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ORIGINAL RESEARCH

Long-Term, Open-Label Venlafaxine Extended-Release Treatment in Children and Adolescents with Major Depressive Disorder

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Retrospective Case Review of Lamotrigine Use for Affective Instability of Borderline Personality Disorder

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Important Safety Information

- SEROQUEL is indicated for the treatment of depressive episodes in bipolar disorder; acute manic episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex; and schizophrenia. Patients should be periodically reassessed to determine the need for treatment beyond the acute response
- **Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis. (See Boxed Warning)**
- **Suicidality in children and adolescents—antidepressants increased the risk of suicidal thinking and behavior (4% vs 2% for placebo) in short-term studies of 9 antidepressant drugs in children and adolescents with major depressive disorder and other psychiatric disorders. Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients. (See Boxed Warning)**
- 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 hyperpyrexia, 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 management of NMS should include immediate discontinuation of antipsychotic drugs
- Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of TD
- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing
- Precautions include the risk of seizures, orthostatic hypotension, and cataracts. 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
- The most commonly observed adverse events associated with the use of SEROQUEL monotherapy versus placebo in clinical trials for schizophrenia and bipolar disorder were dry mouth (9-44% vs 3-13%), sedation (30% vs 8%), somnolence (18-28% vs 7-8%), dizziness (11-18% vs 5-7%), constipation (8-10% vs 3-4%), SGPT increase (5% vs 1%), dyspepsia (5-7% vs 1-4%), lethargy (5% vs 2%), and weight gain (5% vs 1%). The most commonly observed adverse events associated with the use of SEROQUEL versus placebo in clinical trials as adjunct therapy with lithium or divalproex in bipolar mania were somnolence (34% vs 9%), dry mouth (19% vs 3%), asthenia (10% vs 4%), constipation (10% vs 5%), abdominal pain (7% vs 3%), postural hypotension (7% vs 2%), pharyngitis (6% vs 3%), and weight gain (6% vs 3%)

Please see Brief Summary of Prescribing Information, including Boxed Warnings, on adjacent pages.

References: 1. Data on file, DA-SER-51. 2. SEROQUEL Prescribing Information.

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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. Analysis of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.8% 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.

Suicidality in Children and Adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients. [See WARNINGS and PRECAUTIONS, Pediatric Use]. Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. [See WARNINGS and PRECAUTIONS].

INDICATIONS AND USAGE: Bipolar Disorder: SEROQUEL is indicated for the treatment of both depressive episodes associated with bipolar disorder and acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex. Depression: The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients. Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks. Mania: The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy 3 weeks in adjunct therapy. The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Schizophrenia: SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic 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). **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms. Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. 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. Families and caregivers of adults being treated for depression should be similarly advised. It should be noted that SEROQUEL is not approved for use in treating any indications in the pediatric population. **Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia (TD):** 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 TD is unknown. The risk of developing TD 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 TD, 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 TD. 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 producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of TD 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 ketoacidosis or 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 symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose titration period, probably reflecting its α_1 -adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with 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, hypotension, and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid, by increasing the duration of titration to the target dose, a return to the previous dose in a titration schedule is appropriate. **Contraception:** The development of contraceptives was observed in association with quetiapine treatment in chronic dog studies. **Lactation:** Data 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 lactation changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam, at 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 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) 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 to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. 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 0.7% (26/3498) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL treated patients compared to 3% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 7 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥ 240 mg/dL and triglycerides ≥ 200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-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. In bipolar depression trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% for SEROQUEL and 2% for placebo. **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 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 adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% 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. **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, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. 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. In 2 eight-week clinical studies in patients with bipolar depression (N=1048) the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo. (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg 9/348, 2.6%; Placebo, 7/347, 2.0%). **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **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 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 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 tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

