PACKAGE INSERT TEMPLATE FOR RISPERIDONE EXTENDED RELEASE POWDER FOR INTRAMUSCULAR INJECTION

Brand or Product Name

[Product name] ER Powder for IM Injection 25mg
[Product name] ER Powder for IM Injection 37.5mg
[Product name] ER Powder for IM Injection 50mg

Name and Strength of Active Substance(s)

Risperidone 25mg
Risperidone 37.5mg
Risperidone 50mg

Product Description

[Visual description of the appearance of the product (eg colour, odour etc)
eg : White, free flowing extended release powder, composed micro-encapsulated risperidone. Upon reconstitution, risperidone ER powder yields a clear, white 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 metabolized by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxyrisperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation.

General Characteristics of Risperidone after Administration of Risperidone ER in Patients

After a single intramuscular injection with Risperidone ER, the release profile consists of a small initial release of drug (< 1% of the dose), followed by a lag time of 3 weeks. The main release of

drug starts from week 3 onwards, is maintained from 4 to 6 weeks, and subsides by week 7. Oral antipsychotic supplementation should therefore be given during the first 3 weeks of Risperidone ER treatment.

The combination of the release profile and the dosage regimen (intramuscular injection every two weeks) result in sustained therapeutic plasma concentrations. Therapeutic plasma concentrations remain until 4 to 6 weeks after the last Risperidone ER injection. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

The absorption of risperidone from Risperidone ER is complete.

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%, the active metabolite 9-hydroxy-risperidone is 77%. The active antipsychotic fraction and risperidone clearances were 5.0 and 13.7 L/h in extensive metabolizers, respectively, and 3.2 and 3.3 L/h in poor metabolizers of CYP 2D6, respectively.

After repeated intramuscular injections with 25 or 50 mg Risperidone ER every two weeks, median trough and peak plasma concentrations of the active antipsychotic fraction fluctuated between 9.9 - 19.2 ng/ml and 17.9 - 45.5 ng/ml respectively. The pharmacokinetics of risperidone are linear in the dose range of 25 - 50 mg injected every 2 weeks. No accumulation of risperidone was observed during long term use (12 months) in patients who were injected with 25 - 50 mg every two weeks.

The above studies were conducted with gluteal intramuscular injection. Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

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

For risperidone naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone ER.

Risperidone ER should be administered every two weeks by deep intramuscular deltoid or gluteal injection using the appropriate safety needle. For deltoid administration, use the 1-inch needle alternating injections between the two arms. For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. Do not administer intravenously.

Adults

The recommended dose is 25 mg intramuscular every two weeks. Some patients may benefit from a higher doses of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every two weeks. Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first Risperidone ER injection.

Upward dosage adjustment should not be made more frequently than every 4 weeks. The effect of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose. Where patients are not stabilized on oral risperidone the recommended dose is 25 mg Risperidone ER every two weeks. Patients with no previous history of risperidone use should be pre-treated with oral risperidone for several days as clinically feasible, to assess tolerability before the first injection. For those patients stabilized on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered. Patients treated with a dosage of 4 mg or less oral risperidone should receive 25 mg Risperidone ER, patients treated with higher oral doses should be considered for the higher Risperidone ER dose of 37.5 mg. Dose increments from 25 mg to 37.5 mg or from 37.5 mg to 50 mg should be considered after a minimum of four weeks after the previous dose adjustment. The effect of this dosage adjustment on the patient's clinical status should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

Elderly

The recommended dose is 25 mg intramuscular every two weeks. Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first Risperidone ER injection.

Hepatic and Renal Impairment

Risperidone ER has not been studied in hepatically and renally impaired patients. If hepatically or renally impaired patients require treatment with Risperidone ER, a starting dose of 0.5 mg twice daily oral risperidone is recommended during the first week. The second week 1 mg twice daily or 2 mg once daily can be given. If an oral dose of at least 2 mg is well tolerated, an injection of 25 mg Risperidone ER can be administered every 2 weeks.

Children

Risperidone ER has not been studied in children younger than 18 years.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to Risperidone ER, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of Risperidone ER to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun. For schizophrenic patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with Risperidone ER. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

Mode of Administration
Intramuscular injection

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.

