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 eventually 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/medwatch), 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 de-