

CLINICAL CAPSULES

Soft Cheese Risks

Soft white cheeses made with raw milk present a health risk, the U.S. Food and Drug Administration has warned. Such cheeses can cause listeriosis, brucellosis, salmonellosis, and tuberculosis, and they pose a particular risk to pregnant women, newborns, older adults, and those with weakened immune systems.

Consumption of *queso fresco*-style cheeses that were imported from or eaten in Mexico were linked with recent cases of tuberculosis in New York City and found to be contaminated with *Mycobac-*

terium bovis, according to the FDA. The cheeses of greatest concern are those originating in Mexico and Central American countries and include *queso panela*, *asadero*, *blanco*, and *ranchero*. The FDA has warned against consumption of any unripened raw-milk soft cheeses, including those obtained at flea markets or from door-to-door sellers or vendors selling out of their trucks.

TB Trends

The tuberculosis case rate in the United States is declining, but the rate of decline

from 2003 to 2004 was the lowest in a decade, and racial disparities remain a concern, according to the Centers for Disease Control and Prevention.

More than 14,500 cases of TB were reported in the United States in 2004, for a case rate of 4.9 per 100,000. This is the lowest rate ever recorded, but the 3.3% decline from 2003 was smaller than the 6.8% average annual decline between 1993 and 2002. In 2004, minority populations had significantly higher TB rates than the overall U.S. average: The case rate was 26.9/100,000 in Asians, 11.1/100,000 in blacks, 10.1/100,000 in Hispanics, and 1.3/100,000 in whites.

Furthermore, foreign-born individuals have a case rate of 22.5/100,000, compared with 2.6/100,000 for U.S.-born persons and the decline in the TB rate over the last 12 years among foreign-born individuals has been only 34%, compared with 65% among U.S.-born persons.

TB remains a health threat that must be taken seriously, according to the CDC, which is stepping up disease elimination efforts, in part by strengthening global partnerships to address TB among the hardest-hit populations.

HCV and Iron Stores

Hepatitis C virus infection is significantly associated with increased serum levels of ferritin and iron, the third National Health and Nutrition Examination Survey shows.

Among more than 14,400 U.S. residents who participated in NHANES III, nearly 1% had HCV infection. Mean serum levels of ferritin and iron were significantly higher in those with HCV infection, compared with individuals with no liver disease (100 ng/mL vs. 83 ng/mL for ferritin; 229 mcg/dL vs. 101 mcg/dL for iron), reported Ying Shan, M.D., and colleagues at the University of Connecticut, Farmington.

Furthermore, serum levels of ferritin and iron were directly correlated with serum concentrations of ALT, AST, and γ -glutamyl-transpeptidase (Clin. Infect. Dis. 2005;40:834-41).

It remains unclear whether higher iron levels—which have been shown in other studies to be associated with increased risk for persistent viral infection and decreased response to treatment—raise the risk for chronic HCV, or if liver damage increases iron levels, the investigators said. Regardless, it is likely that excess iron contributes to hepatic injury and fibrosis, they concluded, noting that improved understanding of the link between iron levels and liver disease is important for devising strategies to prevent urinary morbidity.

Pseudomonas Infections

Health care providers who identify cases of infection with *Pseudomonas* species in patients with central venous catheters should determine if the patient received a heparin/saline flush recalled earlier this year, and should report cases by calling 800-332-1088 or going to www.fda.gov/medwatch/report.htm.

The flush, preloaded in syringes by IV Flush and distributed by Pinnacle Medical Supply, was initially linked with four cases of *P. fluorescens* bloodstream infections. The FDA issued an alert, and the company recalled the products.

The syringes had been distributed to locations in as many as 17 states, and in an ongoing investigation, 36 associated cases have been identified.

Infections have occurred up to 1 month after receipt of the product; catheters used infrequently can become colonized, and symptoms may not develop until the catheter is used.

Because susceptibility patterns of isolates from affected patients have varied—with some showing resistance to third-generation cephalosporins and carbapenem antibiotics—treatment of potential patients should include targeted antimicrobial therapy. Catheter removal should be considered as well.

—Sharon Worcester

BRIEF SUMMARY of Prescribing Information—Before prescribing, please consult complete Prescribing Information.

INDICATIONS AND USAGE: Bipolar Mania: SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia:** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS: Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability. See full Prescribing Information for more information on the manifestations, diagnosis and management of NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rule out prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop tardive dyskinesia. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely. If antipsychotic treatment is withdrawn, antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL in order to control their underlying illness. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically thereafter. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, blurred vision, or lightheadedness, especially during the initial dose-titration period, probably reflecting its α_1 -adrenoreceptor antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL compared with 0% (0/1600) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (orthostatic hypotension and treatment with antihypertensive medications). The risk of orthostatic hypotension may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cardiac:** The development of cardiac arrest was observed in association with quetiapine treatment in chronic dog studies. Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriate sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. **Seizures:** During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypohydrism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL-treated patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the active control studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL-treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported in schizophrenia trials. The proportions of patients with transaminase elevations ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL, especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may also have this effect. **Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.