For risperidone naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with Risperidone ER.

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). The risk/benefit of further treatment with Risperidone ER should be assessed if clinically relevant orthostatic hypotension persists.

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 in association with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotic drugs, including risperidone, should be discontinued. After the last administration of Risperidone ER, plasma levels of risperidone are present for up to (a minimum) of 6 weeks.

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 ER.

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 ER.

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.

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
Tonsillitis, eye infection, cellulitis, otitis media, onychomycosis, acarodermatitis, bronchopneumonia, tracheobronchitis, otitis media chronic

Blood and Lymphatic Disorders
Granulocytopenia

Immune System Disorders
Drug hypersensitivity

Metabolism and Nutrition Disorders
Polydipsia

Psychiatric Disorders
Blunted affect, confusional state, middle insomnia, listless, anorgasmia

Nervous System Disorders
Hypertonia, balance disorder, unresponsive to stimuli, depressed level of consciousness, movement disorder, Parkinsonian rest tremor, transient ischemic attack, cerebrovascular accident, masked facies, speech disorder, loss of consciousness, muscle contractions involuntary, cerebral ischemia, cerebrovascular disorder, neuroleptic malignant syndrome, diabetic coma

Eye Disorders
Ocular hyperemia, eye discharge, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, lacrimation increased, photophobia, glaucoma

Ear and Labyrinth Disorders
Tinnitus

Cardiac Disorders
Atrioventricular block

Vascular Disorders
Flushing

Respiratory, Thoracic, and Mediastinal Disorders
Epistaxis, wheezing, pneumonia aspiration, dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory disorder, hyperventilation, nasal edema

Gastrointestinal Disorders
Dysphagia, fecaloma, abdominal discomfort, fecal incontinence, lip swelling, cheilitis, aptyalism

Skin and Subcutaneous Tissue Disorders
Erythema, skin discoloration, skin lesion, skin disorder, rash erythematous, rash papular, hyperkeratosis, dandruff, seborrheic dermatitis, rash generalised, rash maculo-papular

Musculoskeletal, Connective Tissue, and Bone Disorders
Joint swelling, joint stiffness, rhabdomyolysis, torticollis

Renal and Urinary Disorders
Enuresis, Dysuria, Pollakiuria

Reproductive System and Breast Disorders
Vaginal discharge, retrograde ejaculation, ejaculation failure, breast enlargement

General Disorders and Administration Site Conditions
Thirst, feeling abnormal, gait disturbance, pitting edema, edema, chills, discomfort, generalised edema, drug withdrawal syndrome, peripheral coldness

Investigations
Body temperature increased, heart rate increased, eosinophil count increased, white blood cell count decreased, hemoglobin decreased, blood creatine phosphokinase increased, hematocrit decreased, body temperature decreased, blood pressure decreased, transaminases increased

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
Very rare : Pancreatitis

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

Eye disorder
Unknown : Retinal artery occlusion

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
Unknown : Injection site reaction including injection site abscess, cellulitis, cyst, haematoma, necrosis, nodule, and ulcer

Overdose and Treatment

While overdosage is less likely to occur with parenteral than with oral medication, information pertaining to oral is presented.

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.

Incompatibilities

Risperidone ER cannot be mixed or diluted with drugs or fluids other than the supplied diluent for administration.

Instruction for Use
[Add suitable instruction & graphic]

Risperidone ER microspheres in the vial must be reconstituted only with the recommended diluent, and must be administered with only the appropriate needle supplied in the dose pack for gluteal (2-inch needle) or deltoid (1-inch needle) administration. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.

Inject the entire contents of the syringe intramuscularly into the selected gluteal or deltoid muscle of the patient. Gluteal injection should be made into the upper-outer quadrant of the gluteal area.

Do not administer intravenously.

Diluent composition

Polysorbate 20, carmellose sodium, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, water for injection.

Storage Conditions
Finished product - Store below ….°C
Reconstituted product (if applicable) - Store below ….°C for …. hours.
* If not, please include this statement - For single use only. Discard any unused portion after opening]

Dosage Forms and Packaging Available
[Packaging type & pack size eg Single glass vial/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]