continued

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 bid). 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/6 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-year 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 tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *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, 0.12, 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 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 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 Transaminase Increased; **Metabolic:** Weight Gain, SGPT increased, SGOT increased; **Nervous:** Agitation, Somnolence, Dizziness, Anxiety; **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, hypotonia, 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 (e.g., 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 $\geq 7\%$ 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 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 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 0.8% (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:** hypotonia, 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, catatonic reaction, hemiplegia; **Rare:** aphasia, buccoglossal 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 transaminase 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:** vasodilation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System: Frequent:** pharyngitis, rhinitis, cough increased; **Dyspnea; Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccup, hyperventilation. **Metabolic and Nutritional System: Frequent:** peripheral edema; **Infrequent:** weight loss, alkaline phosphatase increased, 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: Infrequent:** 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:** glycosuria*, nocturia, polyuria, acute kidney failure. **Special Senses: Infrequent:** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System: Infrequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System: Frequent:** leukopenia; **Infrequent:** leukocytosis, anemia, echthymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocytopenia. **Endocrine System: Infrequent:** 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 Psychological 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 overdose, 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 QTc-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic blocking properties of bromylumolol 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.

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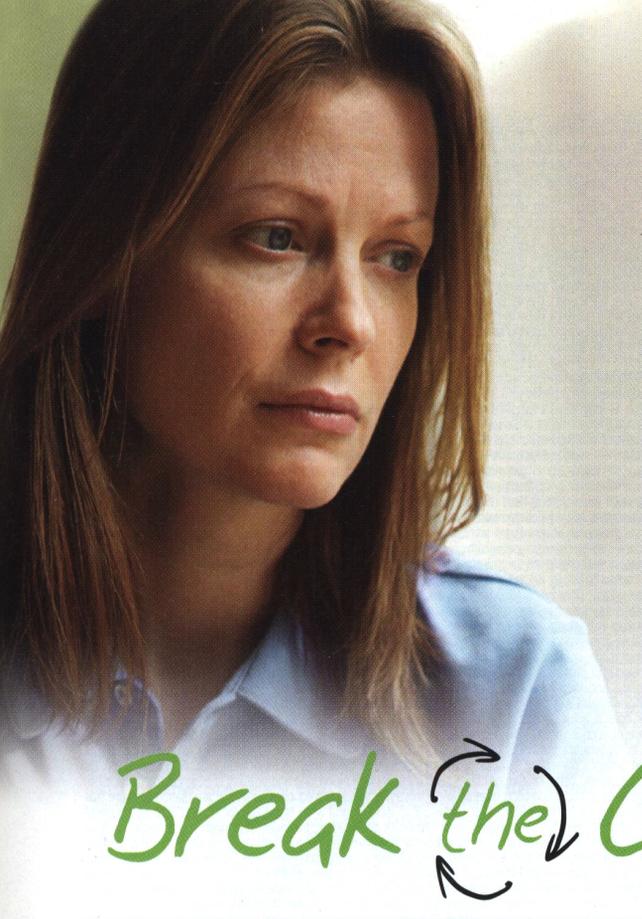
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BPA member since July 2005.

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Still depressed?

- Anxiety, insomnia, low energy
- Currently on an SSRI
- Still suffering

It may be time to make a change

Break *the* Cycle with EFFEXOR XR

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients.

- EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).
- Adult and pediatric patients taking antidepressants can experience worsening of their depression and/or the emergence of suicidality. Patients should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose. Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.

- The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually.

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VENLAFAXINE HCl
EFFEXOR XR® EXTENDED
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The change they deserve.

