

# Study Clarifies Effects of Outpatient Commitment

BY JOYCE FRIEDEN  
Associate Editor, Practice Trends

MONTREAL Outpatient commitment can be a useful tool if it is implemented for a long enough period and combined with more frequent services, Dr. Marvin S. Swartz said at the annual meeting of the American Academy of Psychiatry and the Law.

“We do show that outpatient commitment exerts an effect over and above en-

hanced services,” said Dr. Swartz, who is head of social and community psychiatry at Duke University Medical Center, Durham, N.C. “But if you give outpatient commitment without enhanced services, it has no effect.”

Forty-one states have outpatient commitment statutes, Dr. Swartz said. These laws allow courts to mandate that outpatient psychiatrists attend treatment sessions. If patients refuse to go to the sessions, health care providers can enlist the

aid of law enforcement authorities to bring the patients in.

In a study Dr. Swartz and his colleagues conducted with 331 patients who had recently been hospitalized for a mental illness, patients who had more than 6 months of outpatient commitment were less likely to be readmitted to the hospital compared with those who had less than 6 months’ worth. In addition, those who had 6 months or more of outpatient commitment had a lower mean number of

hospital stays and a much lower number of average days in the hospital—8 days versus 30 days—compared with those either in the control group or with less than 6 months of outpatient commitment.

“This is a significant effect of outpatient commitment,” Dr. Swartz said. “Most of the effect was among folks with psychotic disorders such as schizoaffective disorder and schizophrenia, as opposed to mood disorders or bipolar disorders.”

Those who were violent in the past and had 6 months or more of outpatient commitment were also less likely to be violent, he added.

Overall, “treatment adherence improved with outpatient commitment, and outpatient commitment can reduce violence, victimization, and family strain, and can improve medication adherence and quality of life,” he said.

But outpatient commitment is just a single point on the spectrum of leverage psychiatrists can use to get patients to come for treatment, noted Dr. Paul Appelbaum, chair of psychiatry at Columbia University, New York. Other leverage points include housing, money, and, in some cases, control over parole, he said.

Child custody is another example; a provider might say: “We’ll support your regaining custody of your child, or having more unsupervised visits, but we really can’t do that in good conscience . . . unless you’re coming to treatment regularly,” he said. “Outpatient commitment is one piece of the entire spectrum of coercion or leverage applied to people in outpatient settings.”

Although outpatient commitment causes lots of controversy because of its coercive aspects, that’s the wrong thing to focus on, according to Stephen J. Morse, Ph.D., professor of psychology and law in psychiatry at the University of Pennsylvania, Philadelphia. Dr. Morse noted that there are 25 million people in the United States suffering from schizophrenic disorder, serious or moderate major depressive disorder, or bipolar disorder.

“Now how many doctoral and clinical psychologists and psychiatrists are there? About 90,000 altogether,” he said. “That’s one treating professional for every 232 people” suffering from just those three conditions; assuming only half would work for every 116 people—and that doesn’t take into account people who suffer from other disorders and assumes all providers would be spending 100% of their time on patient care.

“Suppose we said to 25 million people, ‘We can help keep you out of hospital, help you get along with your family, help keep you out of the criminal justice system; we can do all those things for you if you just come for at least 6 months, three times a week.’ You couldn’t begin to treat all the people who would accept under those conditions,” Dr. Morse said. “Why are we talking about coercion of one sort of another when what we ought to talk about is forcing the legislature to produce the services that would make coercion not necessary?”

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

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seven placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

**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 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 patients. 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: Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). **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, 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 (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude causes where the clinical presentation includes both serious medical signs and symptoms (eg, 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 not essential to concurrent therapy; 2) intensive symptomatic 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 pharmacological treatment regimens for 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, dysrhythmic movements has been associated 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 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 (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, 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 providing 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. **Hypotension and Blood Pressure:** Hypotension, in some cases extreme and associated with ketorolac or hypotension or hypotension or hypotension, 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 during treatment. 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, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha_1$ -adrenoreceptor antagonism. Syncope has been reported in 12% (12/100) of the patients treated with SEROQUEL compared with 0% (0/607) 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 (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration, a gradual return to the previous dose is appropriate. **Cataracts:** During clinical trials, cataracts were observed in association with quetiapine treatment in chronic drug dosing. 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. Cataracts:** During clinical trials, cataracts 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, eg, Alzheimer’s dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years of 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 levels of T4 were unchanged. 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 patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct 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. Although increases in cholesterol and triglyceride levels were not demonstrated in clinical trials with SEROQUEL, increased prolipid levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats. **Cardiogenesis:** 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, gynecostasia, 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 of  $>3$  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 using SEROQUEL as monotherapy, serotonergic levels were reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, serotonergic levels were 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 automobile) or operating hazardous machinery until they are reasonably certain that SEROQUEL

