RISPERIDONE

ASPIDON

2 mg Film-Coated Tablet

ANTIPSYCHOTIC

FORMULATION

Each film-coated tablet contains:

Risperidone 2mg

PRODUCT DESCRIPTION

Risperidone (Aspidon) 2 mg is a light orange coloured, round, biconvex, film coated tablet with bisecting line on one side.

PHARMACODYNAMICS

The mechanism of action of risperidone, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Risperidone is a selective monoaminergic antagonist with high affinity for the serotonin type 2 (5HT2), dopamine type 2 (D2), a1 and a2 adrenergic, and H1 histaminergic receptors. Risperidone antagonizes other receptors, but with lower potency. Risperidone has low to moderate affinity for the seretonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity for cholinergic muscarinic or B1 and B2 adrenergic receptors.

PHARMACOKINETICS

Absorption:

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Plasma concentration of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of a solution or tablet, mean peak plasma concentrations of risperidone occured about 1 hour. Peak concentrations of 9-hydroxyrisperidone occured at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect:

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution:

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/Kg. In plasma, risperidone is bound to albumin andα ,-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of it major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma bindin sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism:

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are “poor metabolizers”) and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, where as poor metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydoxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, risperidone is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

In vitro studies demonstrated that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

Excretion:

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations:

Renal Impairment: In patients with moderate to severe (Clcr 59 to 15 mL/min) renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60%, compared to young healthy subjects. Risperidone doses should be reduced in patients with renal disease.

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35%because of the diminished concentration of both albumin and α1-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease.

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients.

Pediatric: The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

INDICATIONS

Risperidone (Aspison) is indicated for the treatment of schizoprenia, and for the short-term treatment of acute manic or mixed episodes associated with bipolar disorders.

DOSAGE AND ADMINISTRATION

Schizophrenia

Adults - Usual Initial Dose- Risperidone (Aspidon) tablets can be administered once or twice daily. Initial dosing is 2 mg per day. May increase the dose at intervals of 24 hours or greater, in increments of 1 to 2 mg per day, as tolerated, to a recommended dose of 4 to 6 mg per day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4 mg to 16 mg per day. However, doses above 10 mg / day have not been shown to be more efficacious than lower doses, and may cause extrapyramidal symptoms and other adverse effects, and are generally not recommended. The safety of doses above 16 mg/day has not been evaluated, doses above this level should not be used. .

Adolescents - The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day.

Doses higher than 6 mg per day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Experience in schizoprenia is lacking in children less than 13 years of age.

Switching From Other Antipsychotics - When switching from other antipsychotics, where medically appropriate, gradual discontinuation of the previous treatment while Risperidone (Aspidon) therapy is initiated is recommended.

Bipolar Mania

Usual Dose

Adults - The initial dose range is 2 mg to 3 mg/ day. The dose may be adjusted at intervals of 24 hours or greater, in increments of 1 mg/day. A dosing range between 1 to 6 mg/day is recommended.

As with all symptomatic treatments, the continued use of Risperidone (Aspidon) must be evaluated and justified on an ongoing basis.

Pediatrics - The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 or 1 mg/day, as tolerated, to the recommended target dose of 1 to 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg/day. Doses higher than 6 mg per day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

As with all symptomatic treatments, the continued use of Risperidone (Aspidon) must be evaluated and justified on an ongoing basis.

Experience is lacking in bipolar mania in children less than 10 years of age.

Dosing in Patients with Severe Renal or Hepatic Impairment

For patients with severe renal impairment (CLcr < 30 mL/min) or hepatic impairment (10-15 points on Child Pugh System), the initial starting dose is 0.5 mg twice daily. The dose may be increased in increments of 0.5 mg or less, administered twice daily. For doses above 1.5 mg twice daily, increase in intervals of one week or greater. Risperidone (Aspidon) should be used with caution in this group of patients.

Dose Adjustments for Specific Drug Interactions

When Risperidone (Aspidon) tablets are co-administered with enzyme inducers (e.g., carbamazepine), the dose of Risperidone (Aspidon) tablets should be increased up to double the patient's usual dose. It may be necessary to decrease the Risperidone (Aspidon) tablets dose when enzyme inducers such as carbamazepine are discontinued. Similar effect may be expected with co-administration of Risperidone (Aspidon) tablets with other enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital).

When fluoxetine or paroxetine is co-administered with Risperidone (Aspidon) tablets, the dose of Risperidone (Aspidon) tablets should be reduced. The Risperidone (Aspidon) tablets dose should not exceed 8 mg per day in adults when co-administered with these drugs. When initiating therapy, Risperidone (Aspidon) tablets should be titrated slowly.

It may be necessary to increase the Risperidone (Aspidon) tablets dose when enzyme inhibitors such as fluoxetine or paroxetine are discontinued.

