

Varenicline, Antidepressants Help Smokers Quit

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Varenicline triples the likelihood that a smoker will quit, compared with placebo, and bupropion and nortriptyline double the odds, according to a pair of evidence reviews published Jan. 24.

The Cochrane Collaboration review of varenicline, a nicotine receptor agonist, based its findings on five randomized controlled trials that included more than

4,900 people, more than 2,400 of whom took varenicline (Cochrane Database Syst. Rev. 2007 Jan. 24 [Epub doi: 10.1002/14651858.CD006103.pub2]).

Findings were validated in all of the studies included in the meta-analysis by measuring exhaled carbon monoxide levels.

At 12 months, the pooled odds of the smokers taking varenicline were 3.22 times as great as those taking placebo to have continuously abstained from smoking, according to the reviewers, led by Kate Cahill,

of the primary health care department at Oxford University (England). At 12 weeks, patients taking varenicline were 4.07 times as likely as those taking a placebo to have continuously abstained from smoking, and at 24 weeks, 3.53 times as likely, according to the reviewers. However, the reviewers said more comparisons with other smoking-cessation strategies are needed.

Three of the studies did compare varenicline with bupropion, an antidepressant. At 12 months, the smokers tak-

ing varenicline were 66% more likely to have abstained from smoking.

The number of smokers needed to treat with varenicline to achieve one more successful quitter is eight, compared with placebo, the reviewers write. By comparison, nicotine replacement therapy requires 20 and bupropion 15.

The reviewers found only one trial of another nicotine agonist, cytisine, that met the reviews' inclusion criteria. That trial increased by 77% the chances that a smoker will abstain from smoking 2 years after treatment.

For varenicline, a derivative of cytisine, the most serious adverse effects were nausea, at rates topping 50%, with discontinuation rates as high as 9.5%. Two of the trials found an increased nausea rate with higher doses, with 17.5% of those taking a



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DR. HUGHES

0.3-mg dose daily reporting nausea to 52% of those taking a 1-mg dose twice a day.

No treatment-related deaths were reported for any patients taking varenicline, although nonfatal serious adverse events occurred in all of them. However, all of the studies judged varenicline to be safe and well-tolerated at all dosages and time periods.

All of the varenicline studies meeting the reviewers' inclusion criteria were funded by Pfizer Inc., which manufactures the medication under the brand name Chantix.

The separate review of antidepressants, an update to an earlier report, identifies 17 new randomized controlled trials since 2004 using the medications for smoking cessation (Cochrane Database Syst. Rev. 2007 Jan. 24 [Epub doi: 10.1002/14651858.CD000031.pub3]), bringing the total number of trials to 53.

In 31 trials testing bupropion as a sole medication, testing a total of 10,000 patients, the drug increased by 94% the chances that a smoker will quit, compared with a placebo, according to the reviewers, led by Dr. John R. Hughes, a professor in the department of psychiatry at the University of Vermont, Burlington.

In 17 trials with a 12-month follow-up period, smokers who take bupropion were 83% more likely than those on placebo to have abstained from smoking. The reviewers said evidence is insufficient to favor bupropion over nicotine replacement therapy or to add bupropion to nicotine replacement therapy.

Nortriptyline also doubles odds of success. Six trials with 975 patients show those taking nortriptyline are 2.34 times more likely to quit, compared with placebo. Other antidepressants did not demonstrate a long-term effect, the reviewers said.

The most serious side effect of the use of the antidepressants for smoking cessation was a 1 in 1,000 risk of seizures. ■

SEROQUEL® (quetiapine fumarate) Tablets

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

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% 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:** Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs:** **Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrene:** 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. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** **Carcinogenesis:** Carcinogenicity studies were conducted in C57BL mice and Wistar rats. There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg 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 all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m² basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. 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 relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in PRECAUTIONS, General). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vivo* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all test strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased 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 50 mg/kg, or 0.6 times the maximum human dose on a mg/m² basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m² basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m² basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 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 embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m² basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m² basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.1, and 0.24 times the maximum human dose on a mg/m² basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use:** Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or older. 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 when compared to younger patients.

