RISPERIDONE
RENUVIE®
1 mg / 2 mg / 4 mg FILM-COATED TABLETS
ANTIPSYCHOTIC

FORMULATION
Each film-coated tablet contains:
Risperidone.....1, 2 or 4 mg

PRODUCT DESCRIPTIONS
Risperidone 1 mg is a pink, film-coated, and round biconvex tablet.
Risperidone 2 mg is an orange, film-coated, capsule-shaped tablet, bisected on one side.
Risperidone 4 mg is an aquamarine, film-coated, biconvex, elliptical shaped tablet.

PHARMACOLOGY
Risperidone is a benzisoxazole derivative antipsychotic agent. Its mechanism of action is unclear but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism.
Risperidone, as a potent D_2 antagonist, improves the positive symptoms of schizophrenia but causes less depression of motor activity and induction of catalepsy than typical antipsychotic drugs. 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. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxyrisperidone.
Risperidone is a selective monoaminergic antagonist with high affinity for $5HT_2$, D_2, α_1 and α_2 adrenergic, and H, histaminergic receptors. Risperidone acts as an antagonist at other receptors, but with lower potency. Risperidone has low to moderate affinity for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity for the D, and haloperidol-sensitive sigma site, and no affinity for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

PHARMACOKINETICS
Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability is 70%. The relative oral bioavailability of risperidone from a tablet is 94% compared with a solution; food does not affect either the rate or extent of absorption of risperidone.
Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dose range of 1 to 16 mg per day (0.5 to 8 mg twice a day). After oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about one hour. Peak concentrations of 9-hydroxyrisperidone occurred at about three hours in extensive metabolizers and 17 hours in poor metabolizers. Steady state concentrations of risperidone are reached in one day in extensive metabolizers and would be expected to reach steady state in about five days in poor metabolizers. Steady state concentrations of 9-hydroxyrisperidone are reached in 5 to 6 days (measured in extensive metabolizers).
Risperidone is rapidly distributed. The volume of distribution is 1 to 2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone and 9-hydroxyrisperidone is 90% and 77%, respectively. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL) and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.
Risperidone is extensively metabolized in the liver by CYP2D6 (also called debrisoquin hydroxylase) to 9-hydroxyrisperidone, which has a similar pharmacological activity as risperidone. CYP2D6 is subject to genetic polymorphism (about 6 to 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 CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 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-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.
Another metabolic pathway of risperidone is N-dealkylation. *In vitro* studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.
Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. A mass balance study of a single 1 mg oral dose of 14C-risperidone administered as a solution to three healthy male volunteers showed that total recovery of radioactivity at one week was 84%, including 70% in the urine and 14% in the feces.
The apparent half-life of risperidone was three hours in extensive metabolizers and 20 hours in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours in extensive metabolizers and 30 hours in poor metabolizers. The overall mean elimination half-life of risperidone and its active metabolite is about 20 hours.

Special Population:
Renal Impairment: In patients with moderate to severe 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 these patients.
Hepatic Impairment: Although the pharmacokinetics of risperidone in patients with liver disease were comparable to those in young healthy subjects, the mean fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. Risperidone doses should be reduced in these patients.
Elderly: In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased by 30%, and elimination half-lives were prolonged compared to young healthy subjects. Risperidone doses should be adjusted in these patients.
Children: The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

INDICATIONS
- **Schizophrenia**
  - Acute and maintenance treatment of schizophrenia in adults
  - Treatment of schizophrenia in adolescents 13 to 17 years old
- **Bipolar Mania**
  - Monotherapy: Short-term treatment of acute manic or mixed episodes associated with Bipolar I disorder in children and adolescents 10 to 17 years old
  - Treatment of moderate to severe manic episodes associated with bipolar disorders in adults
  - In combination with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults
- **Conduct and Other Disruptive Behavior Disorders**
  - Short-term symptomatic treatment (up to 6 weeks) of conduct and other disruptive behavior disorders in children (over 5 years), adolescents and adults with subaverage intellectual functioning or mental retardation, or average IQ, in whom destructive behaviors (e.g., aggression, impulsivity and self injurious behaviors) are prominent.
  - Risperidone is also effective in maintaining the clinical improvement during continuation therapy in children and adolescents who have shown an initial treatment response.
- **Irritability Associated with Autistic Disorders**
  - Treatment of irritability associated with autistic disorder in children and adolescents 5 to 16 yrs old, including symptoms of aggression towards others, deliberate self injuriousness, temper tantrums, and quickly changing moods

