

Latency Costly, but Best in Daytime Sleepiness

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RANCHO MIRAGE, CALIF. In diagnosing a child with an extreme case of daytime sleepiness, there's no good substitute for the multiple sleep latency test. Dr. Timothy F. Hoban said at a conference on sleep disorders in infancy and childhood sponsored by the Annenberg Center for Health Sciences.

Although a simple clinical evaluation

can provide a fairly good indication as to whether the child has daytime sleepiness, it's often difficult to estimate how severe the problem is. "The multiple sleep latency test (MSLT) can help answer that question in an objective way that's been standardized and well validated," said Dr. Hoban of the sleep disorders center at the University of Michigan, Ann Arbor.

Unlike certain questionnaire-based assessments, the MSLT has been validated in children, and provides reliable results as

long as the child is at least 6 or 7 years old. However, the test is expensive and time consuming to perform and must be conducted in a sleep lab. The MSLT may be useful when a child has excessive daytime sleepiness but the clinical history, examination, and polysomnography reveal no specific cause. Dr. Hoban recommended judicious use of the MSLT in evaluations of sleep-disordered breathing, circadian rhythm disorders, narcolepsy, and other disorders of excessive sleepiness.

Developed initially at Stanford (Calif.) University in the 1970s, the MSLT has a simple premise: People who are sleepy will fall asleep faster than those who are not.

After a night of polysomnography to screen for some sleep disrupters and to ensure that the patient has had a good night's sleep, the child is given four or five chances to nap in a dark, quiet environment, with each nap separated by about 2 hours. If the child fails to fall asleep (as measured by EEG tracings) within 20 minutes, the nap opportunity ends. Otherwise the child is allowed to sleep for 15 minutes following the first epoch of sleep.

In addition to the latency of sleep, the MSLT records the presence of sleep-onset REM periods (SOREMPs). The presence of SOREMPs correlates strongly with the presence of narcolepsy. Narcoleptic patients also typically have a sleep latency of 5 minutes or less.

Normal adults have a sleep latency of about 15 minutes, but normal latencies in children can be much longer. Detailed studies have correlated mean sleep latency

with Tanner stage. Children in Tanner stage 1 take an average of 19 minutes to fall asleep, whereas those in stage 5 take about 16.6 minutes; older adolescents take a mean 15.7 minutes to fall asleep.

The MSLT has the advantage of being easily administered to school-age children; it also can be used to assess the response to treatment.

"The net result is that in preadolescent children you can have a sleep latency of 14 or 15 minutes that would be considered solidly normal by adult standards but substantially abnormal for a child," Dr. Hoban said.

In addition to being objective, standardized, and well validated, the MSLT has the advantage of being easily administered to school-age children and also can be used to assess the response to treatment. On the other hand, it's an expensive and time-consuming test, doubly so because it must be preceded by full-night polysomnography. It's sensitive to extraneous influences, such as certain sleep-disrupting medications like Ritalin or even excessive physical activity during the intervals between naps.

Dr. Hoban described a case that illustrated the value of the MSLT. The patient was a 16-year-old with a history of disabling sleepiness for several years. He had first been tested for what were thought to be seizures (that is, episodes characterized by staring or unresponsiveness followed by brief losses of posture from which he quickly recovered).

The patient's MSLT results were striking. "MSLTs this dramatic are very easy to score and recognize," Dr. Hoban said. His strong suspicion that the patient had narcolepsy was confirmed by further analysis of the young man's polysomnograph, which demonstrated frequent nighttime awakenings, another characteristic sign of narcolepsy.

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 seventeen placebo-controlled trials (median duration of 10 weeks) in elderly patients with dementia-related psychosis showed that the risk of death was 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 adjunctive 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 adjunctive therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunctive 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 in schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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

