of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). **For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labelling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.**

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral		
Tablets, film-coated	25 mg (of quetiapine)	Seroquel®, AstraZeneca
	50 mg (of quetiapine)	Seroquel®, AstraZeneca
	100 mg (of quetiapine)	Seroquel®, AstraZeneca
	200 mg (of quetiapine)	Seroquel®, AstraZeneca
	300 mg (of quetiapine)	Seroquel®, AstraZeneca
	400 mg (of quetiapine)	Seroquel®, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia†, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 3.8 mg daily. Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within ther-

apeutic ranges of 0.6–1.4 mEq/L for lithium and 50–120 mcg/mL for valproate. Addition of risperidone to lithium or valproate was shown to be superior to continued monotherapy with lithium or valproate as assessed by reduction of Y-MRS total score.

In a second 3-week, placebo-controlled trial, inpatients and outpatients with bipolar mania receiving lithium, valproate (as divalproex), or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive risperidone or placebo in conjunction with their original therapy. Risperidone was given in a flexible dosage range of 1–6 mg daily, with an initial dosage of 2 mg daily; the mean modal dosage was 3.7 mg daily. Addition of risperidone to lithium, valproate, or carbamazepine therapy (with plasma drug concentrations maintained within therapeutic ranges of 0.6–1.4 mEq/L, 50–120 mcg/mL, or 4–12 mcg/mL, respectively) was not found to be superior to lithium, valproate, or carbamazepine given alone as assessed by reduction of the Y-MRS total score. A possible explanation for the failure of this trial was enzymatic induction of clearance of risperidone and its principal active metabolite, 9-hydroxyrisperidone, by carbamazepine in the subgroup of patients receiving combined therapy with these drugs, resulting in subtherapeutic plasma concentrations of risperidone and 9-hydroxyrisperidone.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combined therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The manufacturer states that efficacy of risperidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) in the treatment of acute manic episodes or for prophylactic use in patients with bipolar disorder.

■ **Autistic Disorder** Risperidone is used for the management of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

Short-term efficacy of risperidone in children and adolescents with autistic disorder has been demonstrated in 2 placebo-controlled trials of 8 weeks' duration in children and adolescents (aged 5–16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of the patients in these 2 trials were under 12 years of age and the majority weighed over 20 kg (weight range: 16–104.3 kg). The principal rating instruments used for assessing efficacy in these trials were the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I), which measures the emotional and behavioral symptoms of autism, including aggression toward others, deliberate self-injuriousness, temper tantrums, and rapidly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

In the first 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5 to 16 years received twice daily placebo or risperidone 0.5–3.5 mg daily on a weight-adjusted basis, starting at 0.25 mg daily or 0.5 mg daily if baseline weight was less than 20 kg or 20 kg or greater, respectively; dosage was then titrated according to clinical response. Risperidone (mean modal dosage of 1.9 mg/day; equivalent to 0.06 mg/kg daily) was found to substantially improve scores on the ABC-I subscale and the CGI-C scale compared with placebo in this study.

In the second 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5–12 years were given an initial risperidone dosage of 0.01 mg/kg daily, which was then titrated up to 0.02–0.06 mg/kg daily based on clinical response. Risperidone (mean modal dosage of 0.05 mg/kg daily; equivalent to 1.4 mg daily) improved scores on the ABC-I subscale compared with placebo.

The efficacy of risperidone for long-term use (i.e., longer than 8 weeks) in children and adolescents with autistic disorder has been demonstrated in an open-label extension of the first 8-week, placebo-controlled trial in which patients received risperidone for 4 or 6 months (depending on whether they received risperidone or placebo in the double-blind study). During the open-label treatment period, patients were maintained on a mean modal risperidone dosage of 1.8–2.1 mg daily (equivalent to 0.05–0.07 mg/kg daily).

Children and adolescents who maintained their positive response to risperidone (defined as at least a 25% improvement on the ABC-I subscale and a CGI-C rating of much improved or very much improved) during the 4–6 month open-label treatment period (average duration of therapy was 140 days) were randomized to receive either risperidone or placebo during an 8-week, double-blind withdrawal trial. A substantially lower relapse rate was observed in the risperidone group compared with the placebo group during the pre-planned interim analysis of data from this trial. Based on the interim analysis results, the study was terminated since a statistically significant effect on relapse prevention was demonstrated. Relapse was defined as at least a 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline for the randomized withdrawal phase). The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Although not curative, pharmacologic agents, such as risperidone, generally are used in children and adolescents with autistic disorder to reduce behavioral disturbances associated with autism and to help facilitate the child's or adolescent's adjustment and engagement in intensive, targeted educational interventions. In clinical studies, risperidone was not found to improve certain core symptoms of autism (e.g., language deficits, impaired social relatedness). However, the drug was more effective than placebo for improving scores on subscales for sensory motor behaviors, affectual reactions, and sensory responses in a controlled study. The possible risks, including clinically important weight gain, tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug, should be considered.

Risperidone also has been used for the treatment in a limited number of adults† with autistic disorder and other pervasive developmental disorders.

Dosage and Administration

■ **Administration** Risperidone is administered orally or by IM injection.

Oral Administration Risperidone is administered orally, either in a once-daily dose or in 2 equally divided doses daily. Because risperidone can cause orthostatic hypotension, twice-daily oral administration may be preferable during initiation of therapy and in patients who may be more susceptible to orthostatic hypotension, such as geriatric or debilitated patients. If once-daily dosing is being considered in geriatric or debilitated patients, it is recommended that the patient be titrated on a twice-daily regimen for 2–3 days at the target dose. Subsequent switching to the once-daily dosing regimen can be done thereafter. Some experts state that once-daily administration of risperidone may be sufficient in most patients receiving maintenance therapy because of the extended half-life of the drug's principal active metabolite (9-hydroxyrisperidone).

In children and adolescents receiving risperidone for the management of irritability associated with autistic disorder who experience persistent somnolence, administering the drug once daily at bedtime, twice-daily administration, or a reduction in dosage may be helpful.

Since food reportedly does not affect the rate or extent of GI absorption of risperidone, the drug can be administered without regard to meals. Compatibility tests show that risperidone oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; such testing also indicates that risperidone oral solution is *not* compatible in cola or tea.

Patients receiving risperidone orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid. Risperidone orally disintegrating tablets should not be divided or chewed.

IM Administration The commercially available risperidone powder for injection containing the drug in extended-release microspheres must be reconstituted prior to administration using the components of the dose pack supplied by the manufacturer. The dose pack should be allowed to reach room temperature before reconstituting the injection. Risperidone extended-release microspheres should be reconstituted using only the diluent in the prefilled syringe supplied by the manufacturer. The entire contents of the prefilled syringe should be injected into the vial, and the vial should be shaken vigorously while the plunger rod is held down with the thumb for at least 10 seconds to ensure a homogeneous suspension; the reconstituted suspension should appear uniform, thick, and milky. The manufacturer's prescribing information should be consulted for additional details on use of the components of the dose pack to reconstitute and administer risperidone injection. The manufacturer states that different dosage strengths of IM risperidone should not be combined in a single administration.

Following reconstitution, immediate use is recommended because the suspension will settle over time. If more than 2 minutes pass before administration, the vial should again be vigorously shaken to resuspend the drug. The contents of the vial must be used within 6 hours of reconstitution and should not be exposed to temperatures exceeding 25°C.

The entire contents of the vial should be administered by deep IM injection into the upper outer quadrant of the gluteal area every 2 weeks, alternating buttocks. The injection should *not* be administered IV.

■ **Dosage** ***Schizophrenia*** Oral Dosage. Risperidone has a bell-shaped dose-response curve, with therapeutic efficacy of oral dosages of 12–16 mg daily lower than that of dosages of 4–8 mg daily in adults. Because dosage information contained in the manufacturer's labeling principally is derived from early clinical studies of the drug in patients not typical of the general population of patients treated in the community (i.e., in hospitalized, chronically-ill schizophrenic patients accustomed to high-dose antipsychotic therapies), dosage of risperidone should be individualized according to the patient's response and tolerance. Clinicians also may consider consulting published protocols for specific dosage information, particularly in geriatric or younger patients, and in those experiencing their first psychotic episode.