DOSAGE AND ADMINISTRATION
General Dosing Recommendations:
- Risperidone may be given with or without meals.
- Gradual withdrawal is advised upon discontinuation of therapy. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (e.g., akathisia, dystonia, and dyskinesia) has been reported.

Switching from other antipsychotics
- It is recommended that gradual discontinuation of the previous treatment should be done when risperidone therapy is initiated. The period of overlapping antipsychotic administration should be minimized. If necessary, when switching patients from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson drugs should be reevaluated periodically.

Recommended Oral Risperidone Dose

SCHIZOPHRENIA		
INITIAL TREATMENT		MAINTENANCE TREATMENT
ADULTS	ADOLESCENTS 13 to 17 YEARS OLD	
Risperidone may be given once or twice a day. **Initial Dose:** 2 mg per day; Dose increases should then occur at intervals not less than 24 hours, in increments of 1 to 2 mg per day, as tolerated, to a **recommended dose** of 4 to 8 mg per day. In some patients, slower titration may be appropriate. Efficacy has been shown with dose range of 4 to 16 mg per day. Doses above 10 mg per day have not shown superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms (EPS). Safety of doses above 16 mg per day has not been evaluated and are therefore not recommended. A benzodiazepine may be added to risperidone when additional sedation is required.	**Initial Dose:** 0.5 mg given as a single-daily dose in the morning or evening. If indicated, dosage adjustments should occur at intervals of not less than 24 hours, in increments of 0.5 or 1 mg per day, as tolerated, to a **recommended dose** of 3 mg per day. Although efficacy has been shown in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg per day, no additional benefit was seen above 3 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied. Patients experiencing persistent somnolence may benefit from administering half the daily dose twice a day.	**Adults:** While it is unknown how long a patient with schizophrenia should remain on risperidone, the effectiveness of risperidone 2 to 8 mg per day at delaying relapse was shown in a controlled trial in patients who had been clinically stable for at least four weeks and were then followed for a period of 1 to 2 years. Patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose. **Adolescents:** There are no data to support the long term use of risperidone beyond eight weeks in adolescents with schizophrenia. The physician who elects to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.
Reinitiation of treatment in patients previously discontinued: It is recommended that after an interval off risperidone, the initial titration schedule should be followed.		
Or, as prescribed by a physician.		

BIPOLAR MANIA		
INITIAL TREATMENT		MAINTENANCE TREATMENT
ADULTS	CHILDREN AND ADOLESCENTS 10 to 17 YEARS OLD	
Initial Dose: 2 to 3 mg once a day; If indicated, dosage adjustments should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6 mg have not been investigated in patients with manic episodes.	**Initial Dose:** 0.5 mg once a day, either in the morning or evening. If indicated, dosage adjustments should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg per day, as tolerated, to **recommended dose** of 2.5 mg per day Although efficacy has been shown in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg per day, no additional benefit was seen above 2.5 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied.Patients experiencing persistent somnolence may benefit from administering half the daily dose twice a day.	There are no data from controlled studies to support use of risperidone in long-term treatment (i.e., beyond three weeks). The physician who elects to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.
Or, as prescribed by a physician.		

