potential to induce extrapyramidal symptoms than classic neuroleptics, it should have a reduced risk of inducing tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic medicines should be considered.
- Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including risperidone, should be discontinued.
- Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.
- Physicians should weigh the risks versus benefits when prescribing antipsychotics including risperidone to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.
- Hyperglycaemia, diabetes mellitus or 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.
- Significant weight gain has been reported with risperidone use. Weight should be monitored regularly.
- Hyperprolactinaemia 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. gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhea). Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.
- 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.
- Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with risperidone during post-marketing surveillance.
- 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.
- 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.
- The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy. Prescriptions for risperidone should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.
- Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha$_{1a}$-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha$_{1a}$-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.
- Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.
- 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.
- Risperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. The potential risk for humans is unknown. Therefore, risperidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Nursing Mothers

Risperidone and 9-hydroxyrisperidone may be present in human breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 medicines or 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 drugs known to prolong the QT interval.

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 or fluoxetine).

CYP3A4 and/or P-gp Inhibitors: Coadministration of risperidone with a strong CYP3A4 and/or P-gp inhibitor (e.g. Itraconazole and Ketoconazole) 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.

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.

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.

Antibacterials: Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Antipsychotics: Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

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

H_1-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.

Sodium Channel Blockers: Quinidine may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Fluoxetine: Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction.

Paroxetine: Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.

Tricyclic antidepressants: Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Sertraline: Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

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.

Diuretics: In elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone.

OVERDOSAGE

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral risperidone and paroxetine. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to risperidone. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

STORAGE

Do not store above 30°C.
Protect from light and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Risperiget (Risperidone) Tablets 1mg are available in pack of 20's.
Risperiget (Risperidone) Tablets 2mg are available in pack of 20's.
Risperiget (Risperidone) Tablets 3mg are available in pack of 20's.
Risperiget (Risperidone) Tablets 4mg are available in pack of 20's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

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