The manufacturer's labeling states that the initial oral dosage of risperidone in adults generally is 1 mg twice daily, with dosage increase in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dosage of 6–8 mg daily (administered once daily or in 2 equally divided doses). However, more recent evidence from open labeled studies and clinical experience with the drug indicates that an initial dosage of 1–2 mg daily, with dosage

increases in increments of 0.5–1 mg daily titrated over 6–7 days, as tolerated, to a target dose of 4 mg daily may be more appropriate for the management of schizophrenia in most otherwise healthy adult patients. Because steady-state plasma concentrations of 9-hydroxyrisperidone (an active metabolite of risperidone) may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of at least 7 days. Lower initial dosages (e.g., 1 mg daily) and slower dosage titrations to an initial target dosage of 2 mg daily may be appropriate for younger patients and in those being treated for their first psychotic episode; dosage may then be titrated up to 4 mg daily depending on clinical response at the lower dosage and adverse neurologic effects. Such patients appear to benefit optimally from risperidone dosage of 1–3 mg daily. A substantial number of patients being treated for their first psychotic episode start to develop extrapyramidal symptoms once dosages are increased above 2 mg daily. Dosage reductions should be considered in any patient who develops extrapyramidal symptoms.

While antipsychotic efficacy has been established in clinical trials at oral dosages ranging from 4–16 mg daily, maximum efficacy of the drug was observed in most patients at risperidone dosages of 4–8 mg daily. In addition, the manufacturer and some clinicians state that dosages exceeding 6 mg daily, when given in 2 divided doses, did not result in further improvement but were associated with increases in some adverse effects, including extrapyramidal manifestations. Therefore, the manufacturer states that dosages exceeding 6 mg (in 2 divided doses) daily generally are not recommended and those exceeding 16 mg daily have not been evaluated for safety. In a single study of once-daily dosing, efficacy results generally were stronger for 8 mg than for 4 mg.

The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to risperidone or concomitant administration with other antipsychotic agents. While immediate discontinuance of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, gradual discontinuance of the drug may be appropriate for most patients. In all cases, the period of overlapping antipsychotic administration should be minimized. The first risperidone dose should be administered in place of the next scheduled parenteral antipsychotic dose in schizophrenic patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral risperidone therapy.

The optimum duration of oral risperidone therapy currently is not known, but maintenance therapy with risperidone 2–8 mg daily has been shown to be effective for up to 2 years. Patients should be reassessed periodically to determine the need for continued therapy with the drug. If risperidone therapy is reinitiated after a drug-free period, the manufacturer recommends that the appropriate recommended schedule of careful dosage titration be employed.

IM Dosage. For the management of schizophrenia, the recommended initial adult IM dosage of risperidone injection extended-release microspheres is 25 mg administered by deep IM injection in the gluteal area every 2 weeks. The manufacturer recommends that patients first receive oral risperidone to establish tolerability of the drug before the extended-release risperidone injection is used. To ensure that adequate plasma antipsychotic concentrations are maintained prior to the main release of risperidone from the injection site, therapy with oral risperidone or another oral antipsychotic agent (e.g., for patients being switched from other oral antipsychotic therapy to IM risperidone) should be given with the first IM injection of risperidone, and such oral therapy should be continued for 3 weeks, then discontinued. If risperidone injection is used in patients previously receiving other oral antipsychotic agents, the need for continuing any concomitant therapy for managing extrapyramidal manifestations should be periodically reevaluated.

Some patients not responding to the initial dosage of 25 mg every 2 weeks may benefit from increasing the IM dosage to 37.5 or 50 mg every 2 weeks. However, the dosage should not be increased more frequently than every 4 weeks, and clinical effects of the increased dosage should not be expected earlier than 3 weeks after the first injection of the higher dose. The maximum IM dosage should not exceed 50 mg every 2 weeks since higher dosages were associated with an increased incidence of adverse effects, but no additional clinical benefit was observed.

Although no controlled studies have been conducted to establish the optimum duration of IM risperidone therapy in patients with schizophrenia, oral risperidone has been shown to be effective in delaying time to relapse with longer term use. It is recommended that responding patients be continued on treatment with IM risperidone at the lowest dose needed. Patients should periodically be reassessed to determine the need for continued treatment.

If therapy with IM risperidone is reinitiated after a drug-free period, oral risperidone (or another oral antipsychotic agent) should again be administered for supplementation.

Bipolar Disorder For the management of acute manic and mixed episodes associated with bipolar disorder as monotherapy or as combined therapy in adults, an initial risperidone oral dosage of 2–3 mg given once daily was found to be effective in clinical trials. Dosage may be increased or decreased by 1 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. In these trials, the short-term (i.e., 3-week) antimanic efficacy of risperidone was demonstrated in a flexible dosage ranging from 1 to 6 mg daily. Safety of dosages exceeding 6 mg daily has not been established.

The optimum duration of risperidone therapy for bipolar disorder currently is not known. While it is generally agreed that pharmacologic 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 beyond 3 weeks. Therefore, the manufacturer states that clinicians who elect to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Autistic Disorder For the management of irritability associated with autistic disorder in children 5 years of age and older and adolescents, an initial risperidone oral dosage of 0.25 mg daily is recommended for patients weighing less than 20 kg and 0.5 mg daily is recommended for patients weighing 20 kg or more. The drug may be administered either once or twice daily.

Dosage should be individualized according to clinical response and tolerability of the patient. After a minimum of 4 days following initiation of therapy, the dosage may be increased to the recommended dosage of 0.5 mg daily for patients weighing less than 20 kg and 1 mg daily for patients weighing 20 kg or more; this dosage should then be maintained for a minimum of 14 days. In patients not responding adequately, increases in dosage may be considered at intervals of 2 weeks or longer in increments of 0.25 mg daily for patients weighing less than 20 kg or 0.5 mg daily for patients weighing 20 kg or more. Exercise caution with risperidone dosages in smaller children who weigh less than 15 kg. Safety and effectiveness in pediatric patients less than 5 years of age not established.

In clinical trials, 90% of patients who responded to risperidone therapy (based on at least 25% improvement in the Irritability subscale of the Aberrant Behavior Checklist [ABC-I]) received dosages from 0.5–2.5 mg daily. The maximum daily dosage in one of the pivotal trials, when the therapeutic effect reached a plateau, was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or more, and 3 mg in patients weighing more than 45 kg. Dosage data for children weighing less than 15 kg currently are lacking.

Once adequate clinical response has been achieved, consider a gradual reduction in dosage to achieve an optimal balance of efficacy and safety. Patients experiencing excessive somnolence may benefit from a once-daily dosage administered at bedtime or administering half the daily dosage twice daily, or a reduction in dosage.

The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Geriatric Patients and Others at Risk of Orthostatic Hypotension Like other α-adrenergic blocking agents, risperidone can induce orthostatic hypotension (e.g., manifested as dizziness, tachycardia, and occasionally syncope), particularly during initiation of therapy with the drug. The manufacturer and some clinicians state that the risk of this effect can be minimized by limiting the initial oral dosage of risperidone to 1 mg twice daily in otherwise healthy adults and to 0.5 mg once or twice daily in geriatric or debilitated patients, in patients with renal or hepatic impairment, and in those predisposed to, or at risk from, hypotension. Dosages in such patients should then be increased gradually at increments of not more than 0.5 mg twice daily as necessary and tolerated. Increases beyond a dosage level of 1.5 mg twice daily generally should occur at intervals of at least 7 days. However, other clinicians recommend initiating risperidone therapy at a dosage of 0.25 mg daily in geriatric patients and gradually increasing the dosage as tolerated. (See Cautions: Geriatric Precautions.) Most geriatric patients should not be maintained at an oral dosage exceeding 3 mg daily.

For geriatric patients with schizophrenia, the recommended IM risperidone dosage of the extended-release injection is 25 mg every 2 weeks. Oral risperidone (or another oral antipsychotic agent) should be given with the first risperidone extended-release injection and should be continued for 3 weeks to ensure that adequate antipsychotic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site.

Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning, slowly rising from a seated position). These patients should avoid sodium depletion or dehydration and circumstances that accentuate hypotension (e.g., alcohol intake, high ambient temperature). Monitoring of orthostatic vital signs should be considered.

