Plasma concentrations of risperidone and its principal active metabolite, 9-hydroxyrisperidone, are increased in patients with severe renal impairment (creatinine clearance less than 30 mL/minute per1.73 m^2), and an increased free fraction of risperidone occurs in patients with severe hepatic impairment. Therefore, lower initial dosages should be used in such patients. (See Dosage and Administration.)

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that risperidone 0.5-, 1-, 2-, 3-. or 4-mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®) which is metabolized in the GI tract to provide about 0.14, 0.28, or 0.-42, 0.63, or 0.84 mg of phenylalanine, respectively, following oral administration.

Because seizures have occurred in 0.3% of patients receiving risperidone in clinical studies, the drug should be administered with caution to patients with a history of seizures.

Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including risperidone. Because aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced dementia of the Alzheimer's type, risperidone and other antipsychotic drugs should be used with caution in patients at risk for aspiration pneumonia.

Because both hypothermia and hyperthermia have been associated with risperidone therapy, the drug should be administered with caution in patients who will be exposed to temperature extremes.

Because risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including driving automobiles, until they are reasonably certain that risperidone therapy does not adversely affect them.

Risperidone has an antiemetic effect in animals; this effect also may occur in humans, and may mask manifestations of overdosage with certain drugs or may obscure the cause of vomiting in various disorders such as intestinal obstruction, Reye's syndrome or brain tumor.

Patients should be advised to inform their clinician if they are taking, or plan to take, any prescription or nonprescription drugs, or have any concomitant illnesses (e.g., diabetes mellitus). Patients also should be advised to avoid alcohol while taking risperidone.

Risperidone is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** The manufacturer states that safety and effectiveness of risperidone in children with schizophrenia or acute mania associated with bipolar I disorder have not been established. However, efficacy and safety of the drug in the treatment of irritability associated with autistic disorder have been established in 2 placebo-controlled trials of 8 weeks' duration in 156 children and adolescents aged from 5–16 years. (See Uses: Autistic Disorder.) Additional safety information also was assessed from a long-term study in patients with autistic disorder and from short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight and who received similar risperidone dosages as patients treated for irritability associated with autistic disorder. Safety and effectiveness of risperidone in pediatric patients with autistic disorder younger than 5 years of age have not been established.

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 patients (0.1%) reportedly developed tardive dyskinesia, which resolved upon discontinuance of therapy. In addition, approximately 15% of children and adolescents receiving 0.5–2.5 mg daily dosages of risperidone developed withdrawal dyskinesia during the discontinuance phase of one long-term (6 month), open-label study.

In long-term, open-label trials in patients with autistic disorder or other psychiatric disorders, a mean body weight gain of 7.5 kg after 12 months of risperidone therapy was reported, which was higher than the normal expected weight gain (i.e., 3–3.5 kg per year adjusted for age, based on the Centers for Disease Control and Prevention normative data). The majority of the weight increase occurred within the first 6 months of drug exposure. Average percentiles at baseline and at 12 months were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index, respectively. When treating pediatric patients with risperidone, the manufacturer recommends that weight gain should be assessed against that expected with normal growth.

Somnolence frequently occurred in placebo-controlled trials in pediatric patients with autistic disorder. Most cases were mild to moderate in severity, occurred early during therapy (peak incidence during the first 2 weeks of therapy), and were transient (median duration of 16 days). Patients experiencing persistent somnolence may benefit from a change in dosage regimen.

Risperidone has been shown to elevate prolactin concentrations in children and adolescents as well as adults. In double-blind, placebo-controlled, 8-week trials in children and adolescents aged from 5–17 years, 49% of risperidone-treated patients had elevated prolactin concentrations compared with 2% of those receiving placebo.

In clinical trials conducted in 1885 children and adolescents with autistic disorder or other psychiatric disorders, galactorrhea and gynecomastia reportedly occurred in 0.8 and 2.3% of risperidone-treated patients, respectively.

The manufacturer states that the long-term effects of risperidone on growth and maturation have not been fully evaluated.

■ **Geriatric Precautions** Clinical studies of risperidone for the management of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. However, serious adverse effects, including an increased risk of death, have been reported in geriatric patients receiving risperidone or other atypical antipsychotic agents in clinical trials in patients with dementia-related psychosis. Risperidone is not approved for the treatment of dementia-related psychosis. (See Geriatric Considerations in Uses: Psychotic Disorders.)

Adverse cerebrovascular events (e.g., stroke, transient ischemic attack), some of which resulted in fatalities, have been reported in clinical studies of risperidone for the management of psychosis in geriatric patients (mean age 85 years; range 73–97) with dementia. Analysis of pooled data from 4 randomized, placebo-controlled studies indicates that adverse cerebrovascular events occurred in approximately 4% of geriatric patients with dementia of the Alzheimer's type, vascular dementia, or mixed dementia receiving risperidone compared with 2% of those receiving placebo. Although many of the patients who experienced adverse cerebrovascular events during the course of these studies had at least one risk factor for cerebrovascular events (e.g., arrhythmia, atherosclerosis, atrial fibrillation, diabetes, heart failure, hypertension, prior history of stroke or transient ischemic attack), the total number of such patients was too small to permit definitive conclusions about the relationship between known risk factors for cerebrovascular events and risperidone therapy. An increased risk of adverse cerebrovascular events has not been identified to date in clinical studies of risperidone for the management of schizophrenia.

An increased risk of death has been reported among geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., risperidone, aripiprazole, olanzapine, quetiapine) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with 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.

A higher incidence of mortality also was observed in geriatric patients with dementia-related psychosis receiving risperidone and furosemide concurrently in placebo-controlled trials when compared with that in patients receiving risperidone alone or placebo and furosemide concurrently. The increase in mortality in patients receiving risperidone and furosemide concurrently was observed in 2 out of 4 clinical trials. The pathological mechanism for this finding remains to be established and no consistent pattern for the cause of death was observed. An increased incidence of mortality in geriatric patients with dementia-related psychosis was observed with risperidone regardless of concurrent furosemide administration.

Risperidone dosage generally should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered. Although geriatric patients exhibit a greater tendency to orthostatic hypotension, the manufacturer states that its risk may be minimized by limiting the initial oral dosage to 0.5 mg twice daily followed by careful titration and close monitoring of orthostatic vital signs in patients for whom this is of concern. More recent evidence however, indicates that even lower initial dosages and slower dosage titration are better tolerated in these patients. Therefore, some clinicians recommend initiating oral risperidone therapy at 0.25 mg daily, and gradually increasing dosages, as tolerated, to a dosage of 2 mg daily in these patients. Higher oral dosages (e.g., 3 or 4 mg daily) may be required in some patients, but are usually associated with greater incidence of extrapyramidal reactions. Most geriatric patients should *not* be maintained at an oral risperidone dosage exceeding 3 mg daily. (See Geriatric Patients and Others at Risk of Orthostatic Hypotension under Dosage and Administration: Dosage.)

■ **Mutagenicity and Carcinogenicity** Risperidone did not exhibit mutagenic potential in in vitro chromosomal aberration studies in human lymphocytes or Chinese hamster cells, 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 in microbial (Ames) test systems.

Statistically significant increases in pituitary gland adenomas and mammary gland adenocarcinomas were observed in female mice receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 18 months. In addition, statistically significant increases were observed in mammary gland adenocarcinomas in both male and female rats, and mammary gland neoplasms and endocrine pancreas adenomas in male rats receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 0.4, 1.5, and 6 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 25 months.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of prolactin-stimulating drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Since in vitro tests indicate that approximately