Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the dopamine D2 and serotonin 2 (5HT2) receptor antagonism. Antagonism at receptors other than D2 and 5HT may explain some of the other effects of RISPERDAL®. RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin 2 (5HT2), dopamine 2 (D2), serotonin 1 (5HT1), and histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 0.5, 2, 3, and 4 mg) for the dopamine D2, serotonin 2 (5HT2), and 5HT1 receptors, weak affinity (Ki of 60 to 800 nM) for the dopamine D4 and histaminergic receptors, and no affinity (when tested at concentrations >10 M) for cholinergic muscarinic or B3 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. Pharmacokinetic studies showed that RISPERDAL® Tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Distribution
Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethizole (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused 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.

Excretion
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 (e.g., the active moiety) results from the combination of risperidone and 9-hydroxyrisperidone. In plasma, risperidone is bound to albumin and α1-acid glycoprotein. The plasma protein binding of 9-hydroxyrisperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethizole (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused 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.

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Metabolism and Drug Interactions
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Monotherapy extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual (4). In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a QD schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses. In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once a day, the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group.

In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANS measures, including a response measure (> 20% reduction in PANS total score), PANS total score, and the BPRS psychosis cluster (derived from PANS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 366 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (mean daily dose 3.1 mg/day) or placebo (n=183) and observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY). In this study, patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator. Bilipar Mania

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials for Bipolar I Disorder with acute manic or mixed episodes. These trials included patients with or without psychotic features. The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, distractibility, aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in YMRS total score. The results of the trials follow:

In one 3-week placebo-controlled trial (n=224), patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of YMRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapidly-cycling course.

In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-4 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mg/L to 1.4 mg/L or 50 mg/mL to 120 mg/mL, respectively) was superior to lithium or valproate alone in the reduction of YMRS total score.

In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mg/L to 1.4 mg/L for lithium, 50 mg/mL to 125 mg/mL for valproate, or 4-12 mg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxyrisperidone.

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia. The efficacy of RISPERDAL® in schizophrenia was established in short-term (6-8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY). The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL® for an adequate period (see DOSAGE AND ADMINISTRATION) and who observes continued absence of symptoms (indicated by the Clinical Global Impression – Improved subscore; see CLINICAL PHARMACOLOGY – Clinical Trials) should periodically reassess the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are 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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic rebound and drug fever. The diagnosis of NMS should be made with caution in patients treated with antipsychotic drugs, since NMS is more likely to occur in these patients. Given these considerations, RISPERDAL® should be prescribed in a manner that is most likely to avoid exacerbation of EPS and/or precipitation of NMS, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate.

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.

Hyperglycemia in Elderly Patients with Dementia-Related Psychosis

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the risk-benefit ratio of antipsychotic drug treatment in patients with dementia-related psychosis is unknown.

The risk of developing tardive dyskinesia increases with the duration of treatment and the cumulative dose of antipsychotic drugs administered to the patient. However, the risk is not exclusively a function of dose. The risk appears to be dose related for most antipsychotic drugs, although atypical antipsychotics appear to be associated with an increased risk of tardive dyskinesia compared to placebo. The incidence of tardive dyskinesia, however, is variable and difficult to predict. It is not possible to predict which patients are likely to develop the syndrome while taking antipsychotic drugs. The risk of developing tardive dyskinesia is unknown.

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

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be terminated at the lowest effective dose and the patient should be periodically reassessed (see DOSAGE AND ADMINISTRATION).

In patients who do require chronic treatment, the smallest possible dose that appears to be effective should be selected (see DOSAGE AND ADMINISTRATION).

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.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients 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. RISPERDAL® is not approved for the treatment of dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polyuria, polydipsia, and increased thirst.

Hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The combination of RISPERDAL® with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).
Potential for Cognitive and Motor Impairment

RISPERDAL® (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 RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 0.5 mg QD or 1 mg BID in normal adults and 0.5 mg BID in the elderly, and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). 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. RISPERDAL® should be used with particular caution in patients with known orthostatic or 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 RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphoria

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. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also BOXED WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.)

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human prolactin mRNA is transcription dependent in vitro, a factor of potential importance if the in vivo half-life of prolactin is long. The effects of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As with other anti-Parkinsonian compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 4% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® 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 RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28-year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruisings, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reyes’s syndrome, and brain tumor.

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 RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson’s Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated in any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product’s premarket testing. Increased plasma concentrations of risperidone and 9- hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians may wish to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.
Antipsychotics have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance of these findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multidimensional study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effects appeared to be in females; since impaired mating behavior was not noted in the Segment I study in males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multidimensional study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all
### Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials1

<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>RISPERDAL® ≤10 mg/day (N=324)</th>
<th>RISPERDAL® 16 mg/day (N=77)</th>
<th>Placebo (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>26%</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Agitation</td>
<td>22%</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Central &amp; peripheral nervous system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>17%</td>
<td>34%</td>
<td>16%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7%</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsa</td>
<td>5%</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Saliva increased</td>
<td>2%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Toothache</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>10%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Coughing</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Body as a whole - general</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Fever</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Dermatological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Visual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Musculo-Skeletal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

1 Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

2 Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of ‘extrapyramidal symptoms’ does not appear to differ for the ‘10 mg/day’ group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

### Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania1

<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>RISPERDAL® ≤10 mg/day Placebo</th>
<th>RISPERDAL® 16 mg/day + Mood Stabilizer</th>
<th>Placebo + Mood Stabilizer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>28%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Agitation</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Manic reaction</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Concentration impaired</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsa</td>
<td>11%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Saliva increased</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Mouth dry</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Body as a whole - general</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Injury</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

1 Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

### Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania1

<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>RISPERDAL® ≤10 mg/day + Mood Stabilizer (N=52)</th>
<th>RISPERDAL® 16 mg/day + Mood Stabilizer (N=51)</th>
<th>Placebo + Mood Stabilizer (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Central &amp; peripheral nervous system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>25%</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>28%</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>Agitation</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Manic reaction</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Concentration impaired</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsa</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Saliva increased</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Mouth dry</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Body as a whole - general</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Injury</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

1 Events reported by at least 2% of patients treated with RISPERDAL® are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

### Dose Dependency of Adverse Events

**Extrapyramidal Symptoms**

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS.
Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%) was associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were explored for dose-relatedness of adverse events. During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events in a Cochran-Armitage Test for trend in these data revealed a positive trend (p<0.05) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, organic dysfunction, asthenia/lassitude/increased fatigueability, and increased pigmentation.

Laboratory Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. Rare: diplopia, eye pain, blepharitis, photophobia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. Rare: decreased serum iron, cachexia, dehydration, hyponatremia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders


Musculo-Skeletal System Disorders

Infrequent: myalgia. Rare: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female


Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholecystolithiasis, hepatocellular damage.

Platelet, Blood Coagulation Disorders

Infrequent: epistaxis, purpura. Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopoenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. Rare: normocytic anemia.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. Infrequent: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. Rare: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. Infrequent: dysarthria, vertigo, stupor, ataxia, confusion. Rare: asterixis, difficulty in concentration, delirium, catatonia, weakness, hyporeflexia, syncope.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. Infrequent: flatulence, diarrhoea, increased appetite, stomatitis, melena, dysphagia, haemorrhagic gastritis. Rare: focal incontinence, eructation, gastralgia, jejunal reflux, rectal incontinence, esophagitis, tongue discoloration, cholecystitis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. Infrequent: edema, rigors, malaise, influenza-like symptoms. Rare: pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. Rare: asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity*. Infrequent: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. Rare: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hyperpigmentation, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events in a Cochran-Armitage Test for trend in these data revealed a positive trend (p<0.05) for several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: increased sputum, pneumonia, stridor. Rare: asthma, increased sputum, aspiration.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, anuria, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of cardiac arrest and/or sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

Management of Overdose

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal plus a laxative should be considered. Because of the rapid disintegration of RISPERDAL® in the gastrointestinal tract, all fragments may not appear in gastric contents obtained with lavage. The possibility of obtundation, seizures, or dysrhythmic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately after overdose. Treatment of seizures if they occur is supportive and symptomatic. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include tarse des points, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatalities associated with multiple drug overdoses.