Particular caution also is warranted in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) and in those for whom such reactions would pose a risk, and cautious dosage titration and careful monitoring are necessary in such patients. Dosage reduction should be considered in any patient in whom hypotension develops.

■ **Dosage in Renal and Hepatic Impairment** Because elimination of risperidone may be reduced and the risk of adverse effects, particularly hypotension, increased in patients with renal impairment, oral risperidone therapy should be initiated at a reduced dosage of 0.5 mg twice daily in adults and increased as necessary and tolerated at increments of 0.5 mg twice daily; increases beyond a dosage level of 1.5 mg twice daily should be made at intervals of at least 7 days. Likewise, this reduced oral dosage should be employed in patients with hepatic impairment because of the risk of an increased free fraction of risperidone in such patients.

If IM risperidone is used for management of schizophrenia in adult patients

with renal or hepatic impairment, the patient should be treated with titrated doses of oral risperidone prior to initiating treatment with the extended-release injection. The recommended starting oral risperidone dosage is 0.5 mg twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dosage of at least 2 mg daily of oral risperidone is well tolerated, an IM dosage of 25 mg of the extended-release injection can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Cautions

Although risperidone differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives. Not all adverse effects of the phenothiazines have been reported with risperidone, but the possibility that they may occur should be considered. Adverse effects of risperidone and the phenothiazines are numerous and may involve nearly all organ systems. Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal. In some patients, unexpected death associated with antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex. (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with schizophrenia who received the drug in 2 short-term (6–8 week) clinical studies and with an incidence of at least twice that of those who received placebo included nervous system (e.g., anxiety, dizziness, extrapyramidal symptoms, somnolence), GI (e.g., constipation, dyspepsia, nausea), dermatologic (e.g., rash), respiratory (e.g., rhinitis), and cardiovascular (e.g., tachycardia) effects. Approximately 9% of patients receiving risperidone in phase 2 or 3 studies discontinued treatment because of adverse effects compared with about 7% of those receiving placebo and 10% of those receiving an active control drug (haloperidol). Adverse effects commonly associated with discontinuance of therapy and considered to be possibly or probably related to risperidone include extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with bipolar mania who received the drug as monotherapy in the US placebo-controlled trial and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, dystonia, akathisia, parkinsonism, vision abnormalities) and GI (e.g., dyspepsia, nausea, increased salivation) effects. In the US placebo-controlled trial of risperidone in conjunction with mood stabilizers (lithium or valproate), the most common adverse effects associated with risperidone administration were somnolence, dizziness, parkinsonism, increased saliva, akathisia, abdominal pain, and urinary incontinence. In the US placebo-controlled trial of risperidone monotherapy, approximately 8% of patients receiving risperidone discontinued therapy because of adverse effects compared with about 6% of those receiving placebo. Adverse effects associated with discontinuance of therapy in this study and considered to be possibly, probably, or very likely related to risperidone included paroniria, somnolence, dizziness, extrapyramidal reaction, and involuntary muscle contractions; each of these occurred in 1 risperidone-treated patient (0.7%) but in none of those receiving placebo. In the US placebo-controlled trial of risperidone used in conjunction with mood stabilizers, there was no overall difference in the incidence of discontinuance because of adverse effects (4% for risperidone and 4% for placebo).

The most frequent adverse effects of oral risperidone reported in at least 5% of pediatric patients with autistic disorder who received the drug in 2 placebo-controlled trials and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, fatigue, tremor, dystonia, dizziness, parkinsonism, automatism, dyskinesia, confusion), GI (e.g., increased appetite, increased salivation, constipation, dry mouth), respiratory (e.g., upper respiratory tract infection), cardiovascular effects (e.g., tachycardia), and weight gain. Somnolence was the most frequent adverse effect in these trials, occurring in 67% of the risperidone-treated patients and in 23% of patients receiving placebo. Average weight gain over 8 weeks was 2.6 kg for the risperidone-treated patients compared with 0.9 kg for patients receiving placebo. Extrapyramidal symptoms occurred in approximately 28% of the risperidone-treated patients compared with 10% of those receiving placebo.

The most frequent adverse effects associated with use of risperidone extended-release IM injection reported in at least 5% of adult patients with schizophrenia in clinical trials and with an incidence of at least twice that of those receiving placebo included somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, and increased weight.

■ **Nervous System Effects** ***Tardive Dyskinesia*** Like other antipsychotic agents (e.g., phenothiazines), risperidone has been associated with tardive dyskinesias. Although it has been suggested that atypical antipsychotics appear to have a lower risk of tardive dyskinesia, whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is as yet unknown. In one open-label study, an annual incidence of tardive dyskinesia of 0.3% was reported in patients with schizophrenia who received approximately 8–9 mg of oral risperidone daily for at least 1 year. The prevalence of this syndrome appears to be highest among geriatric patients (particularly females). The risk of developing tardive dyskinesia and the likelihood that it will become irreversible also appear to increase with the duration of therapy and cumulative dose of antipsychotic agents administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Extrapyramidal Reactions Extrapyramidal reactions occurred in 17% of patients with schizophrenia receiving oral risperidone dosages of 10 mg daily or less and in 34% of patients receiving dosages of 16 mg daily in clinical studies. Although the incidence of extrapyramidal manifestations in patients receiving risperidone dosages of 10 mg daily or less was similar to that reported in patients receiving placebo, the incidence increased as the dosage of the drug increased, suggesting a dose-related effect. At recommended therapeutic dosages of risperidone (4–8 mg daily) for schizophrenia, the severity of extrapyramidal reactions appears to be comparable to placebo and clozapine 400 mg daily, and substantially less than that associated with haloperidol 10 or 20 mg daily. Similarly, the severity of parkinsonian symptoms, as assessed on the parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (ESRS), is also linearly related to risperidone dosages of 2–16 mg daily, with the incidence of parkinsonian symptoms at risperidone dosages of 6 mg daily or less comparable to that of placebo and substantially less than that seen with haloperidol dosages of 20 mg daily.

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents. NMS requires immediate discontinuance of the drug and intensive symptomatic and supportive care. For additional information on NMS, see Neuroleptic Malignant Syndrome under Nervous System Effects: Extrapyramidal Reactions in Cautions, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects Dose-related somnolence was a commonly reported adverse effect associated with risperidone treatment. Approximately 8% of adult patients with schizophrenia receiving 16 mg of oral risperidone daily and 1% of patients receiving placebo reported somnolence in studies utilizing direct questioning or a checklist to detect adverse events, respectively.

Insomnia, agitation, and anxiety have been reported in 20–26% of patients receiving risperidone. In addition, headache, dizziness, and aggressive reaction have been reported in 12–14, 4–7, and 1–3% of schizophrenia patients, respectively.

Adverse nervous system effects reported in 1% or more of patients with schizophrenia who received risperidone in clinical studies include increased sleep duration or dream activity, diminished sexual desire, fatigue, and nervousness. Impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia, dysarthria, vertigo, stupor, paraesthesia,malaise, seizure, and confusion also have been reported in 0.1–1% of patients. In addition, aphasia, cholinergic syndrome, choreoathetosis, coma, delirium, emotional lability, hypoesthesia, hypotonia, hyperreflexia, leg cramps, migraine, nightmares, tongue paralysis, torticollis, withdrawal syndrome, and yawning have been reported in fewer than 0.1% of patients. Mania also has been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Cardiovascular Effects** ***Orthostatic Hypotension*** Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period has been reported in patients receiving risperidone, probably reflecting the drug's α-adrenergic antagonistic properties. The risk of orthostatic hypotension and syncope may be minimized by limiting initial doses in geriatric patients 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. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia). Clinically important hypotension has been observed with concomitant use of risperidone and antihypertensive drug therapy.