CONDUCT AND OTHER DISRUPTIVE BEHAVIOR DISORDERS IN CHILDREN AND ADOLESCENTS 5 to 18 YEARS OLD	
For Patients ≥ 50 kg	**Starting Dose:** 0.5 mg once a day Dosage can be individually adjusted by increments of 0.5 mg once a day not more frequently than every other day, if needed. **Optimum Dose:** 1 mg once a day for most patients However, some patients may benefit from 0.5 mg once a day while others may require 1.5 mg once a day.
For Patients < 50 kg	**Starting Dose:** 0.25 mg once a day Dosage can be individually adjusted by increments of 0.25 mg once a day not more frequently than every other day, if needed. **Optimum Dose:** 0.5 mg once a day for most patients However, some patients may benefit from 0.25 mg once a day while others may require 0.75 mg once a day.
As with all symptomatic treatments, the continued use of risperidone must be evaluated and justified on an ongoing basis.	
Or, as prescribed by a physician.	

Irritability Associated with Autistic Disorder in Children and Adolescents 5 to 16 years old:
- The dosage of risperidone should be individualized according to response and tolerability of the patient.
- The total daily dose of risperidone can be administered once a day, or half the total daily dose can be administered twice a day.

Initial Dose:
Patient Weight
- < 20 kg: 0.25 mg per day
- ≥ 20 kg: 0.5 mg per day

After a minimum of four days from treatment initiation, the dose may be increased to a **recommended dose** of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days.
In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients <20 kg or 0.5 mg per day for patients ≥ 20 kg.
Patients experiencing persistent somnolence may benefit from a once a day dose administered at bedtime or administering half the daily dose twice a day, or a reduction of the dose.
Exercise caution with dosage for smaller children who weigh less than 15 kg.
Once sufficient response has been achieved and maintained, consider gradually lowering the dose to achieve optimum balance of effectiveness and tolerance.
As with all symptomatic treatments, the continued use of risperidone in children and adolescents with autism must be evaluated and justified on an ongoing basis.
Dosage in Special Population (elderly or debilitated patients, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk):
Initial Dose: 0.5 mg twice a day;
Dosage may be increased in increments of not more than 0.5 mg twice a day.
Increases to dosages above 1.5 mg twice a day should occur at intervals of at least one week. In some patients, slower titration may be medically appropriate.
If a once a day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice a day regimen for 2 to 3 days at the target dose. Subsequent switches to a once a day dosing regimen can be done thereafter.
Or, as prescribed by a physician.

CONTRAINDICATION
- Hypersensitivity to risperidone or to any component of the product

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Risperidone is not approved for the treatment of patients with dementia-related psychosis.

Dementia-Related Psychosis
Cerebrovascular adverse events (e.g., stroke, transient ischemia attack), including fatalities, were reported in risperidone trials involving elderly patients (mean age 85 years; range 73 to 97) with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo.

Neuroleptic Malignant Syndrome (NMS)
There have been reports of NMS, a potentially fatal symptom complex, in association with antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. While there is no general agreement about specific pharmacological treatment of NMS, its management 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. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. Careful monitoring of patients is necessary since recurrences of NMS have been reported.

Tardive Dyskinesia
Patients treated with antipsychotic drugs may develop tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements. The risk of developing this syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. The syndrome can also develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia. However, there may be partial or complete remission after withdrawal of antipsychotic treatment. Antipsychotic treatment may suppress or partially suppress the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Risperidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic antipsychotic treatment for patients who suffer from a chronic illness known to respond to antipsychotic drugs, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. Use the smallest dose and the shortest possible duration of treatment in patients who require chronic treatment. Periodically reassess the need for continued treatment. If signs and symptoms of tardive dyskinesia appear in a patient treated with risperidone, drug discontinuation should be considered. However, some patients may require treatment with risperidone despite the presence of the syndrome.

Seizures
Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Potential for Cognitive and Motor Impairment
Risperidone is commonly associated with somnolence and has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery (including automobiles) until they are reasonably certain that risperidone therapy does not affect them adversely.

Suicide
Close supervision of high-risk patients is recommended since the possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescents. Prescribe risperidone in the smallest quantity of tablets consistent with good patient management to reduce the risk of overdose.

Orthostatic Hypotension
Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, particularly during the initial dose-titration period, due to its α-adrenergic antagonistic properties. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive drugs. Risperidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs. Special care should be exercised in patients taking drugs to lower blood pressure.

Venous Thromboembolism (VTE)
Antipsychotic drugs have been reported to cause VTE. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with risperidone and preventive measures undertaken.

