Neuroleptic Malignant Syndrome. Although no cases have been confirmed to date in patients receiving ziprasidone, neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, may occur in patients receiving antipsychotic agents. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Like other antipsychotic agents, use of ziprasidone may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. Although emergence of tardive dyskinesia was not specifically evaluated in clinical studies of ziprasidone, use of the drug was associated with either no change or small reductions in the Abnormal Involuntary Movement Scale (AIMS) scores from baseline in one year-long study of the drug. However, differences among antipsychotic agents in their potential to cause tardive dyskinesia have not been established definitively. For additional information on tardive dyskinesia, see 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 certain atypical antipsychotic agents (e.g., clozapine, olanzapine, quetiapine, 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., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether ziprasidone also is associated with this increased risk. Although there have been few reports of hyperglycemia or diabetes in patients receiving ziprasidone, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.

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., quetiapine, risperidone) in the class, 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 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 managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions **Rash.** Rash and/or urticaria, possibly related to dose and/or duration of therapy, occurred in about 5% of patients in clinical studies and have necessitated discontinuance of the drug in about 17% of these patients. Adjunctive treatment with antihistamines or steroids and/or drug discontinuance may be required. Discontinue ziprasidone if alternative etiology of rash cannot be identified.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension, particularly during initial dosage titration period, has been reported. Use with caution in patients with known cardiovascular or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Nervous System Effects. Seizures occurred in about 0.4% of patients receiving ziprasidone 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., Alzheimer's disease, geriatric patients).

Although not reported in clinical studies with ziprasidone, disruption of the body's ability to reduce core body temperature has been associated with use of other antipsychotic agents. Use caution when ziprasidone 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). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Suicide. Attendant risk with psychotic illnesses; closely supervise high-risk patients. Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

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

Other Metabolic and Endocrine Effects. Prolactin concentrations exceeding 22 ng/mL were reported in about 20% of patients receiving ziprasidone in phase II or III clinical studies compared with about 4, 46, or 89% of those receiving placebo, haloperidol, or risperidone, respectively.

Median weight gain of 0.5 kg occurred in patients receiving ziprasidone compared with no median weight change in those receiving placebo. In clinical studies, ziprasidone reportedly caused less weight gain than clozapine, olanzapine, quetiapine, or risperidone.

For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions: Warnings, in Cautions.

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

Lactation. Not known whether ziprasidone is distributed into milk; use in nursing women is not recommended.

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

Geriatric Use. No substantial differences in safety of oral ziprasidone relative to younger adults have been observed in clinical studies. Ziprasidone mesylate IM injections have not been systematically evaluated in geriatric patients. Lower initial dosages, slower titration, and more careful monitoring during the initial dosing period may be advisable in some geriatric patients. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment. Commercially available ziprasidone mesylate injections contain sulfobutylether β-cyclodextrin sodium, an excipient that is cleared by renal filtration. Therefore, ziprasidone injection should be used with caution in patients with renal impairment.

■ **Common Adverse Effects** Adverse effects occurring in more than 5% of patients with schizophrenia receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (14%) and respiratory tract infection (8%).

Adverse effects occurring in more than 5% of patients with schizophrenia receiving IM ziprasidone 10 or 20 mg and at a frequency twice that reported among those receiving IM ziprasidone 2 mg include somnolence (20%), headache (13%), and nausea (12%).

Adverse effects occurring in more than 5% of patients with bipolar mania receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%).

Drug Interactions

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT interval prolongation; concomitant use contraindicated) when ziprasidone is used with drugs that are known or consistently observed to prolong the QT_c interval (e.g., dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate [no longer commercially available in the US], dolasetron mesylate, probucol, tacrolimus). Ziprasidone also is contraindicated in patients receiving drugs shown to cause QT prolongation as an effect and for which this effect is described in the full prescribing information as a contraindication or a boxed or bolded warning. (See Cautions: Contraindications and Prolongation of QT interval under Warnings/Precautions: Warnings in Cautions.)

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

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effects).

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

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 isoenzyme; potential pharmacokinetic interaction (altered metabolism). Inhibitors or inducers of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 isoenzymes: pharmacokinetic interaction unlikely.

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

Description

Ziprasidone is a benzisothiazolyl piperazine-derivative antipsychotic agent that is chemically unrelated to other currently available antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of antipsychotic action of ziprasidone has not been fully elucidated but, like that of other atypical antipsychotic agents (e.g., olanzapine, risperidone), may involve antagonism of central type 2 serotonergic ($5\text{-}HT_2$) receptors and central dopamine D_2 receptors. As with other drugs that are effective in bipolar disorder, the precise mechanism of antimanic action of ziprasidone has not been fully elucidated. Antagonism of various other receptors (e.g., histamine H_1 receptors, α_1-adrenergic receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with ziprasidone.

Ziprasidone is extensively metabolized in the liver principally via reduction