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AUTHOR GUIDELINES 2002

Introduction

CNS Spectrums is an Index Medicus journal that publishes original scientific literature and reviews on a wide variety of neuroscientific topics of interest to the clinician. *CNS Spectrums* will publish 12 issues in 2002. As the immense prevalence of comorbid diseases among patients seen by psychiatrists and neurologists increases, these physicians will jointly diagnose and treat the neuropsychiatrically ill. Our mission is to provide these physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry; therefore, manuscripts that address crossover issues germane to neurology and psychiatry will be given immediate priority.

Scope of Manuscripts

CNS Spectrums will consider the following types of articles for publication:

Original Reports: Original reports present methodologically sound original data.

Reviews: Reviews are overview articles that summarize and synthesize the literature on various topics in a scholarly and clinically relevant fashion. Suitable topics include mood disorders, schizophrenia and related disorders, personality disorders, substance-use disorders, anxiety disorders, neuroscience, psychosocial aspects of psychiatry, child psychiatry, geriatric psychiatry, and other topics of interest to clinicians. Original flowcharts designed to aid the clinician in diagnosis and treatment will be considered for publication in reviews and are encouraged.

Case Reports: Single or multiple case reports will be considered for publication.

Letters to the Editor: Letters will be considered for publication.

Manuscript Submission

General information: Two copies of the manuscript with a letter on the author's letterhead should be submitted to Jack M. Gorman, Editor (or, in Europe, to Joseph Zohar, International Editor), c/o MedWorks Media, 333 Hudson Street, 7th Floor, New York, NY 10013; (F) 212.328.0600. Authors are also required to submit their manuscripts on computer disk in Microsoft Word format. Disks should be labeled with the word processing program, title of paper, and lead author's name. Accepted manuscripts and letters will be edited for clarity and style.

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Peer review: Authors must provide five names of particularly qualified potential reviewers with no conflict of interest in reviewing the work. Contact information, including complete address, phone, fax numbers, E-mail address, and affiliations, should be included. The corresponding author will be notified by the editors when a decision regarding acceptance has been made. Peer review is anonymous.

Manuscript Preparation

Length: Reviews and Original Reports should not exceed 5,000 words (excluding References). Letters should not exceed 1,500 words. Single Case Reports should not exceed 3,750 words and may be submitted with a photograph, if applicable. Diagnostic/treatment algorithms (see Reviews) should contain an extensive introduction, flowchart or series of graphs that fill 8–12 journal pages, and a concise summary.

Spacing: One space should be left after commas and periods. Manuscripts should be double-spaced.

Abstract: Authors must provide a brief abstract.

References: American Medical Association style. See the following examples:

1. Jones J. Necrotizing *Candida* esophagitis. *JAMA*. 1980;244:2190-2191.
2. Stryer L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1980:559-596.

Continuing Medical Education: Authors must submit four multiple-choice questions (two Type A and two Type K), with answers.

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Disclosure of Commercial Interests

Authors must include a statement about all forms of support, including grant and drug company support. Such information may, at the editor's discretion, be shared with reviewers. If the article is accepted for publication, the editors will consult with the authors as to whether this information should be included in the published paper.

Submission Checklist

- Original manuscript plus one copy, with cover letter on author's letterhead
- Copies of permission letters to reproduce previously published and unpublished material
- A brief abstract of the article
- Two CME multiple-choice questions with answers
- Disk labeled with the word processing program, title of paper, and lead author's name
- Names and addresses of five potential reviewers