Hyperglycemia and Diabetes Mellitus
There have been reports of severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, in patients receiving certain atypical antipsychotic agents, including risperidone. Patients with pre-existing diabetes mellitus who are started on atypical antipsychotics, including risperidone, should be monitored regularly for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyuria, polyphagia, and weakness) during treatment with an atypical antipsychotic 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.

Weight Gain
Significant weight gain has been reported. Monitoring of weight gain is recommended during risperidone therapy. Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

Hyperprolactinemia
Risperidone and other drugs that antagonize dopamine D_2 receptors elevate prolactin levels which persist during chronic use. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Tissue culture studies suggest that cell growth in human breast tumors may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been shown in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinemia and in patients with possible prolactin-dependent tumors.

Priapism
Priapism may occur with risperidone treatment due to its α-adrenergic blocking effects. Severe priapism may require surgical intervention.

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 (ANC<1,000/mm³) should discontinue risperidone and have their WBC monitored until recovery.

Thrombotic Thrombocytopenic Purpura (TTP)
TTP has been reported in a patient receiving risperidone but the relationship with risperidone treatment is unknown.

Dysphagia
Esophageal dysmotility and aspiration have been associated with the use of antipsychotic drugs. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Use risperidone and other antipsychotic drugs with caution in patients at risk for aspiration pneumonia.

Antiemetic Effect
Risperidone may have antiemetic effects and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome and brain tumor.

Body Temperature Regulation
Antipsychotic drugs, including risperidone, may cause disruption of body temperature regulation such as hyperthermia or hypothermia. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Use in Patients with Concomitant Illness
Patients with Parkinson's Disease or dementia with lewy bodies may have increased sensitivity to antipsychotic drugs, including risperidone. Increased sensitivity may manifest as confusion, obtundation, postural instability with frequent falls, EPS, and clinical features consistent with NMS. Use caution when administering risperidone in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Risperidone has not been evaluated or used to any appreciable extent in patients with recent history of myocardial infarction or unstable heart disease. 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 such as class I antiarrhythmics (e.g., quinidine, disopyramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressant (TCA) (amitriptyline), tetracyclic antidepressants, some antihistamines, other antipsychotics, some antimalarials (e.g., chinice and mefloquine), and with medicines causing electrolyte imbalance (e.g., hypokalemia, hypomagnesemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. A lower starting dose is recommended in patients with severe renal impairment (Cl_{cr} <30 mL/min/1.73 m^2) and in patients with severe hepatic impairment. (see **DOSAGE AND ADMINISTRATION**)

INTERACTION WITH OTHER MEDICAMENTS
- **Paliperidone:** Concomitant use of risperidone and paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive antipsychotic fraction exposure.
- **Furosemide:** In risperidone 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 or furosemide alone. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings. 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 or co-treatment with other potent diuretics should be considered prior to the decision to use.
- **Centrally-acting drugs (e.g., opiates, antihistamines, benzodiazepines) and alcohol:** Caution should be used when risperidone is taken in combination with other centrally-acting drugs and alcohol due to increased risk of sedation.
- **Drugs with blood pressure lowering effects:** Because of its potential for inducing hypotension, risperidone may enhance the blood pressure lowering effects of other therapeutic agents.
- **Levodopa and dopamine agonists:** Risperidone may antagonize the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.
- **Cimetidine and ranitidine:** Increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and 9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%.
  CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, quinidine): Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5 to 2.8 fold and 3 to 9 fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The physician should reevaluate the dosing of risperidone when either concomitant fluoxetine or paroxetine is initiated or discontinued.
- **CYP3A4 inhibitor (e.g., verapamil):** Increases the plasma concentration of risperidone.
- **Carbamazepine and other CYP3A4 inducers:** Coadministration of carbamazepine with risperidone decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. The dose of risperidone needs to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of the drug.
- **Phenytoin, rifampicin and phenobarbital:** Coadministration of these drugs with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9 - hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, particularly during initiation or discontinuation of therapy with these inducers.
- **Phenothiazines, TCAs and some beta-blockers:** May increase the plasma concentrations of risperidone but not those of risperidone plus 9-hydroxyrisperidone.
- **Clozapine:** Chronic administration with risperidone may decrease the clearance of risperidone.
- **Topiramate:** Modestly reduced the bioavailability of risperidone, but not that of risperidone plus 9-hydroxyrisperidone. Therefore, this interaction is unlikely to be of clinical significance.
- **Valproate:** Repeated oral doses of risperidone did not affect the pre-dose or average plasma concentrations and exposure of valproate compared to placebo. However, there was a 20% increase in valproate peak plasma concentration after concomitant use of risperidone.
- **Amitriptyline, digoxin, donepezil, erythromycin, galantamine, lithium, psychostimulants (e.g., methylphenidate):** Did not affect the pharmacokinetics of risperidone.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. However, there was one case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to risperidone therapy is unknown.
Neonates exposed to antipsychotic drugs (including risperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms after 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 hospitalization.
Risperidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery
The effect of risperidone on labor and delivery in humans is unknown.
Lactation
Risperidone and 9-hydroxyrisperidone are excreted in human breast milk. Therefore, women receiving risperidone should not breastfeed.

