

BRIEF SUMMARY OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials in outpatients (See **CLINICAL PHARMACOLOGY**). 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 Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two prior cases of NMS (2/2387 (0.1%)) have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (myoglobinuria) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other concomitant therapy; 2) intensive supportive measures, including treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential re-introduction 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 rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. 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 cases of 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 most closely meets individual patients' needs and that is consistent with the goals of chronic treatment generally reserved for patients who appear to suffer from a chronic illness that (1) 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 despite the presence of the syndrome.

PRECAUTIONS: General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration, possibly reflecting its α -adrenergic antagonist properties. Syncope was reported in 1% (2/2162) of the patients treated with SEROQUEL, compared with 0% (0/206) on placebo and about 0.5% (2/420) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration it rate target, a rapid reduction in rate may be necessary. A gradual decrease is appropriate. 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 (dehydration, hypovolemia and treatment with antihypertensive medications). **Cataracts:** The development of cataracts was observed in patients treated with SEROQUEL in long-term clinical trials (see **Animal Toxicology**). 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 examination or an appropriately sensitive, non-invasive measurement technique, is recommended and should be performed at least annually during chronic treatment. **Seizures:** During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) 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. **Hypothyroidism:** 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. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and were unchanged in nearly all patients. The clinical course 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% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment. **Cholesterol and Triglyceride Elevations:** In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases in total cholesterol and triglycerides of approximately 1% 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, gynecomatia, 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. The proportions of patients with transaminase elevations of 3 times or more the upper limit of normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for 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 the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% 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 the drug does not affect them adversely. **Fragility:** One case of priapism in a patient receiving SEROQUEL has been reported for 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 share this capacity. Severe priapism may require surgical intervention. **Respiration:** Although there is no known mechanism by which SEROQUEL might disrupt 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

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have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of mortality among antipsychotic 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 schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the possibility of misuse. **Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used with 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 elderly patients (see **Orthostatic Hypotension**). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity 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. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast-feed or be nursed to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in dry climates and dehydration. **Diagnosis of Disease:** 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. The following interactions have been observed in patients 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 SEROQUEL:** Phenytoin: Coadministration of quetiapine (250 mg bid) and phenytoin (100 mg bid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be necessary to treat symptoms of epilepsy. **Enzyme Induction:** 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). **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (800 mg bid) did not affect the oral clearance of quetiapine or the oral clearance of quetiapine (150 mg bid). Dose 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 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with other potent 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 b.i.d.) was not affected by the presence of quetiapine. **Clonidine:** Clonidine administered as 250 mg bid did not affect the steady-state pharmacokinetics of quetiapine (250 mg bid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Anticholinergic:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotropic disorders had no clinically relevant effect on the clearance of anticholinergic agents or on the pharmacokinetics of quetiapine. **Phenytoin:** Phenytoin did not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipsychotics. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** **Carcinogenesis:** Carcinogenicity studies were conducted in C57BL/6 mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. The maximum human dose is equivalent to 10 mg/kg in mice and 3.0 times the maximum human dose (800 mg/day) on a mg/m² basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m² basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m² basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. In female mice, statistically significant increases in thyroid gland follicular adenomas were observed in female rats at doses of 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 liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with 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. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32-fold in males and 6-fold in females, respectively, compared to controls. Similar increases have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see **Hyperprolactinemia** in **PRECAUTIONS, General**). **Mutagenesis:** The mutagenic potential of quetiapine was tested in an *in vitro* bacterial mutagenesis assay 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 test 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 male and female 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 period without treatment. 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 for impaired mating and fertility in female rats was 10 mg/kg or 0.1 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 rabbits during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 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. No evidence of an increase in the number 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 (1.2 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. In rats, there was a statistically significant increase in 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 periparturient reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.1, 0.12 and 0.12 times the maximum human dose on a mg/m² basis. However, in a preliminary periparturient 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. **Laboratory and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown.