WARNINGS: 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 (quetiapine) 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 dysrhythmias). 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 cases where the clinical presentation includes both serious medical illness (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 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 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 reinduction 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 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, 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 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. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme, and associated with ketonuria, hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for 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 antidiabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some cases, syncope, especially during the initial dose-escalation period, probably reflecting its α_1 -adrenoreceptor antagonist properties. Syncope was reported in 1% (23/257) of the patients treated with SEROQUEL compared with 0% (0/607) on placebo and about 0.4% (2/529) 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 with the first therapeutic dose, a return to the next therapeutic dose on the schedule is appropriate. **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 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 appropriately sensitive methods, is recommended at initiation of treatment and at monthly intervals during chronic treatment. **Seizures:** During clinical trials, seizures occurred in 0.6% (182/302) 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 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 weeks of treatment and maintained with 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% (122/319) 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% (241/56) of SEROQUEL treated patients compared to 7% (12/205) 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. Hyperlipidemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicated 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 epidemiological 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 12% (60/500) for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-escalation. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunctive therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect their adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism 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 properties, or wearing heavy clothing. Heat stroke, rigidity, dysmimolysis 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. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for 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 in the 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 cautioned of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be advised 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. **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 and dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in a systematic manner when initiating ODS after a two-week period without treatment should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychiatric disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine:** 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 when used in combination with phenytoin. Carbamazepine: Coadministration of quetiapine (250 mg bid) and carbamazepine (400 mg bid) increased the mean oral clearance of quetiapine by 2-fold. **Valproic Acid:** Coadministration of quetiapine (150 mg bid) and valproic acid (500 mg bid) increased the mean oral clearance of quetiapine by 10%. **Lithium:** Coadministration of quetiapine (250 mg bid) and lithium (300 mg bid) had no effect on the steady-state pharmacokinetic parameters of lithium. **Antihypertensive Agents:** Administration of multiple daily doses up to 750 mg/day (on a bid schedule) of quetiapine to subjects with selected psychiatric disorders had no clinically relevant effect on the clearance of antihypertensive or urinary recovery of antihypertensive metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antihypertensives. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis: Carcinogenicity studies were conducted in F344 male and B6Wistar rats. Quetiapine was administered in the diet to mice at 20, 75, 250 and 750 mg/kg and to rats by gavage at doses of 0.3, 0.9, and 3.0 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose on a mg/m² basis (0.60 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. Mammary gland adenocarcinomas were statistically significantly increased in female rats at doses of 250 and 750 mg/kg or 1.5 and 4.5 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 renal 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 remains unknown. Antimutagenicity: Antimutagenicity studies have shown that quetiapine orally elevate prokaryotic levels of mutagenesis. Serum measurements in a 1-year toxicity study showed that quetiapine increased median sperm prokaryotic levels a maximum of 3.2- 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 relevance of this increased incidence of prolactin-mediated mammary gland tumors to rat is human risk is unknown (see Hyperprolactinemia in PRECAUTIONS, General). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vivo* mammalian gene mutation assay in *Neurospora crassa*. **Adverse Findings Observed in Preclinical Studies:** Quetiapine may have been used for all test species. Quetiapine did produce a reproductive no evidence of changes 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 oral 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. **Embryofetal Toxicity:** 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 plasma 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. This database includes 405 patients treated with SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunctive therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 814 patient-years. Refer to the full Prescribing Information for details of adverse event data collection. **ADVERSE FINDINGS OBSERVED IN CONTROL TRIALS:** **ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS:** **Bipolar Mania:** Overall, discontinuations due to adverse events were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunctive 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 prescriber should be aware that the figures in the tables and tabulations in the full Prescribing Information cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence in the population studied. Table 1, in the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) 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, Digestive: Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transpeptidase Increased, Metabolic and Nutritional: Weight Gain, SGPT Increased, SGOT Increased, Nervous: Agitation, Somnolence, Dizziness, Anxiety, 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, hypotension, hypertension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresis, peripheral edema, sweating, 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 from the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, 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) as adjunctive 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 (Adjunctive Therapy):** Body as a Whole: Headache, Asthenia, Abdominal Pain, Back Pain, Cardiovascular: Postural Hypotension, Digestive: Dry Mouth, Constipation, Metabolic and Nutritional: Weight Gain, Nervous: Somnolence, Dizziness, Tremor, Agitation, Respiratory: Pharyngitis. 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%). 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 of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were analyzed for dose-relatedness of adverse events. Logistic regression analysis 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 spontaneously complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertension, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS, General). Administration of multiple daily doses of quetiapine (400 mg bid) resulted in a 20% decrease in body weight when compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunctive therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo. **ECG Changes:** Between group comparisons for pooled studies in schizophrenia trials the proportions of patients meeting a weight gain criterion of $\geq 2\%$ of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). 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