Human Experience

Fremarcking experience included eight reports of acute RISPERDAL® (risperidone) overdose with doses ranging from 20 to 300 mg and no fatalities. 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. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include tarse des points, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatalities associated with multiple drug overdoses.

Drug Abuse and Dependence

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for the development of such symptoms and the emergence of any other clinical manifestation of primary interest that may be related to CNS depression. If an increase in the dose of RISPERDAL® is required or if the drug is used in combination with other CNS depressants, then the possibility of the development of a depressive picture is increased. If symptomatic depression occurs in a patient on RISPERDAL®, a causal relationship cannot be ruled out.Continued...
**Pharmacology and Precautions**

Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/d has not been evaluated in clinical trials.

**Maintenance Therapy**

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/d to 8 mg/d at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at a 1 mg QD initial dose, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

**Reinitiation of Treatment in Patients Previously Discontinued**

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

**Switching From Other Antipsychotics**

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

**Bipolar Mania**

**Usual Dose**

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

**Maintenance Therapy**

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

**Pediatric Use**

Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

**Dosage in Special Populations**

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal or hepatic impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). 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 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

**Co-Administration of RISPERDAL® with Certain Other Medications**

Co-administration of dopamine reuptake inhibitors or other agents (e.g., propranolol, labetalol, clonidine) with risperidone would be expected to cause decreases in the plasma concentrations of active moieties (the sum 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. In patients who are already on one of these agents, the dose of risperidone should not be decreased.

**Fluoxetine and Paroxetine**

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2-5.28 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the plasma concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

**Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets**

**Tablet Accessing**

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blister packs of 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

**Tablet Administration**

Using dry hands, remove the tablet from the blister unit and immediately place the entire tablet on the tongue. The RISPERDAL® M-TAB® Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

**HOW SUPPLIED**

RISPERDAL® (risperidone) tablets are imprinted “JANSSEN”, and either “R0.5”, “R1”, or “R2”, and the strength “0.25”, “0.5”, or “1”, and the strength “1”, “2”, “3”, or “4”.

- 0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-01, 4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

- 0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-01, 0.5 mg red-brown tablets: bottles of 60 NDC 50458-302-01.

- 1 mg white tablet: bottles of 60 NDC 50458-303-00, blister pack of 100 NDC 50458-303-01, bottles of 500 NDC 50458-303-00.

- 2 mg orange tablet: bottles of 60 NDC 50458-302-05, blister pack of 100 NDC 50458-302-01, bottles of 500 NDC 50458-302-01.


- 4 mg green tablet: bottles of 60 NDC 50458-350-05, blister pack of 100 NDC 50458-350-01.

- RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated pipette (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

**DOSAGE AND ADMINISTRATION**

**RISPERDAL® tablets** are available in strengths of 0.5 mg, 1 mg, 2 mg, 4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28, long-term care packaging of 30 tablets NDC 50458-395-35.

- 0.5 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long-term care packaging of 30 tablets NDC 50458-315-35.

- 2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

- 4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

**Storage and Handling**

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture. Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture. Keep out of reach of children.

Rx Only

7503231

Revised March 2006

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RISPERDAL® tablets are manufactured by:

- JOLLC, Gurabo, Puerto Rico or Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:

- Janssen Pharmaceutica N.V., Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:

- JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and oral solution are distributed by:

- Janssen, L.P., Titusville, NJ 08560

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