CHILDREN AND ADOLESCENTS
Before risperidone is prescribed to a child or adolescent with conduct disorder, they should be fully assessed for physical and social causes of aggression behavior (e.g., pain or inappropriate environmental demands). Close monitoring of the sedative effects of risperidone in this population is recommended because of possible consequences on learning ability. A change in time of administration of risperidone could improve the impact of sedation on attention faculties of children and adolescents. Regular evaluation of endocrinological status, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects, is recommended because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in children and adolescents.
Regular examination of EPS and other movement disorder should also be conducted during treatment with risperidone.
The safety and effectiveness of risperidone in children less than 13 years old with schizophrenia have not been established.
The safety and effectiveness of risperidone in children less than 10 years old with bipolar disorder have not been established.
The safety and effectiveness of risperidone in pediatric patients less than 5 years old with autistic disorder have not been established.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Body as a Whole: Fatigue, asthenia, pyrexia, feeling abnormal, pain, infection, fall, increased body temperature, influenza, viral infection, malaise, face edema, discomfort, chills, peripheral coldness
Cardiovascular System: Tachycardia, chest pain, increased heart rate, syncope, orthostatic hypotension, hypotension, palpitations, hypertension, transient ischemic attack, peripheral edema, pitting edema, chest discomfort, sinus bradycardia, sinus tachycardia, atroventricular block first degree, Bundle branch block left/right, flushing, ECG abnormal, QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), cardiac arrest, *Torsade de Pointes*, atrial fibrillation
Digestive System: Vomiting, nausea, constipation, drooling, dry mouth, abdominal pain, upper abdominal pain, dyspepsia, abdominal discomfort, salivary hypersecretion, diarrhea, stomach discomfort, toothache, tongue spasm, gastroenteritis, dysphagia, fecaloma, fecal incontinence, gastritis, lip swelling, cheilitis, aptyalism, thirst, intestinal obstruction, pancreatitis
Hemic and Lymphatic System: Anemia, granulocytopenia, increased eosinophil count, decreased white blood cell count, decreased hemoglobin, decreased hematocrit, neutropenia, agranulocytosis, thrombocytopenia
Hepatic: Increases in: alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase; jaundice
Metabolic/Endocrine and Nutritional Disorders: Increased/decreased appetite, polydipsia, anorexia, diabetic coma, hyperglycemia, glucose urine present, diabetic ketoacidosis, diabetes mellitus, hypoglycemia, water intoxication; increases in: weight, blood glucose, blood creatine phosphokinase, blood prolactin; ejaculation failure, ejaculation disorder, ejaculation delayed, decreased libido, anorgasmia, erectile dysfunction, sexual dysfunction, retrograde ejaculation, priapism, inappropriate antidiuretic hormone secretion
Musculoskeletal System: Back pain, arthralgia, pain in extremity, joint stiffness, buttock pain, abnormal posture, joint swelling, myalgia, neck pain, musculoskeletal chest pain, joint stiffness, muscular weakness, rhabdomyolysis
Nervous System: Somnolence, insomnia, sedation, parkinsonism, akathisia, dizziness, postural dizziness, dyskinesia, anxiety, headache, tremor, dystonia, nervousness, lethargy, convulsion, paresthesia, depression, confusional state, depressed level consciousness, cerebrovascular accident, gait disturbance, listless, dysarthria, disturbance in attention, balance disorder, hypersomnia, sluggishness, agitation, blunted affect, sleep disorder, sleep apnea syndrome, unresponsive to stimuli, abnormal coordination, loss of consciousness, speech disorder, hypoesthesia, movement disorder, tardive dyskinesia, cerebral ischemia, NMS, vertigo, mania
Respiratory System: Cough, productive cough, nasopharyngitis, rhinorrhea, nasal congestion, rhinitis, upper/lower respiratory tract infection, sinusitis, dyspnea, epistaxis, pharyngolaryngeal pain, sinus congestion, pneumonia, pulmonary congestion, pharyngitis, tonsillitis, bronchitis, bronchopneumonia, tracheobronchitis, wheezing, pneumonia aspiration, dysphonia, respiratory tract congestion, rales, respiratory disorder, nasal edema, hyperventilation
Skin and Appendages: Rash (erythematous, papular, generalized, maculopapular), hypersensitivity, dry skin, dandruff, seborrheic dermatitis, hyperkeratosis, acne, subcutaneous abscess, eczema, cellulitis, erythema, pruritus, localized infection, onychomycosis, acarodermatitis, skin discoloration, skin lesion, skin disorder, anaphylactic reaction, angioedema, alopecia
Special Senses: Ear pain, ear infection, otitis media, chronic otitis media, tinnitus, eye infection, blurred vision, blepharospasm, ocular hyperemia, eye discharge, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, increased lacrimation, photophobia, glaucoma, reduced visual acuity, conjunctivitis
Urogenital and Reproductive System: Urinary tract infection, urinary incontinence, urinary retention, galactorrhea, enuresis, pollakiura, cystitis, dysuria, irregular menstruation, menstrual disorder, delayed menstruation, amenorrhea, gynecomastia, vaginal discharge, breast enlargement, breast discomfort, oligomenorrhea