ADVERSE REACTIONS: The information below is derived from a clinical trial database for SEROQUEL consisting of over 3700 patients. Of these approximately 3700 subjects, approximately 3400 (2300 in schizophrenia, 405 in acute bipolar mania, and 698 in bipolar depression) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 992.6 patient-years. Refer to the full Prescribing Information for details of adverse event data collection. **Adverse Findings Observed in Short-Term, Controlled Trials: Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Bipolar Disorder:** Depression: Overall, discontinuations due to adverse events were 12.3% for SEROQUEL 300 mg vs 19.0% for SEROQUEL 600 mg and 5.2% for placebo. Mania: Overall, discontinuations due to adverse events were 5.7% for SEROQUEL vs 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs 5.9% for placebo in adjunct therapy. **Schizophrenia:** Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence (0.8% vs 0% for placebo) and hypotension (0.4% vs 0% for placebo) were considered to be drug related (see PRECAUTIONS). **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 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, Back Pain, Fever. **Cardiovascular:** Tachycardia, Postural Hypotension. **Digestive:** Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl Transpeptidase Increased. **Metabolic:** Weight Gain, SGPT increased, SGOT increased. **Nervous:** Agitation, Somnolence, Dizziness, Anxieties, **Respiratory:** Pharyngitis, Rhinitis; **Skin and Appendages:** Rash. **Special Senses:** Amblyopia. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). († Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonnia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.) 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) 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; **Metabolic and Nutritional:** Weight Gain; **Nervous:** Somnolence, Dizziness, Tremor, Agitation; **Respiratory:** Pharyngitis. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). († Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.) Table 3, in the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 8-weeks) of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 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 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression: Gastrointestinal**

Disorders: Dry Mouth, Constipation, Dyspepsia, Vomiting; **General Disorders and Administrative Site Conditions:** Fatigue; **Metabolism and Nutrition Disorders:** Increased Appetite; **Nervous System Disorders:** Sedation, Somnolence, Dizziness, Lethargy; **Respiratory, Thoracic, and Mediastinal Disorders:** Nasal Congestion. 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 dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%). († Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.) 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:** 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, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse events potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight gain criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials 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. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Events are categorized by body system and listed in order of decreasing frequency according to the following 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:** hypertonnia, dysarthria; **Infrequent:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonie reaction, hemiplegia; **Rare:** aphasia, buccalossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased, neuralgia, stuttering, subdural hematoma. **Body as a Whole: Frequent:** flu syndrome; **Infrequent:** neck pain, pelvic pain, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged. **Digestive System: Frequent:** anorexia; **Infrequent:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, 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; **Infrequent:** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System: Frequent:** pharyngitis, rhinitis, cough increased, dyspnea; **Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccups, hyperventilation. **Metabolic and Nutritional System: Frequent:** peripheral edema; **Infrequent:** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System: Frequent:** sweating; **Infrequent:** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System: Frequent:** dysmenorrhea, vaginitis, urinary incontinence, metrorrhagia, impotence, dysuria, vaginal moniliasis, abnormal ejaculation, cystitis, urinary frequency, amenorrhea, female lactation, leukorrhea, vaginal hemorrhage, vulvovaginitis, orchitis; († adjusted for gender) **Rare:** gynecomastia, nocturia, polyuria, acute kidney failure. **Special Senses: Frequent:** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System: Frequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System: Frequent:** leukopenia; **Infrequent:** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia, lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocytopenia. **Endocrine System: Frequent:** hypothyroidism, diabetes mellitus; **Rare:** hyperthyroidism. **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS). **DRUG ABUSE AND DEPENDENCE: Controlled Substance Class:** SEROQUEL is not a controlled substance. **Physical and Psychologic dependence:** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior. **OVERDOSAGE: Human experience:** Experience with SEROQUEL in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation. **Management of Overdosage:** In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine) should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade. In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers. SEROQUEL is a trademark of the AstraZeneca group of companies ©AstraZeneca 2006. AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850 Made in USA 30417-00 Rev. 10/06