PACKAGE INSERT TEMPLATE FOR RISPERIDONE TABLET & RISPERIDONE ORAL SOLUTION

Brand or Product Name

[Product name] Tablet 1mg
[Product name] Tablet 2mg
[Product name] Tablet 3mg
[Product name] Tablet 4mg
[Product name] Oral Solution 1mg/ml

Name and Strength of Active Substance(s)

[Tablet]
Risperidone 1mg
Risperidone 2mg
Risperidone 3mg
Risperidone 4mg

[Oral solution]
Risperidone 1mg/ml

Product Description

[Visual description of the appearance of the product (eg colour, markings, flavour etc) eg :
Tablet - White, circular flat beveled edge tablets marked '100' on one side
Oral solution – Clear, colourless solution]

Pharmacodynamics

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacokinetics

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

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

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.

Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4 - 5 days of dosing. Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

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 88%, that of 9-hydroxy-risperidone is 77%.

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.

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

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

Indication

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

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

Recommended Dosage

Schizophrenia

Switching from other antipsychotics

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

Adults

Risperidone may be given once daily or twice daily. Patients should start with 2 mg/day risperidone. The dosage may be increased on the second day to 4 mg. From then on the dosage can be maintained unchanged, or further individualized, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms. Since the safety of doses above 16 mg/day has not been evaluated, doses above this level should not be used. A benzodiazepine may be added to risperidone when additional sedation is required.

Elderly

A starting dose of 0.5 mg b.i.d. is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d. increments to 1 to 2 mg b.i.d. Risperidone is well tolerated by the elderly.

Children

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

Renal and liver disease

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

It is not advisable to take Risperidone Oral Solution in a cup of tea.

Mode of Administration
Oral

Contraindications

Contraindicated in patients with a known hypersensitivity to the product.

Warnings and Precautions
[Specific package insert requirement for risperidone]

WARNINGS:

Hyperglycemia and Diabetes Mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Elderly Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. The incidence of mortality was 4.0% for risperidone-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67 - 100).

Concomitant use with Furosemide

A higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or furosemide alone. The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

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

Cerebrovascular Adverse Events (CAE)

In placebo-controlled trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, (cerebrovascular accidents and transient ischemic attacks), including fatalities, in patients treated with risperidone compared to patients receiving placebo.

Alpha-blocking Activity

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.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/ EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia.

Because risperidone has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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 antipsychotic drugs, including risperidone, should be discontinued.

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including risperidone, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Weight Gain

Significant weight gain has been reported. Monitoring weight gain is advisable when risperidone is being used.

QT Interval

As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval.

Effects on Ability to Drive and Use Machines

Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Other

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.

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

Interactions with Other Medicaments

Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs.

Risperidone may antagonize the effect of levodopa and other dopamine agonists.

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

Caution is advised when prescribing risperidone with drugs known to prolong the QT interval.

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone. Similar effects may be observed with other CYP 3A4 hepatic enzyme inducers. When carbamazepine or other CYP 3A4 hepatic enzyme inducers are initiated or discontinued, the physician should re-evaluate the dosing of risperidone.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of risperidone.

Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitors, galantamine and donezepil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. When risperidone is taken together with other highly protein bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

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

Food does not affect the absorption of risperidone.

Statement on Usage During Pregnancy and Lactation

[Specific package insert requirement for antipsychotic]

Pregnancy and lactation

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

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

The safety of risperidone for use during human pregnancy has not been established. In experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed. No teratogenic effect of risperidone was noted in any study.

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

Adverse Effects / Undesirable Effects

Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

The following is a list of additional ADRs associated with risperidone :

Infections and Infestations
Lower respiratory tract infection, infection, gastroenteritis, subcutaneous abscess

Blood and Lymphatic Disorders
Neutropenia

Metabolism and Nutrition Disorders
Hyperglycaemis

Psychiatric Disorders
Depression, initial insomnia

Nervous System Disorders
Paresthesia, convulsion

Eye Disorders
Blepharospasm

Ear and Labyrinth Disorders
Vertigo

Cardiac Disorders
Bradycardia

Vascular Disorders
Hypertension

Gastrointestinal Disorders
Toothache, tongue spasm

Skin and Subcutaneous Tissue Disorders
Eczema

Musculoskeletal, Connective Tissue, and Bone Disorders
Buttock pain

Reproductive System and Breast Disorder
Menstruation delayed, ejaculation delayed, oligomenorrhea, breast discomfort.

General Disorders
Pain, gait abnormal

Investigations
Weight decreased, gamma-glutamyltransferase increased, hepatic enzyme increased, glucose urine present

Adverse events first identified as ADRs during postmarketing experience with risperidone are included below :

Blood and Lymphatic Disorders
Uncommon : Thrombocytopenia

Unknown: Agranulocytosis

Immune System Disorders
Unknown : Anaphylactic reaction

Endocrine Disorders
Rare : Inappropriate antidiuretic hormone secretion

Metabolism and Nutrition Disorders
Uncommon : Diabetes Mellitus
Rare : Hypoglycaemia
Very rare : Diabetic ketoacidosis
Unknown : Water intoxication

Psychiatric Disorders
Uncommon : Mania

Cardiac Disorders
Uncommon : Atrial fibrillation

Respiratory, Thoracic, and Mediastinal Disorders
Rare : Sleep apnea syndrome

Gastrointestinal Disorders
Rare: Intestinal obstruction, pancreatitis

Hepatobiliary Disorders
Rare : Jaundice

Skin and Subcutaneous Tissue Disorders
Uncommon: Angioedema, alopecia

Renal and Urinary Disorders
Uncommon : Urinary retention

Reproductive System and Breast Disorders
Unknown : Priapism

General Disorders
Rare : Hypothermia

Investigations

Uncommon : Electrocardiogram QT prolonged

Overdose and Treatment

Symptoms
In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of 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. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to risperidone. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size eg
Tablet - Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box
Oral solution - 30 ml and 100 ml amber glass bottles/box]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]

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