



RISPERIDONE

RISPOND™

1/2/4 mg Film Coated Tablet

ANTIPSYCHOTIC

PRODUCT DESCRIPTION

Risperidone Tablets 1 mg - White coloured, circular, biconvex, film Coated tablets
Risperidone Tablets 2 mg - Orange coloured, circular biconvex film coated tablets
Risperidone Tablets 4 mg - Orange coloured, circular biconvex film coated tablets with breakline on one surface

FORMULATION/COMPOSITION:

Each film-coated tablet contains
Risperidone 1 mg/2 mg/4 mg

PHARMACODYNAMICS/PHARMACOKINETICS:

Pharmacodynamics:
Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT₂ and dopaminergic D₂ receptors. Risperidone binds also to alpha₁-adrenergic receptors, and, with lower affinity, to H₁-histaminergic and alpha₂-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D₂ antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catlepsy 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 is metabolised 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. 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. 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.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1.2 l/kg. In plasma, Risperidone is bound to albumin and alpha₁-acid glycoprotein. The plasma protein binding of Risperidone is 90% that of 9-hydroxy-risperidone is 77%.

Biotransformation and elimination

Risperidone is metabolised 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. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolizers convert Risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 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 CYP 2D6.

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 metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, Risperidone plus 9-hydroxy-risperidone 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.

Linearity/non-linearity

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

INDICATIONS:

Risperidone is indicated for the treatment of schizophrenia.

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

Risperidone is indicated for the 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.

Risperidone is 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 sub average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors 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.

DOSAGE AND MODE / ROUTE OF ADMINISTRATION:

Posology

Schizophrenia

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, and is therefore not recommended.

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.

Paediatric population

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 optimize 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 of Risperidone must be evaluated and justified on an on-going 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.

Persistent aggression in patients with moderate to severe 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. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.

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, 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 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.

Method of administration

Risperidone is for oral use. 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.

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 medicines should be re-evaluated periodically.

CONTRAINDICATIONS & PRECAUTION(S), WARNING(S)

Hypersensitivity to the active substance or to any of the excipients

PRECAUTIONS & WARNING:

Elderly patients with dementia

Increased mortality in elderly people with dementia

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 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 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. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide

In the Risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus Risperidone (7.3%; 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 (mainly thiazide diuretics used in low dose) 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)

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with Risperidone 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 (95% exact 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-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

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 post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of Risperidone should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10³/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.

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 antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, 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). Parkinson's disease may worsen with Risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, and 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 utilized 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.

Hyperprolactinaemia

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 Galactorrhoea).

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with relevant medical history, Risperidone should be used with caution in patients with pre-existing Hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

paroxetine). It is expected that other CYP 2D6 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.

Paediatric Population:

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

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

Examples:

Examples of drugs that may potentially interact or that were shown not to interact with Risperidone are listed below:

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 CYP 3A4 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 200mg/day increased the plasma concentrations of Risperidone and decreased the plasma concentrations of 9-hydroxyrisperidone.

Antipsychotics:

- Phenothiazines may increase the plasma concentrations of Risperidone but not those of the active antipsychotic fraction.

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:

- H₂-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of Risperidone, but only marginally of 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.

- Sertaline, 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, dehydro Aripiprazole.

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.

ADVERSE EFFECTS:

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 post marketing experience with Risperidone by frequency category estimated from RISPERIDONE clinical trials. The following terms and frequencies are applied: very common (≥1/10), common (≥1/100 to <1/10), uncommon (<1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	faecal incontinence, Faecaloma, gastroenteritis, dysphagia, flatulence	pancreatitis, intestinal obstruction, swollen tongue, cheilitis	ileus
Skin and subcutaneous tissue disorders		rash, erythema	urticaria, pruritis, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin lesion	drug eruption, dandruff	angioedema
Musculoskeletal and connective tissue disorders		muscle spasms, musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain	rhabdomyolysis	
Renal and urinary disorders		urinary incontinence	Pollakiuria, urinary retention, dysuria		
Pregnancy, puerperium, and neonatal conditions				drug withdrawal syndrome neonatal	
Reproductive system and breast disorders			erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder ^a , gynaecomastia, Galactorrhea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge	priapism, menstruation delayed, breast engorgement, breast enlargement, breast discharge	
General disorders and administration site conditions		oedema, pyrexia, chest pain, asthenia, fatigue, pain	face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort	hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration	
Hepatobiliary disorders			transaminases increased, gamma-glutamyl transferase increased, hepatic enzyme increased	jaundice	
Injury, poisoning and procedural complications		fall	procedural pain		

^a Hyperprolactinemia can in some cases lead to gynaecomastia, 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 post-marketing environment with Risperidone.

^d Extrapyramidal disorder may occur: Parkinsonism (salivary hyper secretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hyperkinesia, 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, Chorea/hypertonia, athetosis, and myoclonus), dystonia.

Dystonia includes dystonia, hypertension, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, opharyngeal 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 convolution; **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, the following adverse reaction has been noted with the use of Paliperidone products and can be expected to occur with Risperidone.

Cardiac disorders: Postural orthostatic tachycardia syndrome

Class effects:

As with other antipsychotics, very rare cases of QT prolongation have been reported post marketing 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 (frequency unknown).

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 and other disruptive behaviour 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 12-16 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 paediatric patients than in adult populations are described below.

Elderly patients with dementia:

Transient ischaemic 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.

Paediatric population:

In general, type of adverse reactions in children is expected to be similar to those observed in adults.

The following ADRs were reported with a frequency ≥5% in paediatric 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, diarrhoea, and enuresis.

OVERDOSE AND TREATMENT:

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 Risperidone and paroxetine.

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 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. 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.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Risperidone Tablets 1 mg/2 mg/4 mg are packed in Blister pack of 10's (box of 10's and 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder
Brown & Burk Philippines Inc.
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor., Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:

MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur-635 126 (T.N.), India.

CAUTION STATEMENT:

FOOD

MICRO LABS LIMITED, BANGALORE, INDIA								
1	Product Name	Rispond			Colours Used ■ BLACK			
2	Strength	1,2 & 4 mg						
3	Component	Leaflet						
4	Category	Export - Philippines						
5	Dimension	250 x 360 mm						
6	Artwork Code	EXG-ML01I-1492/B						
7	Pharma Code	N/A						
8	Reason for Change	in Address T.N. inserted						
		Prepared by (DTP)	Checked by (PD)	Approved by				
Sign	Kanthalraju L. <th>Head CQA</th> <th>Head Production/ Packing (Site)</th> <th>Head QC (Site)</th> <th>Head QA (Site)</th>			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)	
Date	14-06-2021							