CONTRAINDICATION

Risperidone (Aspidon) is contraindicated in patients with a known hypersensitivity to the product. Hypersensitivity reactions including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone.

WARNINGS and PRECAUTIONS

Elderly patients with dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Cerebrovascular adverse reactions (e.g. Stroke, transient ischemic attack), including fatalities were reported in patients (mean age 85years; range 73 - 97) in trials of risperidone in elderly patients with dementia-related psychosis.

Risperidone (Aspison) is not approved for the treatment of dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS)

Antipsychotic drugs including risperidone can cause a potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase(CPK), myoglobinuria, rhabdomyolysis, and acute renal failure.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

If signs and symptoms of tardive dyskinesia appear in a patient treated with risperidone, consider drug discontinuation.

Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including risperidone, 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, including risperidone, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including risperidone, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including risperidone,

Should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Orthostatic Hypotension

Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of risperidone-treated patients in Phase 2 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment [see Dosage and Administration (2.1, 2.4)]. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease(history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medication.

Leukopenia, Neutropenia, and Agranulocytosis

Events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count(WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently 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 <1000/mm3) should discontinue risperidone and have their WBC followed until recovery.

Seizures

Risperidone should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Priapism

Priapism has been reported. Severe priapism may require surgical intervention.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with risperidone treatment. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

PREGNANCY AND LACTATION

Pregnancy

Adequate and well controlled studies with risperidone have not been conducted in pregnant women.

Neonates exposed to antipsychotic drugs (including risperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There was no increase in the incidence of malformations in embryo-fetal studies in rats and rabbits at 0.4–6 times MHRD.Increased pup mortality was noted at all doses in peripostnatal studies in rats. Risperidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress,and feeding disorder in neonates following in utero exposure to antipsychotics in the third trimester.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 hospitalization.

Lactation

Risperidone and 9-hydroxyrisperidone are present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from risperidone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

Pharmacokinetic-related Interactions

The dose of risperidone should be adjusted when used in combination with CYP2D6 enzyme inhibitors (e.g., fluoxetine, and paroxetine) and enzyme inducers (e.g., carbamazepine). Dose adjustment is not recommended for risperidone when co-administered with ranitidine, cimetidine, amitriptyline, or erythromycin.

Effect of Risperidone on other drugs

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

Pharmacodynamic-related Interactions

Centrally-Acting Drugs and Alcohol - Given the primary CNS effects of risperidone, caution should be used when risperidone is taken in combination with other centrally-acting drugs and alcohol.

Drugs with Hypotensive Effects - Because of its potential for inducing hypotension, risperidone may enhance the hypotensive effects of other therapeutic agents with this potential.

Levodopa and Dopamine Agonists - Risperidone may antagonize the effects of levodopa and dopamine agonists.

Clozapine - Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

ADVERSE EFFECTS

The most common adverse reactions in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

The most common adverse reactions that were associated with discontinuation from clinical trials(causing discontinuation in >1% of adults and/or >2% of pediatrics) were nausea, somnolence, sedation, vomiting, dizziness, and akathisia..

"For Suspected Adverse Reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient must seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., 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.

In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with 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 AND CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Risperidone (Aspidon) 2 mg Film-Coated Tablet - Alu/Clear PVC Blister Pack of 10's (Box of 20's) - DRP-2703

DATE OF FIRST AUTHORIZATION

September 20, 2006

DATE OF REVISION

September 2016

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad - 382721, Tal: Kadi, City Indrad
Dist.: Mehsana, India

Imported and Distrubuted by:
TORRENT PHARMA PHILIPPINES INC.
Units 3 & 4, 34th Floor, Zuellig Building
Makati Avenue Corner Paseo de Roxas
Makati City, PHILIPPINES

RISPERIDONE

ASPIDON

1 mg Film-Coated Tablet

ANTIPSYCHOTIC

FORMULATION

Each film-coated tablet contains:

Risperidone, USP 1mg

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Adolescents - The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day.

Doses higher than 6 mg per day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Experience in schizoprenia is lacking in children less than 13 years of age.

Switching From Other Antipsychotics - When switching from other antipsychotics, where medically appropriate, gradual discontinuation of the previous treatment while Risperidone (Aspidon) therapy is initiated is recommended.

Bipolar Mania

Usual Dose

Adults - The initial dose range is 2 mg to 3 mg/ day. The dose may be adjusted at intervals of 24 hours or greater, in increments of 1 mg/day. A dosing range between 1 to 6 mg/day is recommended.

As with all symptomatic treatments, the continued use of Risperidone (Aspidon) must be evaluated and justified on an ongoing basis.

Pediatrics - The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 or 1 mg/day, as tolerated, to the recommended target dose of 1 to 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg/day. Doses higher than 6 mg per day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

As with all symptomatic treatments, the continued use of Risperidone (Aspidon) must be evaluated and justified on an ongoing basis.

