# RAXIDONE®

**Warning**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Meta-analysis of 17 controlled trials of atypical antipsychotic drugs revealed an increased risk of death (between 1.6 to 1.7 times) compared to placebo in elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs . Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Risperidone is not approved for the treatment of patients with dementia-related psychosis.

## DESCRIPTION

**RAXIDONE** is the trademark of Risperidone, an antipsychotic agent.

Each **RAXIDONE** 1, 2 and 4 Coated Tablet contains Risperidone 1, 2 and 4 mg, respectively.

Each 1ml of **RAXIDONE** Solution contains Risperidone 1mg.

## CHEMISTRY

Risperidone is: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one.

## CLINICAL PHARMACOLOGY

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 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. Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food. Risperidone is metabolized by CYP 2D6 to 9-hydroxyrisperidone, which has a similar pharmacological activity as Risperidone , and both compounds are excreted in urine (70%) and feces (14%).

## INDICATIONS

- **RAXIDONE** is indicated for the treatment of acute and chronic schizophrenic psychoses, 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
- **RAXIDONE** also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia
- **RAXIDONE** is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
- **RAXIDONE** is indicated in the treatment of conduct and other disruptive behavior disorders in children, adolescents and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviors (e.g. aggression, impulsivity and self- injurious behaviors) are prominent
- **RAXIDONE** is indicated for the treatment of manic episodes associated with bipolar disorders. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviors.

## DOSAGE

- ***Schizophrenia:***

Switching from other antipsychotics:

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

Adults:

**RAXIDONE** may be given once daily or twice daily. Patients should start with 2 mg/day **RAXIDONE**. The dosage may be increased on the second day to 4 mg, from then 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 **RAXIDONE** 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 2 mg b.i.d. **RAXIDONE** is well tolerated by the elderly.

Children:

Experience in schizophrenia is lacking in children less than 15 years of age.

- ***Conduct and Other Disruptive behavior disorders***

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

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 **RAXIDONE** must be evaluated and justified on an ongoing basis.

Experience is lacking in children less than 5 years of age.

- ***Bipolar mania:***

Adults:

**RAXIDONE** should be administered on a once daily schedule, starting with 2 or 3 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Efficacy was demonstrated in flexible doses over a range of 1 to 6 mg per day. As with all symptomatic treatments, the continued use of **RAXIDONE** must be evaluated and justified on an ongoing basis.

Children:

Experience is lacking in bipolar mania in children and adolescents less than 18 years of age

- ***Renal and Hepatic Impairment***

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. 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. **RAXIDONE** should be used with caution in these groups of patients

**Notes**

- **RAXIDONE** can be given with or without meals.
- **RAXIDONE** may be given as tablets or oral solution.
- The pharmacokinetics of Risperidone , 9-hydroxy-Risperidone and the active antipsychotic fraction in children are similar to those in adults.

## ADVERSE EFFECTS

**RAXIDONE** is generally well tolerated. In many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events reported in association with the use of **RAXIDONE** are listed below (see also Warnings) :

**Common effects:**

- Insomnia, agitation, anxiety, headache.
- Sedation has been reported more frequently in children and adolescents than in adults; it is usually mild and transient

**Less common effects:**

- Somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/ vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, urinary incontinence, angioedema, rhinitis, rash and other allergic reactions.
- **RAXIDONE** has a lower propensity to induce extrapyramidal symptoms than classical neuroleptics. However, in some cases, extrapyramidal symptoms, which are usually mild and reversible, may occur.
- Occasionally, (orthostatic) hypotension and (reflex) tachycardia, or hypertension, have been reported.
- **RAXIDONE** can induce a dose-dependent increase in plasma prolactin concentration.
- Weight gain and edema have been reported during treatment.
- Cerebrovascular adverse events, including cerebrovascular accidents and transient ischemic attacks, have been reported during treatment with **RAXIDONE**.
- Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases.
- As with classical neuroleptics, the following have occasionally been reported in psychotic patients: water intoxication, tardive dyskinesia, neuroleptic malignant syndrome, body temperature disregulation and seizures
- Very rare cases of QT prolongation have been reported in postmarketing experience

## USE IN PREGNANCY

The safety of **RAXIDONE** for use during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of Risperidone during the last trimester of pregnancy. Although, 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. Therefore, **RAXIDONE** should only be used during pregnancy if the benefits outweigh the risks.

## USE IN LACTATION

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 **RAXIDONE** should not breast feed.

## INTERFERENCE WITH CLINICAL AND LABORATORY TESTS

- A decrease in neutrophil and/or thrombocyte count has been reported.
- Increased hepatic enzyme levels have been reported
- Hyperglycemia or exacerbation of pre-existing diabetes has been reported very rarely (see also Adverse Effects).

## DRUG INTERACTIONS

- **RAXIDONE** should be used with caution in combination with other centrally acting drugs. **RAXIDONE** may antagonize the effect of levodopa and other dopamine-agonists.
- Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of Risperidone . Similar effects may be observed with other hepatic enzyme inducers. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of **RAXIDONE** should be re-evaluated and - if necessary - decreased.
- 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. 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 **RAXIDONE**.
- In 2 of 4 of the **RAXIDONE** placebo-controlled trials in elderly patients with dementia, 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. Caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

## CONTRAINDICATIONS

Risperidone is contraindicated in patients with a known hypersensitivity to the product.

## WARNINGS

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death (see also Drug Interactions, Boxed warning)
- Due to the alpha-blocking activity of Risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **RAXIDONE** should be used with caution in patients with known cardiovascular disease, and the dosage should be gradually titrated as recommended (see Dosage). A dose reduction should be considered if hypotension occurs.
- 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 **RAXIDONE** 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, 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 **RAXIDONE**, should be discontinued. Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including **RAXIDONE**, 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.
- Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see Adverse Effects).
- 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.
- For elderly patients with dementia, for pediatric patients with conduct and other disruptive behavior disorders, and for patients with renal or hepatic impairment see Dosage for specific recommendations.

## OVERDOSE

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. Overdosages of up to 360 mg have been reported. The available evidence suggests a wide safety margin. In overdose, rare cases of QT-prolongation have been reported. 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 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 **RAXIDONE**. 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.

## PRECAUTIONS

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

## HOW SUPPLIED

- Boxes of 30 blistered Tablets of **RAXIDONE** 1.
- Boxes of 20 blistered Tablets of **RAXIDONE** 1.
- Boxes of 30 blistered Tablets of **RAXIDONE** 2.
- Boxes of 20 blistered Tablets of **RAXIDONE** 2.
- Boxes of 30 blistered Tablets of **RAXIDONE** 4.
- Boxes of 20 blistered Tablets of **RAXIDONE** 4.
- Bottles of 60ml of **RAXIDONE** Solution (1 mg/ml).
- Hospital packs of different presentations.

Store at a temperature between 15and 30°C.

Do not use after the expiry date shown on the package.

## THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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Prescribing Information Available Upon Request

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