Other Cardiovascular Effects Pooled analysis of results of placebo-controlled studies indicates that risperidone therapy is not associated with statistically significant changes in ECG parameters (e.g., PR, QT, or QT_c intervals, heart rate). In pivotal clinical studies, however, tachycardia, which may be dose dependent, occurred in 3 or 5% of patients with schizophrenia receiving daily oral dosages of risperidone of 10 mg or less or 16 mg, respectively. In addition, palpitation, hypertension, hypotension, AV block, and myocardial infarction have occurred in 1% or more of patients receiving risperidone. Ventricular tachycardia, angina pectoris, atrial premature complexes (APCs, PACs), T-wave inversions, ventricular extrasystoles, ST depression, and myocarditis have occurred in fewer than 0.1% of patients receiving the drug in clinical trials. Atrial fibrillation, pulmonary embolism, cerebrovascular disorders (including stroke and transient ischemic attack) (see Cautions: Geriatric Precautions), and rarely, sudden death and/or cardiopulmonary arrest also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Endocrine and Metabolic Effects** Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been

reported in patients receiving certain atypical antipsychotic agents, including risperidone. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., risperidone, clozapine, olanzapine, quetiapine).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., risperidone, quetiapine) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

Similar to other antipsychotic agents, risperidone causes elevated prolactin concentrations, which may persist during chronic use of the drug. Risperidone appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents. The clinical importance of elevated serum prolactin concentrations is as yet unknown for most patients receiving these drugs. Gynecomastia and breast pain in men have been reported in fewer than 0.1% of patients. In addition, galactorrhea, amenorrhea, and impotence have been reported with agents that increase serum prolactin concentrations, including risperidone.

Hyponatremia, weight gain or loss, increased serum creatine kinase (CK, creatine phosphokinase, CPK) concentrations, thirst, and diabetes mellitus have been reported in 0.1–1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, decreased serum iron concentrations, cachexia, dehydration, disorders in antidiuretic hormone, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, and hypoglycemia have been reported in fewer than 0.1% of patients. Precocious puberty and pituitary adenomas also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **GI Effects** Adverse GI effects that have been reported in 5–13% of patients with schizophrenia receiving oral risperidone in clinical studies include constipation, nausea, dyspepsia, and vomiting. Abdominal pain, increased salivation, and toothache also have been reported in 1–4% of patients receiving risperidone in clinical studies. In addition, anorexia and reduced salivation were reported in 1% or more of patients receiving risperidone in clinical trials. Flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, and gastritis have also been reported in 0.1–1% of patients. In addition, fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, lingual discoloration, cholelithiasis, lingual edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, and hematemesis have been reported in fewer than 0.1% of patients receiving the drug in clinical trials. Although a causal relationship to risperidone has not been established, intestinal obstruction has been reported during postmarketing surveillance.

■ **Respiratory Effects** Rhinitis has been reported in 8–10% of patients with schizophrenia receiving oral risperidone and was the most common adverse respiratory effect reported during clinical studies. In addition, cough, sinusitis, pharyngitis, upper respiratory infections, and dyspnea have been reported in 1–3% of patients receiving risperidone in clinical studies. Hyperventilation, bronchospasm, pneumonia, and stridor also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Asthma, increased sputum, and aspiration have been rarely reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, apnea also has been reported during postmarketing surveillance.

■ **Dermatologic Effects and Sensitivity Reactions** Rash and dry skin have been reported in about 2–5% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, adverse dermatologic effects that have been reported in 1% or more of patients receiving risperidone include seborrhea and increased pigmentation. Increased or decreased sweating, acne, alopecia, hyperkeratosis, pruritus, and skin exfoliation were reported in 0.1–1% of patients in clinical trials. Bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, and urticaria have been rarely reported.

Although a causal relationship has not been established, hypersensitivity reactions, including anaphylaxis, angioedema, and photosensitivity have been reported in patients receiving risperidone.

■ **Genitourinary Effects** Adverse genitourinary effects reported in 1% or more of patients with schizophrenia receiving oral risperidone include polyuria, polydipsia, menorrhagia, orgasmic dysfunction, and vaginal dryness. In addition, urinary incontinence, hematuria, dysuria, nonpuerperal lactation, amenorrhea, breast or perineal pain in females, leukorrhea, mastitis, dysmenorrhea, intermenstrual bleeding, and vaginal hemorrhage have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Urinary retention, cystitis, and renal insufficiency also have been reported in fewer than 0.1% of patients.

In male patients, erectile dysfunction and ejaculation failure were reported in up to 1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, rare cases of priapism have been reported. While a causal relationship to risperidone use has not been established, other drugs with α-adrenergic blocking effects have been reported to cause priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

■ **Musculoskeletal Effects** Back or chest pain and arthralgia have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, myalgia has been reported in 0.1–1% of patients. Arthrosis, synostosis, bursitis, arthritis, and skeletal pain also have occurred in fewer than 0.1% of patients.

■ **Hematologic Effects** Anemia, hypochromic anemia, epistaxis, and purpura have been reported in 0.1–1% of adult patients with schizophrenia and granulocytopenia has been reported in 0.1–1% of children and adolescents with autistic disorder receiving oral risperidone in clinical studies. Normocytic anemia, leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly, hemorrhage, superficial phlebitis, thrombophlebitis, and thrombocytopenia also have been reported in fewer than 0.1% of patients. In addition, thrombotic thrombocytopenic purpura occurred in at least one patient (a 28 year-old female patient) receiving risperidone in a large, open-labeled study. This patient experienced jaundice, fever, and bruising but eventually recovered after receiving plasmapheresis. The relationship of this adverse event to risperidone therapy is unknown.

■ **Hepatic Effects** Increased SGOT and increased SGPT have been reported in 0.1–1% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, and hepatocellular damage have been reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, jaundice also has been reported during postmarketing surveillance.

■ **Ocular and Otic Effects** Abnormal vision has been reported in 1–2% of patients with schizophrenia receiving oral risperidone in clinical studies. Abnormal accommodation and xerophthalmia also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. In addition, diplopia, ocular pain, blepharitis, photopsia, photophobia, abnormal lacrimation, tinnitus, hyperacusis, and decreased hearing have been reported in fewer than 0.1% of patients.

■ **Other Adverse Effects** Chest pain and fever have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. Although a causal relationship to the drug has not been established, pancreatitis and aggravated parkinsonian syndrome has been reported during postmarketing surveillance.

■ **Precautions and Contraindications** Risperidone shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone, the manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored 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. (See Cautions: Endocrine and Metabolic Effects.) Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the antipsychotic; in other cases hyperglycemia resolved with discontinuance of the suspect drug. For further information on the management of diabetes risks in patients receiving atypical antipsychotics, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Because of the possibility of orthostatic hypotension, caution should be observed in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease (see Cautions: Geriatric Precautions), conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia), and patients receiving antihypertensive agents. Since patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies, clinicians should be aware that risperidone has not been evaluated or used to any appreciable extent in such patients. Patients receiving risperidone should be advised of the risk of orthostatic hypotension, especially during the period of initial dosage titration. (See Cautions: Cardiovascular Effects.)

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including risperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with more frequent falling, extrapyramidal adverse effects, and clinical features consistent with neuroleptic malignant syndrome. (For additional information on extrapyramidal adverse effects and neuroleptic malignant syndrome, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

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 per 1.73 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 one-third of human breast cancers are prolactin-dependent, risperidone should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Reproductive studies in rats and rabbits using risperidone dosages of 0.4–6 times the maximum recom-

mended human dosage on a mg/m² basis have not revealed evidence of fetal malformation. However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m² basis. In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m² basis. It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams. In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m² basis. Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown. Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy. Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. The effect of risperidone on labor and delivery in humans is unknown.

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m² basis. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dosage was not found in these studies in either rats or dogs.

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk. The manufacturer states that women receiving risperidone should avoid nursing.

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents. While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines). The exact mechanism of antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Risperidone

Oral		
Solution	1 mg/mL	Risperdal®, Janssen
Tablets	0.25 mg	Risperdal® (scored), Janssen
	0.5 mg	Risperdal® (scored), Janssen
	1 mg	Risperdal® (scored), Janssen
	2 mg	Risperdal® (scored), Janssen
	3 mg	Risperdal® (scored), Janssen
	4 mg	Risperdal® (scored), Janssen
Tablets, orally disintegrating	0.5 mg	Risperdal® M-TAB®, Janssen
	1 mg	Risperdal® M-TAB®, Janssen
	2 mg	Risperdal® M-TAB®, Janssen
	3 mg	Risperdal® M-TAB®, Janssen
	4 mg	Risperdal® M-TAB®, Janssen
Parenteral		
For injectable suspension, extended-release, for IM use	25 mg	Risperdal® Consta® (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	37.5 mg	Risperdal® Consta® (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	50 mg	Risperdal® Consta® (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** *Schizophrenia* Ziprasidone is used for the symptomatic management of schizophrenia. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

Efficacy of ziprasidone in the treatment of acute manic and mixed episodes has been demonstrated in 2 short-term (3 weeks' duration), double-blind, pla-

turer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paliperidone

Oral		
Tablets, extended-release	3 mg	Invega®, Janssen
	6 mg	Invega®, Janssen
	9 mg	Invega®, Janssen

Selected Revisions January 2009, © Copyright, December 2007, American Society of Health-System Pharmacists, Inc.