Experience is lacking in bipolar mania in children less than 10 years of age.

Dosing in Patients with Severe Renal or Hepatic Impairment

For patients with severe renal impairment (CLcr < 30 mL/min) or hepatic impairment (10-15 points on Child Pugh System), the initial starting dose is 0.5 mg twice daily. The dose may be increased in increments of 0.5 mg or less, administered twice daily. For doses above 1.5 mg twice daily, increase in intervals of one week or greater. Risperidone (Aspidon) should be used with caution in this group of patients.

Dose Adjustments for Specific Drug Interactions

When Risperidone (Aspidon) tablets are co-administered with enzyme inducers (e.g., carbamazepine), the dose of Risperidone (Aspidon) tablets should be increased up to double the patient's usual dose. It may be necessary to decrease the Risperidone (Aspidon) tablets dose when enzyme inducers such as carbamazepine are discontinued. Similar effect may be expected with co-administration of Risperidone (Aspidon) tablets with other enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital).

When fluoxetine or paroxetine is co-administered with Risperidone (Aspidon) tablets, the dose of Risperidone (Aspidon) tablets should be reduced. The Risperidone (Aspidon) tablets dose should not exceed 8 mg per day in adults when co-administered with these drugs. When initiating therapy, Risperidone (Aspidon) tablets should be titrated slowly.

It may be necessary to increase the Risperidone (Aspidon) tablets dose when enzyme inhibitors such as fluoxetine or paroxetine are discontinued.

CONTRAINDICATION

Risperidone (Aspidon) is contraindicated in patients with a known hypersensitivity to the product. Hypersensitivity reactions including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone.

WARNINGS and PRECAUTIONS

Elderly patients with dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Cerebrovascular adverse reactions (e.g. Stroke, transient ischemic attack), including fatalities were reported in patients (mean age 85years; range 73 - 97) in trials of risperidone in elderly patients with dementia-related psychosis.

Risperidone (Aspison) is not approved for the treatment of dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS)

Antipsychotic drugs including risperidone can cause a potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase(CPK), myoglobinuria, rhabdomyolysis, and acute renal failure.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

If signs and symptoms of tardive dyskinesia appear in a patient treated with risperidone, consider drug discontinuation.

Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including risperidone, 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, including risperidone, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including risperidone, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including risperidone,

Should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Orthostatic Hypotension

Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of risperidone-treated patients in Phase 2 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment [see Dosage and Administration (2.1, 2.4)]. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease(history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medication.

Leukopenia, Neutropenia, and Agranulocytosis

Events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count(WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently 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 <1000/mm3) should discontinue risperidone and have their WBC followed until recovery.

Seizures

Risperidone should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Priapism

Priapism has been reported. Severe priapism may require surgical intervention.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with risperidone treatment. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

PREGNANCY AND LACTATION

Pregnancy

Adequate and well controlled studies with risperidone have not been conducted in pregnant women.

Neonates exposed to antipsychotic drugs (including risperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There was no increase in the incidence of malformations in embryo-fetal studies in rats and rabbits at 0.4–6 times MHRD.Increased pup mortality was noted at all doses in peripostnatal studies in rats. Risperidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress,and feeding disorder in neonates following in utero exposure to antipsychotics in the third trimester.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 hospitalization.

Lactation

Risperidone and 9-hydroxyrisperidone are present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from risperidone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

Pharmacokinetic-related Interactions

The dose of risperidone should be adjusted when used in combination with CYP2D6 enzyme inhibitors (e.g., fluoxetine, and paroxetine) and enzyme inducers (e.g., carbamazepine). Dose adjustment is not recommended for risperidone when co-administered with ranitidine, cimetidine, amitriptyline, or erythromycin.

Effect of Risperidone on other drugs

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

Pharmacodynamic-related Interactions

Centrally-Acting Drugs and Alcohol - Given the primary CNS effects of risperidone, caution should be used when risperidone is taken in combination with other centrally-acting drugs and alcohol.

Drugs with Hypotensive Effects - Because of its potential for inducing hypotension, risperidone may enhance the hypotensive effects of other therapeutic agents with this potential.

Levodopa and Dopamine Agonists - Risperidone may antagonize the effects of levodopa and dopamine agonists.

Clozapine - Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

ADVERSE EFFECTS

The most common adverse reactions in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

The most common adverse reactions that were associated with discontinuation from clinical trials(causing discontinuation in >1% of adults and/or >2% of pediatrics) were nausea, somnolence, sedation, vomiting, dizziness, and akathisia..

"For Suspected Adverse Reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient must seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., 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.

In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with 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 AND CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Risperidone (Aspidon) 1 mg Film-Coated Tablet - Alu-Clear PVC Blister Pack of 10's (Box of 50's) - DRP-3785

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