does not affect them adversely. **Prilapim:** One case of prilapim 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  $\alpha_1$ -adrenoreceptor blocking effects have been reported to induce prilapim, and it is possible that SEROQUEL may share this capacity. Severe prilapim may require surgical intervention. **Body 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, eg, 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. 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 bipolar disorder and schizophrenia, close supervision of high risk patients should accompany drug therapy. Frequent and close supervision is indicated in patients who are at high risk for suicide, especially with poor 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 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 therapy or increases in dose. **Interference with Cognitive and Motor Performance:** Since serotonergic activity 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 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. **Nursing:** Patients should be advised not 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 avoiding overheating. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs had 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 drugs. SEROQUEL may potentiate the effects of levodopa and dopamine agonists. **Effect of Other Drugs on Quetiapine:** 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 required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, 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 17% 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 66%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg bid 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 ketoneconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 33% increase in maximum plasma concentration. **Other Inhibitors of P450 3A (eg, 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 bid dosing. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproate 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. **Antipsy: Administration of multiple daily doses up to 750 mg/day (on a bid schedule) of quetiapine to subjects with selected psychiatric disorders had no effect on the clearance of antipsychotic or anticholinergic or urinary organic anion metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipsychotics. **Cardiogenesis, Mutagenesis, Impairment of Fertility: Cardiogenesis:** Cardiogenesis 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. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (300 mg bid) on a mg/m<sup>2</sup> basis. There were statistically significant increases in thyroid follicular adenomas in male rats at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from decreased metabolism and clearance of endogenous thyroid hormones 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- and 19-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 prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see **Hyperproliferation in PRECAUTIONS, General**). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* 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 *S. typhimurium* 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m<sup>2</sup> basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Beagle dogs. **General 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% (232) 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 tolerance 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 oral clearance of SEROQUEL was reduced by 30% to 50% in elderly patients 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 914 patients. **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. 3.1% 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 somnolence and hypotension were considered to be 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 SEROQUEL (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) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. **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, Dizziness, Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transaminases Increased, Metabolic and Nutritional: Weight Gain, SGPT increased, SGOT increased, Nervous: Agitation, Somnolence, Dizziness, Anxiety, Respiratory: Pharyngitis, Rhinitis, Skin and Appendages: Rash, Special Senses: Amblyopia. \*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, hypernatremia, hypotension, increased appetite, infection, insomnia, leukopenia, muscle, nervousness, paresthesia, peripheral edema, swelling, tremor, and weight loss. 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 (9%), 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. **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, Gastroenteritis, Weight Gain; Nervous: Somnolence, Dizziness, Tremor, Agitation; Respiratory: Pharyngitis. \*Events for which the SEROQUEL incidence was equal to or less than placebo are not listed, but included the following: akathisia, diarrhea, insomnia, and nausea. 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%). **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose-related Adverse Events:** Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of 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 (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hyperreflexia, hyperkinesia, neck rigidity, and tremor), and (3) use of anti-parkinsonian drugs. The proportions of patients meeting the criteria for 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 0.6% (1/166) 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:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses  $\geq$  75 mg/day during any phase of a trial within the pre-marketing database of approximately 2000 patients treated for schizophrenia. All reported events are included except those already listed by 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 occurred during treatment 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:** hypotonia, dysarthria. **Infrequent:** abnormal dreams, dyskinesia, laryngitis, abnormal gait, dizziness, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased, urinary retention, incoordination, paranoic reaction, abnormal gait, myoclonus, delusions, panic reaction, apathy, ataxia, depersonalization, postural, bruxism, catatonal reaction, hypotension. **Rare:** anisocoria, stuttering, schizophrenia, choreoathetosis, delirium, emotional lability, euphoria, libido increased, neuralgia, glossitis, subdural hematoma. **Body as a Whole: Frequent:** flu syndrome. **Infrequent:** neck pain, pelvic pain. **Cardiovascular System: Frequent:** tachycardia. **Infrequent:** abnormal ECG, tachycardia, abnormal heart block, 1st degree, congestive heart failure, ST elevated, thrombophlebitis, 1st wave flattening ST abnormally, increased QRS duration. **Respiratory System: Frequent:** pharyngitis, rhinitis, cough increased, dyspnea. **Infrequent:** pneumonia, epistaxis, asthma. **Rare:** hiccup, 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:** pruritus, skin acne, contact dermatitis, maculopapular rash, skin rash, skin ulcer, skin infection, skin discoloration, allergic dermatitis, psoriasis. **Digestive System: Frequent:** anorexia. **Infrequent:** increased salivation, increased appetite, gamma glutamyl transaminase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, tooth, tooth caries, facial acne, postnasal drip, reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema. **Rare:** glossitis, hematemesis, intestinal obstruction, ileus, melena, pancreatitis. **Cardiovascular System: Frequent:** palpitation. **Infrequent:** vasodilation, 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, atrial fibrillation, atrial block 1st degree, congestive heart failure, ST elevated, thrombophlebitis, 1st wave flattening ST abnormally, increased QRS duration. **Respiratory System: Frequent:** pharyngitis, rhinitis, cough increased, dyspnea. **Infrequent:** pneumonia, epistaxis, asthma. **Rare:** 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