Quetiapine Fumarate

■ Quetiapine is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Quetiapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Short-term efficacy of quetiapine for the management of schizophrenia has been established by placebo-controlled studies of 6 weeks' duration principally in hospitalized patients with schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions); emotion (e.g., flatness, inappropriate affect); thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization); attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

In clinical studies in patients with schizophrenia, quetiapine was more effective than placebo in reducing the severity of symptoms associated with this disorder. Quetiapine appears to improve both positive and negative manifestations of schizophrenia. Results from comparative clinical studies and meta-analyses suggest that quetiapine is at least as effective as chlorpromazine or haloperidol in reducing positive and negative symptoms of schizophrenia.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., quetiapine, aripiprazole, olanzapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

Although the efficacy of quetiapine for long-term use has not been established in controlled studies, the manufacturer states that beneficial effects of the drug were maintained for up to 4 years in some patients during an open-label extension study in patients who achieved an initial response to treatment during double-blind clinical studies. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Quetiapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder. Efficacy of quetiapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 placebo-controlled studies of 12 weeks' duration in patients who met the DSM-IV criteria for bipolar disorder and who met diagnostic criteria for an acute manic episode (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from these studies. The principal rating instrument used for assessing manic symptoms in these studies was the Young Mania Rating Scale (YMRS) score, an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In these studies, quetiapine was shown to be superior to placebo in reduction of the YMRS total score after 3 and 12 weeks of treatment.

Efficacy of quetiapine when used in combination with lithium or divalproex sodium in the management of acute manic episodes has been demonstrated in a placebo-controlled study of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic episodes (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from enrollment and patients included in the study may or may not have received an adequate course of therapy with lithium or divalproex sodium prior to randomization. Quetiapine was shown to be superior to placebo when added to lithium or divalproex sodium alone in the reduction of YMRS total score. However, in a similarly designed study, quetiapine was associated with an improvement of YMRS scores but did not demonstrate superiority to placebo.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic (e.g., olanzapine) may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Quetiapine also is used for the treatment of depressive episodes associated with bipolar disorder. Efficacy of quetiapine in the treatment of depressive episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 8 weeks' duration in patients with bipolar I or II disorder (with or without a rapid-cycling course). Patients in these studies received fixed daily quetiapine dosages of 300 or 600 mg once daily. The principal rating instrument used for assessing depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. In both studies, quetiapine was found to be superior to placebo in reduction of MADRS scores at week 8, with improvements in scores evident within one week of treatment. In addition, patients receiving 300 mg of quetiapine daily demonstrated significant improvements compared to placebo recipients in overall quality of life and satisfaction related to various areas of functioning.

Dosage and Administration

■ **Administration** Quetiapine is administered orally. While food reportedly can marginally increase the peak concentration and oral bioavailability of quetiapine, the drug generally can be administered without regard to meals.

Dispensing and Administration Precautions Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). Accordiog to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Dispensing and Administration Precautions under Warnings/Precautions: General Precautions in Cautions.)

■ **Dosage** Dosage of quetiapine fumarate is expressed in terms of quetiapine and must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

Higher maintenance dosages of quetiapine may be required in patients receiving the antipsychotic drug concomitantly with phenytoin or other hepatic enzyme-inducing agents (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids), and an increase in the maintenance dosage of quetiapine may be required to reestablish efficacy in patients receiving such concomitant therapy. (See Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes and also Phenytoin.)

Patients receiving quetiapine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustments. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer states that if quetiapine therapy is reinitiated after a drug-free period of less than 1 week, dosage titration is not necessary. However, if quetiapine therapy is reinitiated after a drug-free period exceeding 1 week, dosage generally should be titrated as with initial therapy.

Schizophrenia For the management of schizophrenia, the recommended initial dosage of quetiapine in adults is 25 mg twice daily. Dosage may be increased in increments of 25–50 mg 2 or 3 times daily on the second or third day, as tolerated, to a target dosage of 300–400 mg daily in 2 or 3 divided doses by the fourth day. Because steady-state plasma concentrations of quetiapine may not be attained for 1–2 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of not less than 2 days, usually in increments or decrements of 25–50 mg twice daily. Effective dosages of quetiapine in clinical trials generally ranged from 150–750 mg daily. While the manufacturer states that increasing quetiapine dosages beyond 300 mg daily usually does not result in additional therapeutic effect, dosages of 400–500 mg daily apparently have been required in some patients, and a dosage range of 300–800 mg daily has been recommended. Safety of quetiapine in dosages exceeding 800 mg daily has not been established.

The optimum duration of quetiapine therapy currently is not known, but the efficacy of maintenance therapy with antipsychotic agents used in the treatment of schizophrenia is well established. Patients responding to quetiapine therapy should continue to receive the drug as long as clinically necessary and tolerated but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically. The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with remitted first- or multiple-episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

If antipsychotic therapy is to be discontinued in patients with schizophrenia, precautions should include slow, gradual dose reduction over many months, more frequent clinician visits, and use of early intervention strategies. Patients and their family and caregivers should be advised about early signs of relapse, and clinicians should collaborate with them to develop plans for action should they emerge. The treatment program should be designed to respond quickly to evidence of prodromal symptoms or behaviors or exacerbations of schizophrenic symptoms.

Bipolar Disorder For the management of depressive episodes associated with bipolar I or II disorder, the recommended dosage of quetiapine in adults is 50 mg administered once daily at bedtime on the first day of therapy. The dosage of quetiapine should then be increased to 100 mg once daily on the second day of therapy, 200 mg once daily on the third day of therapy, and 300 mg once daily on the fourth day of therapy. In clinical trials demonstrating clinical efficacy, quetiapine was given in a dosing schedule of 50, 100, 200, and 300 mg once daily on days 1–4, respectively; patients who received 600 mg daily received 400 mg daily on day 5 and 600 mg daily on day 8. Although antidepressant efficacy was demonstrated with quetiapine at dosages of 300 mg daily and 600 mg daily, no additional benefit was seen in the 600-mg daily group.

For the management of acute mania associated with bipolar I disorder (alone or in conjunction with lithium or divalproex sodium), the recommended initial dosage of quetiapine in adults is 100 mg daily, administered in 2 divided doses. The dosage of quetiapine should be increased in increments of up to 100 mg daily in 2 divided doses to 400 mg daily on the fourth day of therapy. Subsequent dosage adjustments up to 800 mg daily by the sixth day of therapy should be made in increments not exceeding 200 mg daily. Data indicate that most patients respond to 400–800 mg daily. The safety of quetiapine dosages exceeding 800 mg daily has not been established.

The APA states that for patients treated with an antipsychotic agent during an acute episode in bipolar disorder, the need for ongoing antipsychotic treatment should be reassessed upon entering the maintenance phase. The APA recommends that antipsychotics be slowly tapered and discontinued unless they are required to control persistent psychosis or provide prophylaxis against recurrence. While maintenance therapy with atypical antipsychotics may be considered, there currently is limited evidence regarding their efficacy in the maintenance phase compared with that of agents such as lithium or valproate. The manufacturer of quetiapine states that efficacy of the drug has not been systematically evaluated for more than 12 weeks as monotherapy of acute manic episodes associated with bipolar I disorder or for more than 3 weeks as combined therapy with divalproex or lithium. In addition, the manufacturer of quetiapine states that efficacy of the drug has not been systematically evaluated for more than 8 weeks in the management of depressive episodes in patients with bipolar I or II disorder. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis.