OVERDOSAGE & MANAGEMENT
Signs and symptoms of risperidone overdosage include drowsiness and sedation, tachycardia and hypotension, and EPS. Some cases have been associated with hyponatremia, hypokalemia, prolonged QT, widened QRS, and seizure. *Torsade de Pointes* has been reported in association with combined overdose of risperidone and paroxetine. No fatalities have been reported in overdosage of 20 to 300 mg risperidone. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation in case of acute overdosage. Consider gastric lavage (after intubation if the patient is unconscious) and use of charcoal together with laxative. There may be risk of aspiration with induced emesis because of the possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose. Start cardiovascular monitoring immediately and include continuous ECG monitoring to detect possible arrhythmias. Alpha-blocking properties of bretylium might be additive to those of risperidone which may result in problematic hypotension. There is no specific antidote to risperidone overdose. Institute appropriate supportive measures. Consider the possibility of multiple drug involvement. Treat hypotension and circulatory collapse with appropriate measures such as IV fluids and/or sympathomimetic agents. Do not use epinephrine and dopamine since β-stimulation may worsen hypotension in the setting of risperidone-induced α-blockade. Administer anticholinergic medication in cases of severe EPS. Continue close medical supervision and monitoring until the patient recovers.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Risperidone 1 mg film-coated tablet, in Box of 30's (in Blister Foil) - DR-XY53118
Risperidone 2 mg film-coated tablet, in Box of 30's (in Blister Foil) - DR-XY53116
Risperidone 4 mg film-coated tablet, in Box of 30's (in Blister Foil) - DR-XY53119

STORAGE CONDITION
Keep the product out of reach and sight of children. Store at temperatures not exceeding 30°C.

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

Trusted Quality Healthcare.
Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
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