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BENZISOX®

Film Coated Tablets

(Risperidone Tablets USP 2mg)

COMPOSITION

Benzisox 1 mg tablets: Each film coated tablet contains Resperidone 1mg.
Benzisox 2 mg tablets: Each film coated tablet contains Resperidone 2mg.
Benzisox 3 mg tablets: Each film coated tablet contains Resperidone 3mg.
Benzisox 4 mg tablets: Each film coated tablet contains Resperidone 4mg.

DESCRIPTION

Benzisox (Risperidone) is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole derivates.

PHARMACOKINETIC PROPERTIES

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 cytochrome P- 450 IID6 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 in one day in most patients. Steady-state of 9-hydroxy- risperidone is reached within 4 to 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 alphal acid glycoprotein. The plasma protein binding of risperidone is 88%, which of 9-hydroxy-risperidone is 77%. 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. A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency. The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active moiety in children are similar to those in adults.

PHARMACODYNAMIC PROPERTIES

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotonergic 5-HT2 and dopaminergic D2 receptors. Risperidone also binds to alpha 1-adrenergic receptors, and, with lower affinity to H1-histaminergicand 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 acUvfiyTcTtfie negative and affective symptoms of schizophrenia.

INDICATIONS

Benzisox is indicated for the treatment of a broad range of patients with schizophrenia, including first episode psychosis, 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. Benzisox alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. Benzisox is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. In addition, Benzisox is indicated for the treatment of behavioral disturbances in patients with dementia in whom symptoms such as aggressiveness (verbal outbursts, physical violence), activity disturbances (agitation wandering) or psychotic symptoms are prominent. Benzisox is also indicated as adjunctive therapy to mood stabilizers in 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 behaviour. Benzisox is indicated in the treatment of conduct and other disruptive behaviour disorders in children, adolescents and adults with sub average intellectual functioning or mental retardation in whom destructive behaviour (e.g., Aggression, impulsivity and self- injurious behaviour) are prominent.

DOSAGE AND ADMINISTRATION

a. Schizophrenia
Adults

Benzisox may be given once daily or twice daily.
Patients should start with Benzisox 2 mg/day. 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 Benzisox 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. Benzisox 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. Benzisox should be used with caution in this group of patients until further experience is gained.

Behavioural disturbances in patients with Dementia

A starting dose of 0.25 mg b.i.d., is recommended. This dosage can be individually adjusted by increments of 0.25 mg b.i.d., not more frequently than every other day, if needed. The optimum dose is 0.5 mg b.i.d. for most patients. Some patients, however, may benefit from doses up to 1 mg b.i.d. Once patients have reached their target dose, a once daily dosing regimen can be considered.

Switching from other antipsychotics.

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

b. Bipolar mania - adjunctive therapy

A starting dosage of 2 - 3 mg once daily (o.d.) is recommended. This dosage can be individually adjusted by increments of up to 1 mg/day not more frequently than every other day. Most patients will benefit from doses between 1 - 6 mg/day.

Conduct and other disruptive behaviour 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 Benzisox must be evaluated and justified on an ongoing basis. Experience is lacking in children aged less than 15 years.

CONTRAINDICATIONS

Benzisox is contraindicated in patients with known hypersensitivity to the product.

ADVERSE REACTIONS

Based on extensive clinical experience including long term use Benzisox is generally well tolerated. In many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the uses of Benzisox are listed below:

Common:

Insomnia, agitation, anxiety, headache. Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Less common:

Somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions. Benzisox has a lower propensity to induce extrapyramidal symptoms than classical neuroleptics. However, in some cases the following extrapyramidal symptoms may occur; tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. These are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary. Occasionally, (orthostatic) hypotension, and (reflex) tachycardia or hypertension have been observed following administration of Benzisox (see Precautions).A mild fall in neutrophil and/or thrombocyte count has been reported. Benzisox can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia,

disturbances of the menstrual cycle and amenorrhoea. Weight gain (see Precautions), oedema and increased hepatic enzyme levels have been observed during treatment with Benzisox. Cerebrovascular accidents have been observed during treatment with Benzisox. As with classical neuroleptics, the following have occasionally been reported 'in psychotic patients: water intoxication due to either polydipsia or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), tardive dyskinesia, neuroleptic malignant syndrome, body temperature disregulation and seizures.

WARNINGS & PRECAUTIONS

Due to alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Risperidone should be used with caution in patients with known cardiovascular disease (e.g., Heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see dosage and administration). 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 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. The Neuroleptic Malignant Syndrome characterized by hyperthermia, muscle rigidity autonomic instability, altered consciousness and elevated CPK levels has been reported to occur with classical neuroleptics. In this event, all antipsychotic drugs, including risperidone, should be discontinued. For specific dosage recommendations for elderly patients with renal or liver disease and patients with dementia, refer to dosage and administration. Caution is also due when prescribing risperidone to patients with Parkinson's disease since, theoretically, it might cause a deterioration of the disease. 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 possibility of weight gain.

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 antipsychotic, including risperidone. Assessment of the relationship between atypical antipsychotic 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 these 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 adverse events in patients treated with the atypical antipsychotic. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotic are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotic 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 antipsychotic should undergo fasting blood glucose testing at the beginning of treatment. Any patient treated with atypical antipsychotic should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotic 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.

INTERACTIONS

The risk of using risperidone in combination with other drugs has not been systemically evaluated. 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. 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 risperidone 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 antipsychotic fraction. Fluoxetine may increase the plasma concentration of risperidone but less so of the 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. Food does not affect the absorption of risperidone.

PREGNANCY & LACTATION

The safety of risperidone for use during human pregnancy has not been established. 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, risperidone should only be used during pregnancy if the benefits outweigh the risks. In animaW>tudies, 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 breastfeed.

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.

OVERDOSAGE

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. Over dosages of up to 360mg 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 over dosage, 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 Benzisox, 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 -shouW continue urrtt) the patient recovers.

STORAGE

Store below 25°C in a dry place. Protect from light.

PRESENTATION

1. Benzisox 1 mg tablets: Blister pack of 1X20 film coated tablets.
2. Benzisox 2 mg tablets: Blister pack of 1X20 film coated tablets.
3. Benzisox 3 mg tablets: Blister pack of 1X20 film coated tablets.
4. Benzisox 4 mg tablets: Blister pack of 1X20 film coated tablets.

TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

بینزِی سوکس
(ریسپریڈون)

فلم کوٹڈ گولیاں

خوراک

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ پر ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 25°C سے کم درجہ حرارت پر، نمی اور روشنی سے محفوظ رکھیں۔

Manufactured by:
HIGHNOON LABORATORIES LTD.
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