Switching to or Concomitant Use with Other Antipsychotic Agents The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to quetiapine or concerning concomitant use of quetiapine with other antipsychotic agents. Although abrupt discontinuance of the previous antipsychotic agent may be acceptable for some patients with schizophrenia, gradual discontinuance may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. In patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral quetiapine therapy, the first oral dose of quetiapine should be administered in place of the next scheduled dose of the long-acting preparation. The need for continuing existing drugs used for the symptomatic relief of extrapyramidal manifestations should be reevaluated periodically.

■ **Special Populations** The manufacturer states that because quetiapine is substantially metabolized in the liver and because the pharmacokinetics of quetiapine appear to be altered in patients with hepatic impairment, an initial dosage of 25 mg daily should be used in adults with hepatic impairment. The dosage should be increased by 25–50 mg daily according to clinical response and tolerability until an effective dosage is reached.

Although elimination of quetiapine was reduced in patients with severe renal impairment (e.g., creatinine clearance of 10–30 mL/minute), the plasma quetiapine concentrations were similar to those in patients with normal renal function; therefore, the manufacturer states that dosage adjustment is not necessary in such patients.

Geriatric or debilitated patients and patients predisposed to hypotension or in whom hypotension would pose a risk (e.g., patients with dehydration or hypovolemia, those receiving antihypertensive drugs, patients with known cardiovascular or cerebrovascular disease) should have a slower rate of dosage titration and should receive lower target dosages of quetiapine. The risk of orthostatic hypotension can be minimized by limiting the initial dosage of quetiapine to 25 mg twice daily. If orthostatic hypotension occurs during titration to the target dosage, the manufacturer recommends a return to the previous dosage in the titration schedule.

Cautions

■ **Contraindications** Known hypersensitivity to quetiapine or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death 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., quetiapine, aripiprazole, olanzapine, risperidone) 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. The manufacturer states that quetiapine is not approved for the treatment of dementia-related psychosis. (See Dosage and Administration: Special Populations and see also Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Worsening of Depression and Suicidality Risk. Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs with therapy. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared to placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or

other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Bipolar Disorder. It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Quetiapine is approved for use in treating bipolar depression in adults. (See Bipolar Disorder under Uses.)

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including quetiapine. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Use of antipsychotic agents, including quetiapine, may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving all atypical antipsychotic agents, including quetiapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., quetiapine, clozapine, olanzapine, risperidone).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others in the class (e.g., quetiapine, risperidone), available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored 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, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Cautions: Endocrine and Metabolic Effects and see also Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions Contact dermatitis, maculopapular rash, and photosensitivity reactions were reported infrequently during clinical trials. Anaphylaxis and Stevens-Johnson syndrome have been reported during postmarketing surveillance.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension with associated dizziness, tachycardia, and/or syncope, particularly during the initial dosage titration period, has been reported. The risk of orthostatic hypotension and syncope may be minimized by limiting initial dosage. (See Dosage and Administration: Special Populations.) Use with caution in patients with known cardiovascular (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities) or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Ocular Effects. The development of cataracts in association with quetiapine was observed in animal studies. Lens changes also have been reported in some patients receiving long-term quetiapine therapy, although a causal relationship has not been established. Because the possibility of lens changes cannot be excluded, the manufacturer recommends ophthalmologic examination of the lens by methods adequate to detect cataract formation (e.g., slit lamp exam) be performed at the initiation of quetiapine therapy, or shortly thereafter, and at 6-month intervals during chronic quetiapine therapy.

Nervous System Effects. Seizures occurred in 0.6% of patients receiving quetiapine in controlled clinical trials. Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., dementia of the Alzheimer's type, geriatric patients).

Somnolence occurred in 16–18 or 34% of patients receiving quetiapine as monotherapy (for the treatment of schizophrenia or bipolar disorder) or in conjunction with lithium or divalproex sodium (for the treatment of bipolar disorder), respectively, during clinical studies compared with 4–11% of those receiving placebo.

Endocrine Effects. Dose-related decreases in total and free thyroxine (T4) of approximately 20% were observed in patients receiving quetiapine dosages at the higher end of the therapeutic dosage range during clinical studies. These decreases were maximal during the first 2–4 weeks of therapy and were maintained without adaptation or progression during more chronic therapy. Generally, these changes were not considered clinically important and were reversible upon discontinuance of quetiapine, regardless of duration of therapy. Increases in TSH were observed in about 0.4 or 12% of patients receiving quetiapine alone or in conjunction with lithium or divalproex sodium, respectively. In patients receiving quetiapine monotherapy, thyroid replacement therapy was necessary in some patients who experienced increases in TSH.

Although not observed in patients receiving quetiapine during clinical trials, increases in prolactin concentrations and associated increases in mammary gland neoplasia were reported in animal studies.

Metabolic Effects. During clinical studies, 23 or 21% of patients with schizophrenia or acute mania receiving quetiapine gained at least 7% of their baseline weight compared with 6–7% of those receiving placebo. In patients receiving quetiapine as adjunctive therapy for acute mania, 13% gained at least 7% of their baseline weight compared with 4% of those receiving placebo.

Increases from baseline in cholesterol and triglyceride concentrations of 11 and 17%, respectively, were reported in patients receiving quetiapine compared with slight decreases in patients receiving placebo in clinical studies in patients with schizophrenia. These changes were weakly related to increases in weight observed in patients receiving quetiapine. For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions, in Cautions.

Hepatic Effects. Asymptomatic, transient, and reversible increases in serum transaminases, principally ALT, have been reported in patients receiving quetiapine; these changes usually occurred within the first 3 weeks and resolved despite continued quetiapine therapy.

Sexual Dysfunction. One case of drug-induced priapism was reported in clinical studies of quetiapine.

Body Temperature Regulation. Although not reported in clinical studies with quetiapine, disruption of the body's ability to reduce core body temperature has been associated with use of antipsychotic agents. Use caution when quetiapine is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

GI Effects. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia).

Suicide. Attendant risk with bipolar disorder and psychotic illnesses; closely supervise high-risk patients. In clinical studies in patients with bipolar depression, the incidence of treatment-emergent suicidal ideation or suicide attempt in quetiapine-treated patients was low (1.7–2.6%) and similar to that observed with placebo (2%). Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Dispensing and Administration Precautions. Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. These medication errors may be associated with adverse CNS (e.g., mental status deterioration, hallucination, paranoia, muscle weakness, lethargy, dizziness) and GI effects (e.g., nausea, vomiting, diarrhea). As of November 2001, 4 patients had required emergency room visits and 3 patients reportedly had been hospitalized because of dispensing errors involving these 2 agents. One female patient 25 years of age experienced fever and respiratory arrest after mistakenly taking Seroquel® for 3 days instead of taking Serzone®, and even-

tually died, although a causal relationship has not been established. FDA also is concerned that several patients unintentionally ingested Serzone® or Seroquel® for a prolonged period of time before the error was discovered. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients).

Patients should be advised to question the dispensing pharmacist regarding any changes in the appearance of their prescription in terms of shape, color, or size of the tablets. Dispensing errors involving Seroquel® (quetiapine) and Serzone® (nefazodone) should be reported to the manufacturers or directly to the FDA MedWatch program by phone (800-FDA-1088), by fax (800-FDA-0178), by the Internet (http://www.fda.gov/Safety/MedWatch/default.htm), or by mail (FDA Safety Information and Adverse Event Reporting Program, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787).

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Quetiapine is distributed into milk in animals. Not known whether quetiapine is distributed into milk in humans. The manufacturer states that women receiving quetiapine should not breast-feed.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment (4%) compared with placebo (2%) in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of quetiapine in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. In clinical studies, approximately 7% of 3400 patients were 65 years of age or older. While no substantial differences in safety relative to younger adults were observed, factors that decrease pharmacokinetic clearance, increase the pharmacodynamic response, or cause poorer tolerance (e.g., orthostasis) may be present in geriatric patients. (See Dosage and Administration: Special Populations and see also Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Increased plasma concentrations expected in patients with hepatic impairment; dosage adjustment may be necessary. (See Dosage and Administration: Special Populations.)

Renal Impairment. Clearance may be decreased in patients with severe renal impairment, but dosage adjustment is not necessary.