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 of schizophrenic inpatients (See CLINICAL PHARMACOLOGY). The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically controlled. There is no general agreement on which clinical trials to use 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 possible 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 (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 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 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 therapy is available. There is no general agreement on specific pharmacological 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 permanent are believed to increase as the cumulative dose 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 be associated with an increase in the severity 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 not susceptible to other forms of therapy. In patients 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 therapy should be discontinued. 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 period, probably reflecting its α_1 -adrenoreceptor antagonist properties. Syncope was reported in 1 (1/22162) patients treated with SEROQUEL compared to 0 (0/206) on placebo and about 0.5% (1/2420) 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 to the target dose, a return to the previous dose in the titration schedule is appropriate. SEROQUEL should be used with particular caution in patients with known cardiovascular disease, including congestive heart failure, aortic stenosis, 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 association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients on long-term treatment with SEROQUEL. However, there is no evidence that SEROQUEL use had 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 appropriately 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 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.3% (1/206) on placebo and 0.4% (1/2420) 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. **Hydroxylation:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free plasma levels of the drug in patients with hepatic impairment. The therapeutic dose range 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 TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free plasma levels of the drug. **Thyroid Function:** In patients with hyperthyroidism, 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 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 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 feature 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 tumorogenesis 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 the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 8% for SEROQUEL compared to 1% for placebo. These elevations and 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 10% of patients on SEROQUEL compared to 1% 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. **Fragility:** One case of priapism in a patient receiving SEROQUEL has been reported to date. Appropriate care is advised when prescribing SEROQUEL for patients who are 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 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 risk of suicidal thoughts and actions has been observed in patients with a history 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 risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant illnesses is limited. SEROQUEL has not been evaluated or used in any approved clinical trials in patients with severe heart failure, 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 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 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. **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 antipsychotics, patients should be advised that if they are taking, or plan to take, any prescription or over-the-counter drugs, SEROQUEL 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 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 systematically 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 psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL should be used with caution in patients taking other antihypertensive medications. 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 (400 mg tid for 6 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). **Disagreement regarding quetiapine is not resolved.** **Other Antipsychotics:** Administration of multiple daily doses of haloperidol (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 indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** In a study of human toxicokinetics, the pharmacokinetics of quetiapine (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. **Lithium:** Concomitant administration of lithium (250 mg tid) with quetiapine (300 mg tid) did not alter steady-state pharmacokinetic parameters of either drug. **Antipyretic:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrene or urinary recovery of antipyrene metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrene. **Human Toxicology:** **Reproductive and 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. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 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 (800 mg/day) on a mg/m² basis (rats). 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 thyroid cancer is unknown. **Thyroid Function:** 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 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 prolactin-mediated. The mechanism of action of prolactin-induced 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 *S. typhimurium* bacterial gene mutation assays and in *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 not induce a statistically significant increase in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No increase in mutagenicity was observed 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 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 150 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 reproductive toxicity of quetiapine was evaluated in pregnant rabbits. Fetuses dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at oral 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. There was, however, evidence of embryofetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 150 mg/kg, or 0.6 and 1.8 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). There was an increased incidence of a minor soft tissue anomaly (carpal/larval laxity) 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 deaths) was observed at the high dose in the rat study and at all doses in the rabbit study. In a perinatal 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 perinatal study, there were increases in fetal doses and decreases in pupal weights in rats at doses of 100 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.

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Nursing Mothers: SEROQUEL was excreted in milk of lactating mothers 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 1000 patients who were included in the clinical trials, 11% (110) 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 15% 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:** Rash; **Respiratory System:** Rhinitis; **Special Senses:** Ear pain.

Adverse events which were 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, hyperaesthesia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia 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 placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose-response relationship between the incidence of adverse events and the increase in body weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial 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 EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hyperreflexia, 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 score. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial 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 EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hyperreflexia, 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 score. **Laboratory and Pathology:** An assessment of the effects of SEROQUEL on laboratory parameters 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 significantly greater incidence of weight gain on SEROQUEL (23%) compared to placebo (6%). **Laboratory and Pathology:** An assessment of the effects of SEROQUEL on laboratory parameters 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 significantly greater incidence of weight gain on SEROQUEL (23%) compared to placebo (6%). **Laboratory and Pathology:** An assessment of the effects of SEROQUEL on laboratory parameters to treat EPS. **Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (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 in 3- to 6-week placebo-controlled clinical trials with the premarketing evaluation 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 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:** hyperreflexia, dysarthria; **Inrequent:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, abnormal ocular movements, abnormal accommodation, hyperreflexia, tremor, inattention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatoniac reaction, hemiplegia; **Rare:** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** **Frequent:** flu syndrome; **Inrequent:** neck pain, pelvic pain, suicide attempt, malaise, chills, sinusitis, reaction, chills, face edema, monilia; **Rare:** abdomen enlarged. **Digestive System:** **Frequent:** anorexia; **Inrequent:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hiccups, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** **Frequent:** palpitation; **Inrequent:** 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, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased PDS duration. **Respiratory System:** **Frequent:** rhinitis, rhinorrhea, cough increased, dyspnea; **Inrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccups, hyperventilation. **Metabolic and Nutritional System:** **Frequent:** peripheral edema; **Inrequent:** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages:** **Frequent:** sweating; **Inrequent:** pruritis, acne, eczema, contact dermatitis, maculopapular rash, subconjunctival hemorrhage, skin ulcer; **Rare:** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** **Inrequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System:** **Frequent:** leukopenia; **Inrequent:** leukocytosis, anemia, hemolysis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; **Rare:** hemophysis, thrombocytopenia. **Endocrine System:** **Inrequent:** abnormal thyroid function tests, increased prolactin, hyperthyroidism; **Rare:** abnormality of thyroid function tests. **Genitourinary System:** **Inrequent:** abnormality of thyroid function tests, increased prolactin, hyperthyroidism; **Rare:** abnormality of thyroid function tests, increased prolactin, hyperthyroidism. **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely 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.

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

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



Well!

Accepted!

WELL!

Efficacy you look for in an atypical antipsychotic

- Proven to reduce positive and negative symptoms¹⁻⁴

ACCEPTED!

An excellent side-effect profile

- The only first-line atypical antipsychotic with an EPS* profile no different from placebo across the entire dosing range (up to 800 mg).^{1,2,5}

*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



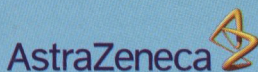
Seroquel[®]

quetiapine fumarate

25 mg, 100 mg, 200 mg & 300 mg tablets

Treatment patients can LIVE with!

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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Please see Brief Summary of full Prescribing Information on following page.

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