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Nursing Mothers: SEROQUEL was excreted in milk of lactating animals during lactation. SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast-feed. **Pediatric Use:** The delayed effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) 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, cause drug tolerance or drug interaction 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

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: 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 dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The following treatment-emergent adverse experiences occurred at an incidence rate of 1% or more, and were at least as frequent among SEROQUEL treated patients, treated at doses of 75 mg/day or greater than among placebo treated patients in 3- to 6-week placebo-controlled trials. **Body as a Whole:** Headache, Asthenia, Abdominal pain, Back pain, Fever; **Nervous System:** Somnolence, Dizziness; **Digestive System:** Constipation, Dry Mouth, Dyspepsia; **Cardiovascular System:** Postural hypotension, Tachycardia; **Metabolic and Nutritional Disorders:** Weight gain; **Skin and Appendages System:** Rash; **Respiratory System:** Rhinitis; **Special Senses:** Ear pain. **Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following:** pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hyperreflexia, tremor, depression, anorexia, pharyngitis, dry skin, dryness and urinary tract infection. Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials Dose-related Adverse Events:** Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to three placebo groups to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In three additional placebo-controlled clinical trials 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 Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain:** 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 significant greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). **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**). An assessment of hematology parameters in short-term, placebo-controlled trials revealed no clinically important differences between the SEROQUEL and placebo groups. Exploratory 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 QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/166) for placebo. The incidence of tachycardia 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:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as determined by the Adverse Events Reporting System (AERS) section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported below are associated with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** Frequent: hyperreflexia, dysarthria; Infrequent: abnormal dreams, dyskinesia, thinking abnormal, laryngeal dyskenesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased, urinary retention, incoordination, paranoiac reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, derealization, stupor, bruxism, catatoniac reaction, hypotonia; Rare: apathia, amnesia, buccoglossal syndrome, choreoathetosis, delirium, and body laceration; **ophthalmia;** libido decreased; **neurological;** stuttering, subconjunctival hemorrhoma. **Body as a Whole:** Frequent: flu symptoms; **Infrequent:** neck pain, pelvic pain, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged; **Digestive System:** Frequent: anorexia; **Infrequent:** increased salivation, increased appetite, gamma glutamyl transaminase increased, gingivitis, dysphagia, flatulence, gastritis, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, local intolerance; **Gastrointestinal:** reflux, gum hyperplasia, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis; **Cardiovascular System:** Frequent: palpitation; **Infrequent:** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, aortic aneurysm, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration; **Respiratory System:** Frequent: pharyngitis, rhinitis, cough increased, dyspnea; **Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccup, hyperventilation; **Metabolic and Nutritional System:** Frequent: peripheral edema; **Infrequent:** weight loss, alkaline phosphatase increased, hyperkinesia, alcohol intolerance, dehydration, hypokinesia, creatinine increased, hypocalcemia; **Rare:** dyscystitis, gout, hand edema, hyperkinesia, 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, vaginal moniliasis, abnormal ejaculation, cystitis, urinary frequency, amenorrhea, female lactation, leukorrhea, vaginal hemorrhage, urinary incontinence, urinary tract infection; **Rare:** gynecomastralia, nocturia, polyuria, acute kidney failure; **Special Senses:** Infrequent: conjunctivitis, abnormal vision, dry eyes, linitis, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma; **Musculoskeletal System:** Infrequent: pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain; **Hemic and Lymphatic System:** Frequent: leukopenia, eosinophilia; **Rare:** thrombocytopenia, thrombocytopenic purpura, leukopenia, lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocytopenia; **Endocrine System:** Infrequent: hypothyroidism, diabetes mellitus; **Rare:** hyperthyroidism. *adjusted for gender **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy included the following: rarely leukopenia/thrombocytopenia. If a patient develops a low white cell count/considerable discoloration of the stool, possible risk factors for leukopenia/thrombocytopenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: SEROQUEL is not a controlled substance.

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*Extrapyramidal symptoms.

- The most common adverse events associated with the use of SEROQUEL are dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The majority of adverse events are mild or moderate
- As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension


Accepted!

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References: 1. Small JG, Hirsch SR, Arvanitis LA, et al, and the Seroquel Study Group. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry*. 1997;54:549-557. 2. Arvanitis LA, Miller BG, and the SEROQUEL Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry*. 1997;42:233-246. 3. Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *J Clin Psychopharmacol*. 1996;16:158-169. 4. Data on file, Study S91, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. 5. SEROQUEL[®] (quetiapine fumarate) Prescribing Information, Rev 1/01, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware.


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