■ **Common Adverse Effects** The most common adverse effects reported in 5% or more of patients receiving quetiapine therapy for schizophrenia or bipolar disorder and at a frequency twice that reported among patients receiving placebo in clinical trials include somnolence, sedation, asthenia, lethargy, dizziness, dry mouth, constipation, increased ALT, weight gain, dyspepsia, abdominal pain, postural hypotension, and pharyngitis.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g., erythromycin, fluconazole, itraconazole, ketoconazole): potential pharmacokinetic interaction (increased serum quetiapine concentrations). Use with caution.

Inducers of CYP3A4 (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin): potential pharmacokinetic interaction (increased quetiapine metabolism and decreased serum quetiapine concentrations). Dosage adjustment may be necessary if these drugs are initiated or discontinued in patients receiving quetiapine. (See Drug Interactions: Phenytoin.)

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP1A2, CYP3A4, CYP2C9, CYP2C19, or CYP2D6: pharmacokinetic interaction unlikely.

■ **Alcohol** Potential pharmacologic interaction (additive CNS effects). Avoid alcoholic beverages during quetiapine therapy.

■ **Cimetidine** Concomitant use of cimetidine (400 mg 3 times daily for 4 days) and quetiapine (150 mg 3 times daily) decreased mean clearance of quetiapine by 20%. However, dosage adjustment of quetiapine is not necessary.

■ **Divalproex** Potential pharmacokinetic interaction. Increased maximum plasma quetiapine concentrations, with no effect on extent of quetiapine absorption or mean clearance. Decreased maximum plasma valproic acid concentrations and extent of absorption (not clinically important).

■ **Fluoxetine, Haloperidol, Imipramine, Risperidone** No effect on steady-state pharmacokinetics of quetiapine observed.

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Lithium** No effect on steady-state lithium pharmacokinetics observed.

■ **Lorazepam** Potential pharmacokinetic interaction (decreased clearance of lorazepam). Concomitant use of quetiapine (250 mg 3 times daily) and lorazepam (single 2-mg dose) resulted in a 20% decrease in the mean clearance of lorazepam.

■ **Phenytoin** Concomitant use of quetiapine (250 mg 3 times daily) and phenytoin (100 mg 3 times daily) resulted in a fivefold increase in quetiapine clearance. An increase in quetiapine dosage may be required; caution advised if phenytoin is withdrawn and replaced with a noninducer of CYP3A4 (e.g., valproate).

■ **Thioridazine** Potential pharmacokinetic interaction (increased oral clearance of quetiapine).

■ **Other CNS Agents** Potential pharmacologic interaction (additive CNS effects). Use with caution.

Description

Quetiapine is a dibenzothiazepine-derivative antipsychotic agent. The drug is pharmacologically similar to clozapine, but differs pharmacologically from other currently available first-generation (typical) antipsychotic agents (e.g., phenothiazines, butyrophenones). Because of these pharmacologic differences, quetiapine is considered an atypical or second-generation antipsychotic agent.

The exact mechanism of quetiapine's antipsychotic action in schizophrenia and its mood stabilizing action in bipolar disorder has not been fully elucidated but may involve antagonism at serotonin type 1 (5-hydroxytryptamine [5-HT_{1A}]) and type 2 (5-HT_{2A}, 5-HT_{2C}) receptors, and at dopamine (D_1, D_2) receptors.

Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related to their affinity for and blockade of central dopamine D_2 receptors; however, antagonism at dopamine D_2 receptors does not appear to account fully for the antipsychotic effects of quetiapine. Results of in vivo and in vitro studies indicate that quetiapine is a comparatively weak antagonist at dopamine D_2 receptors. Receptor binding studies show quetiapine is a weak antagonist at D_1 receptors. Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D_3, D_4, and D_5 receptors also have been identified; quetiapine possesses no affinity for the dopamine D_4 receptor.

The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. The apparently low incidence of extrapyramidal effects associated with quetiapine therapy suggests that the drug is more active in the mesolimbic than in the neostriatal dopaminergic system. In contrast to typical antipsychotic agents (e.g., chlorpromazine) but like other atypical antipsychotic drugs (e.g., clozapine), quetiapine does not cause sustained elevations in serum prolactin concentrations and therefore is unlikely to produce adverse effects such as amenorrhea, galactorrhea, and impotence.

Quetiapine exhibits α_1- and α_2-adrenergic blocking activity; blockade of α_1-adrenergic receptors may explain the occasional orthostatic hypotension associated with the drug. Quetiapine also blocks histamine H_1 receptors, which may explain the sedative effects associated with the drug. Quetiapine possesses little or no affinity for β-adrenergic, γ-aminobutyric acid (GABA), benzodiazepine, or muscarinic receptors.

Quetiapine is extensively metabolized in the liver principally via sulfoxidation and oxidation to inactive metabolites. In vitro studies suggest that the cytochrome P-450 (CYP) 3A4 isoenzyme is involved in the metabolism of quetiapine to the inactive sulfoxide metabolite, which is the principal metabolite. The mean terminal half-life of quetiapine is about 6 hours. Following oral administration of a single dose of quetiapine, approximately 73 and 20% of the dose is excreted in urine and feces, respectively; less than 1% of the dose is excreted unchanged. Based on in vitro studies, quetiapine and 9 of its metabolites do not appear likely to inhibit CYP isoenzymes 1A2, 3A4, 2C9, 2C19, or 2D6.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months

of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). **For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.**

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral

Tablets, film-coated	25 mg (of quetiapine)	Seroquel®, AstraZeneca
	50 mg (of quetiapine)	Seroquel®, AstraZeneca
	100 mg (of quetiapine)	Seroquel®, AstraZeneca
	200 mg (of quetiapine)	Seroquel®, AstraZeneca
	300 mg (of quetiapine)	Seroquel®, AstraZeneca
	400 mg (of quetiapine)	Seroquel®, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia†, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 3.8 mg daily. Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within ther-

desipramine recommends that the drug *not* be used in children. Although a causal relationship between the use of desipramine and the risk of sudden death has not been established, many clinicians recommend that desipramine *not* be used in children with this disorder when tricyclic antidepressant therapy is contemplated.

The US Food and Drug Administration (FDA) also has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of desipramine in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Geriatric Precautions** Geriatric patients may be at risk of drug-induced toxicity when treated with desipramine, a tricyclic antidepressant that is known to be eliminated mainly by the kidneys. In this patient population, the ratio of plasma concentrations of the principal metabolite, 2-hydroxydesipramine, to desipramine appears to be increased, most likely because of decreased renal elimination that occurs with aging. Therefore, particular attention should be paid to desipramine dosage and it may be useful to monitor renal function in these patients. Desipramine use in geriatric patients also has been associated with an increased risk of falling and mental confusion. (See Cautions: Geriatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Pharmacokinetics

■ **Absorption** Desipramine hydrochloride appears to be well absorbed from the GI tract. Peak plasma concentrations occur within 4–6 hours after oral administration.

■ **Distribution** Limited data indicate that desipramine is distributed into milk in concentrations similar to those present in maternal plasma.

■ **Elimination** The plasma half-life of desipramine ranges from 7 to longer than 60 hours. Desipramine is metabolized principally via oxidation to 2-hydroxydesipramine, which retains some of the parent compound's ability to block the uptake of amines and may have particularly prominent cardiac depressant activity.

Chemistry and Stability

■ **Chemistry** Desipramine is a dibenzazepine-derivative tricyclic antidepressant that is the active metabolite of imipramine. Desipramine hydrochloride occurs as a white to off-white crystalline powder and is soluble in water and in alcohol. The drug has pK_as of 1.5 and 10.2.

■ **Stability** Desipramine hydrochloride tablets should be stored in tight containers at room temperature, preferably less than 30°C, and protected from excessive heat. Commercially available desipramine hydrochloride tablets have expiration dates of 5 years following the date of manufacture.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of desipramine, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Desipramine Hydrochloride

Oral		
Tablets	10 mg*	**Desipramine Hydrochloride Tablets**
	25 mg*	**Desipramine Hydrochloride Tablets**
	50 mg*	**Desipramine Hydrochloride Tablets**
	75 mg*	**Desipramine Hydrochloride Tablets**
	100 mg*	**Desipramine Hydrochloride Tablets**
	150 mg*	**Desipramine Hydrochloride Tablets**
Tablets, film-coated	10 mg	**Norpramin®**, Sanofi-Aventis
	25 mg	**Norpramin®**, Sanofi-Aventis
	50 mg	**Norpramin®**, Sanofi-Aventis
	75 mg	**Norpramin®**, Sanofi-Aventis
	100 mg	**Norpramin®**, Sanofi-Aventis
	150 mg	**Norpramin®**, Sanofi-Aventis

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Doxepin Hydrochloride

■ Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant.