SEROQUEL® (quetiapine fumarate) Tablets

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in psychiatric illness, and close supervision of high-risk patients should be maintained throughout drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**). **Information for Prescribers:** Physicians are advised to consult the full Prescribing Information for details of the following issues to discuss with patients for whom they prescribe SEROQUEL: Orthostatic Hypotension, Interference with Cognitive and Motor Performance, Pregnancy, Nursing, Concomitant Medication, Alcohol, and Heat Exposure and Dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychiatric disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 1.5-fold without affecting the extent of absorption or mean oral clearance. **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 35% increase in maximum plasma concentration of quetiapine. Caution is advised when quetiapine is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs: Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg bid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrine:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychiatric disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in C57BL/6 mice and Wistar rats. There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg and in female mice at 1.5 and 4.5 times the maximum human dose and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m² basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent thyroid tissue. However, the proportions of thyroid follicular cell adenomas in this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. Serum measurements in a 1-year toxicity study showed that quetiapine increased mean serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be related to the increase in prolactin. However, the mechanism of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see **Hyperprolactinemia**). **PRECAUTIONS, General: Mutagenesis:** The mutagenic potential of quetiapine was tested in *in vitro* bacterial gene mutation assays and in an *in vivo* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m² basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week post-treatment period. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m² basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m² basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m² basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m² basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rats dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.2 to 2.4 times the maximum human dose on a mg/m² basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m² basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m² basis) and in rabbits at 50 and 100 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m² basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study in a pre/postnatal reproductive study in rats. No drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m² basis. However, in a preliminary pre/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL is excreted in milk of lactating animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 3400 patients in clinical studies with SEROQUEL, 7% (222) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer monitoring or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients.

ADVERSE REACTIONS: The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 400 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 14.3 patients considered to be fully Prescribing Information for details of adverse event data collection. **Adverse Findings Observed in Short-Term, Controlled Trials: Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Bipolar Mania:** Overall, discontinuations due to adverse events were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. **Schizophrenia:** Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to adverse events were more frequent in patients treated by drug related (see **PRECAUTIONS**): Somnolence 0.8% vs 0% for placebo and Hypotension 0.4% vs 0% for placebo. **Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials:** The following treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) when the incidence in patients treated with placebo was less than 1% are listed in the following table. **Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy):** Body as a Whole: Headache, Pain, Asthenia, Abdominal Pain, Back Pain, Fever; Cardiovascular: Tachycardia, Postural Hypotension; Digestive: Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transpeptidase Increased; Metabolic and Nutritional: Weight Gain, SGPT Increased, SGOT Increased; Nervous: Agitation, Somnolence, Dizziness, Anxiety;

SEROQUEL® (quetiapine fumarate) Tablets

Respiratory: Pharyngitis, Rhinitis; **Skin and Appendages:** Rash; **Special Senses:** Amblyopia. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (8%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). Table 2 enumerates the incidence of treatment-emergent adverse events that occurred during therapy (up to 3 weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. Events for which the SEROQUEL incidence was equal to or less than placebo are not listed, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypotonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss. **Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy):** Body as a Whole: Headache, Asthenia, Abdominal Pain, Back Pain; Cardiovascular: Postural Hypotension; Digestive: Dry Mouth; Constipation; **Metabolic and Nutritional:** Weight Gain; **Nervous:** Somnolence, Dizziness, Tremor, Agitation; **Respiratory:** Pharyngitis. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose-related Adverse Events:** Logistic regression analyses revealed a positive dose response (p<0.05) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (an index of EPS severity that includes parkinsonism and akathisia), (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonía, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS, and the use of concomitant anticholinergic medications to treat EPS. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting a weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportions of patients meeting the same weight criterion were 13% compared to 4% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**). **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including PR interval, QT interval, and QTc interval. However, the proportions of patients with tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.8% (1/169) for SEROQUEL compared to 0% (0/171) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Events are categorized by body system and listed in order of decreasing frequency according to the following definition: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in at least 1/1000 patients; rare events are those occurring in at least 1/10,000 patients; very rare events are those occurring in fewer than 1/10,000 patients. **Nervous System:** Frequent: hypertonía, dysarthria; Infrequent: abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, parosmia, ataxia, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, tremor, cataplexy, reaction, hemiparesis, tongue edema; Rare: glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** Frequent: palpitation; Infrequent: vasodilation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, 1 wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; Rare: angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System:** Frequent: pharyngitis, thin, cough increased, dyspnea; Infrequent: pneumonia, epistaxis, asthma. **Rare:** hiccup, hyperventilation. **Metabolic and Nutritional System:** Frequent: peripheral edema; Infrequent: weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; Rare: glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** Frequent: sweating; Infrequent: pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; Rare: exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** Infrequent: dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginitis, menorrhagia*, abnormal spigulation*, cystitis, urinary retention, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis* (*adjusted for gender); Rare: gynecocystitis*, nocturia, polyuria, acute kidney failure. **Special Senses:** Infrequent: conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; Rare: abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** Infrequent: pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, muscle pain; Rare: myalgia, myopathy. **Immune and Lymphatic System:** Frequent: leukopenia, anemia. **Endocrine System:** Infrequent: hypothyroidism, diabetes mellitus; Rare: hyperthyroidism. **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. **Physical and Psychologic Dependence:** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE: Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL, alone resulting in death, coma or QTc prolongation. **Management of Overdosage:** In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, Delaware 19850-5437

© AstraZeneca 2004 Rev 07/04