Uses

■ **Depressive and Anxiety Disorders** Doxepin shares the pharmacologic actions of the other tricyclic antidepressants and is used principally in the treatment of depression and/or anxiety in psychoneurotic patients, depression and/or anxiety associated with alcoholism or organic disease, and psychotic depressive disorders with associated anxiety, including involutional depression and manic-depressive disorders. Symptoms of psychoneurosis that respond well to doxepin include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension, and worry.

For further information on treatment of major depression and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidality risks, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Chronic Idiopathic Urticaria** Doxepin also has been effective in the management of chronic idiopathic urticaria† and may be used as an alternative to antihistamines, which generally are considered as first-line therapy in patients with this condition.

Dosage and Administration

■ **Administration** Doxepin hydrochloride is administered orally. Although doxepin has been administered in up to 3 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time. Administration of the entire daily dose at bedtime may reduce daytime sedation.

Each dose of the oral concentrate should be diluted with approximately 120 mL of water, whole or skimmed milk, or orange, grapefruit, tomato, prune, or pineapple juice just prior to administration; the solution is physically incompatible with many carbonated beverages. For patients requiring doxepin therapy while on methadone maintenance, doxepin solution and methadone syrup can be mixed together with Gatorade®, lemonade, orange juice, sugar water, Tang®, or water, but not with grape juice. Bulk dilution and storage are not recommended by the manufacturers.

Doxepin is applied topically to the skin as an antipruritic. (See Doxepin Hydrochloride 84:08.)

■ **Dosage** Dosage of doxepin hydrochloride is expressed in terms of doxepin. There is a wide range of dosage requirements, and dosage must be carefully individualized. Initial dosages should be low and generally range from 30–150 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level which produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. The manufacturers state that dosages exceeding 300 mg daily rarely produce additional therapeutic benefits. Hospitalized patients under close supervision may generally be given higher dosages than outpatients. Patients with very mild symptomatology or organic brain syndrome should usually be given lower than average dosages and may obtain satisfactory improvement with 25–50 mg of doxepin daily. The manufacturers state that appropriate dosage in geriatric patients should be selected with caution, usually initiating therapy at the low end of the dosage range since decreased hepatic, renal, or cardiac function occurs more frequently in these patients.

When doxepin is administered as a single daily dose, the maximum daily dose recommended by the manufacturers is 150 mg. Commercially available 150-mg capsules of doxepin are intended for maintenance therapy only and are not recommended for initial therapy. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun, although anxiolytic effects may develop more rapidly.

After symptoms are controlled, dosage should be gradually reduced to the lowest level which will maintain relief of symptoms. To avoid the possibility of precipitating withdrawal symptoms, doxepin should not be terminated abruptly in patients who have received high dosages for prolonged periods.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Cautions

Doxepin shares the pharmacologic actions and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Pediatric Precautions** Safety of doxepin in children younger than 12 years of age has not been established.

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of doxepin in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Lactation** Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk. Sedation and serious respiratory depression were reported in a nursing infant whose mother was receiving 75 mg of doxepin daily; substantial concentrations of the active metabolite of the drug were detected in the infant's serum and urine. In addition, poor sucking and swallowing while nursing, drowsiness, muscle hypotonia, and vomiting were reported in a nursing infant whose mother was receiving 35 mg of doxepin daily. Because of the potential for serious adverse reactions to doxepin and/or its active metabolite in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pharmacokinetics

■ **Absorption** The pharmacokinetics of doxepin have not been extensively studied, but the drug is well absorbed from the GI tract in animals. Peak plasma concentrations usually occur within 2 hours after oral administration of the drug.

■ **Distribution** Doxepin is highly bound to plasma proteins.

Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk in concentrations reportedly ranging from about 30–140% and 10–115%, respectively, of those in maternal serum and that substantial concentrations of the active metabolite have been detected in the serum and urine of nursing infants whose mothers were receiving 75–150 mg of doxepin daily.

■ **Elimination** The plasma half-life of doxepin is 6–24.5 hours. The drug appears to be metabolized via the same pathways as are other tricyclic antidepressants; its *N*-demethylated metabolite is pharmacologically active.

Chemistry and Stability

■ **Chemistry** Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant. The drug occurs as a white powder, is freely soluble in water and in alcohol, and has a pK_a of 8. Doxepin hydrochloride oral concentrate has a pH of 4–7.

■ **Stability** Doxepin hydrochloride capsules should be stored in tight, light-resistant containers at a temperature between 15–30°C and the oral concentrate should be stored at a temperature between 20–25°C. Commercially available doxepin hydrochloride capsules have an expiration date of 36 months and the oral concentrate has an expiration date of 24 months following the date of manufacture.

Doxepin hydrochloride oral concentrate is physically incompatible with many carbonated beverages, but is compatible with some other beverages. (See Dosage and Administration: Administration.) Bulk preparation and storage of dilutions of the commercially available oral concentrate are not recommended by the manufacturers.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of doxepin, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Doxepin Hydrochloride

Oral		
Capsules	10 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	25 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	50 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	75 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	100 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
	150 mg (of doxepin)*	Doxepin Hydrochloride Capsules
		Sinequan®, Pfizer
Solution, concentrate	10 mg (of doxepin) per mL*	Doxepin Hydrochloride Oral Solution (Concentrate)
		Sinequan® Oral Concentrate, Pfizer

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Imipramine Hydrochloride
Imipramine Pamoate

■ Imipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Imipramine hydrochloride and imipramine pamoate are administered orally. Although imipramine hydrochloride has been administered in up to 4 divided doses throughout the day, it is long-acting and the entire oral daily dose may be administered at one time. Imipramine pamoate may also be used to administer the daily oral dose of imipramine, but it has no advantages over the hydrochloride. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation may be given the entire daily dose in the morning.

■ **Dosage** Dosage of imipramine salts is expressed in terms of imipramine hydrochloride.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Major Depressive Disorder There is a wide range of oral dosage requirements, and dosage must be carefully individualized. Initial dosages of imipramine should be low and generally range from 75–100 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. Hospitalized patients under close supervision may generally be given higher dosages than outpatients, and manufacturers state that dosages of greater than 200 mg daily are not recommended for outpatients. Geriatric patients should usually be given lower than average dosages. Manufacturers state that therapy should be initiated with 25–50 mg daily as imipramine hydrochloride (e.g., Tofranil®) in these patients and that optimal dosage rarely exceeds 100 mg daily. If the daily dosage is established at 75 mg or more, imipramine pamoate (e.g., Tofranil®-PM) may be administered. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. If maintenance therapy is necessary, manufacturers recommend an adult dosage of 50–150 mg daily. To avoid the possibility of precipitating withdrawal symptoms, imipramine should not be terminated abruptly in patients who have received high dosage for prolonged periods.

Functional Enuresis in Children For the treatment of functional enuresis in children who are at least 6 years of age, the usual initial oral dosage of imipramine hydrochloride is 25 mg daily, administered 1 hour prior to bedtime. If a satisfactory response is not obtained within 1 week, dosage may be increased to 50 mg nightly for children younger than 12 years of age or 75 mg nightly for children 12 years of age and older. Dosages higher than 75 mg daily do not improve results and may increase the risk of adverse reactions. For children who are early-night bedwetters, better results may be obtained by administering 25 mg in midafternoon and again at bedtime. Dosage of imipramine hydrochloride for the treatment of functional enuresis in children should not exceed 2.5 mg/kg daily. Long-term effects of the drug in children have not been determined; therefore, after a satisfactory response has been maintained, imipramine hydrochloride should be gradually withdrawn. If dosage is gradually reduced after a favorable response of many weeks, relapses may be less frequent; children who relapse may not respond to subsequent treatment with imipramine. (See Cautions: Pediatric Precautions.)

Cautions

Imipramine shares the pharmacologic actions, uses, and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Although the clinical importance is not known, ECG changes have been reported in pediatric patients receiving twice the recommended maximum daily dosage.