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BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist into significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS AND DOSAGE AND ADMINISTRATION**). Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represents such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI.** These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. **Serotonin Syndrome**—The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **Mydriasis**—Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS: General**—**Discontinuation of Treatment with Effexor XR.** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, vertigo, tremor, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. **Insomnia and Nervousness:** Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to discontinuation in 1% of both depressed patients with Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0.9% of SAD and PD patients. **Changes in Weight: Adult Patients:** In short-term MDD trials, 7% of Effexor XR patients had $\geq 5\%$ loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had $\geq 7\%$ loss of body weight, and 0.3% discontinued for weight loss. In 12-week SAD trials, 3% of Effexor XR patients had $\geq 7\%$ loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had $\geq 7\%$ loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. **Pediatric Patients:** Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P < 0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P < 0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥ 12 years old. **Changes in Height: Pediatric Patients:** In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm ($n=122$), while placebo patients grew an average of 1.0 cm ($n=132$); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm ($n=146$), while placebo patients grew an average of 0.7 cm ($n=147$). During the 16-week, placebo-controlled SAD study, both the Effexor XR ($n=109$) and the placebo ($n=112$) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥ 12 years old. **Changes in Appetite: Adult Patients:** Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD

studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. **Pediatric Patients:** Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. **Activation of Mania/Hypomania:** Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. **Hypomania:** Hypomania and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. **Seizures:** In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. **Abnormal Bleeding:** Abnormal bleeding (most commonly ecchymosis) has been reported. **Serum Cholesterol Elevation:** Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. **Use in Patients With Concomitant Illness:** Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients with underlying medical conditions that may be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers and other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexor.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions—Alcohol:** A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. **Cimetidine:** Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. **Diazepam:** A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. **Haloperidol:** Venlafaxine decreased total oral dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 89%, but the haloperidol elimination half-life was unchanged. **Lithium:** A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. **Drugs Highly Bound to Plasma Proteins:** Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. **Drugs That Inhibit Cytochrome P450 Isoenzymes:** CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. **Drugs Metabolized by Cytochrome P450 Isoenzymes:** Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. **Imipramine:** Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} , and $t_{1/2}$ increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUC increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. **Risperidone:** Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4:** Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. **Indinavir:** In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max} . Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2:** Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9:** Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19:** Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see **Diazepam** above). **MAOIs:** See **CONTRAINDICATIONS** and **WARNINGS. CNS-Active Drugs:** Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans** (see **WARNINGS: Serotonin Syndrome**): Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. **Electroconvulsive Therapy (ECT):** There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis:** There was no increase in tumors in mice and rats given up to 7 times the maximum recommended human dose (MRHD) on a mg/m² basis. **Mutagenesis:** Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in *Salmonella* bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. **Impairment of Fertility:** No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy—Teratogenic Effects—Pregnancy Category C:** Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. **Nonteratogenic Effects:** Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNINGS** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS—General, Changes in Height and Changes in Weight**). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant

were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS: Associated with Discontinuation of Treatment**—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. **Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD**—**Body as a Whole**: asthenia, headache, flu syndrome, accidental injury, abdominal pain. **Cardiovascular**: vasodilatation, hypertension, palpitation. **Digestive**: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. **Metabolic/Nutritional**: weight loss. **Nervous System**: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. **Respiratory System**: pharyngitis, yawn, sinusitis. **Skin**: sweating. **Special Senses**: abnormal vision. **Urogenital System**: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. **Vital Sign Changes**: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). **Laboratory Changes**: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR**—N=6,870. "Frequent"—events occurring in at least 1/100 patients; "infrequent"—1/100 to 1/1,000 patients; "rare"—fewer than 1/1,000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypertension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary aneurysm, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pailor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distention, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and Lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; Rare: eosinophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia, hypochlosterolemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, toricollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hyperventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, nirosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastrasia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, uterolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonias, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease (including pulmonary eosinophilia), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS AND WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C025, revised August 2006.

Take a closer look at Dialogues

Time to Talk™

Dialogues is a unique patient support and education program that is designed to help you foster successful therapy

Dialogues offers patients access to a call center to speak with a health care provider for patient support and education to reinforce your efforts

Dialogues supplies feedback and updates about these patient calls to you, their physician

Encourage your **EFFEXOR XR** patients to enroll in **Dialogues** by calling 866-313-3737 — and you can visit mddpatientsupport.com

- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

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VENLAFAXINE HCl
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The change they deserve.

Please see brief summary of Prescribing Information on adjacent pages.

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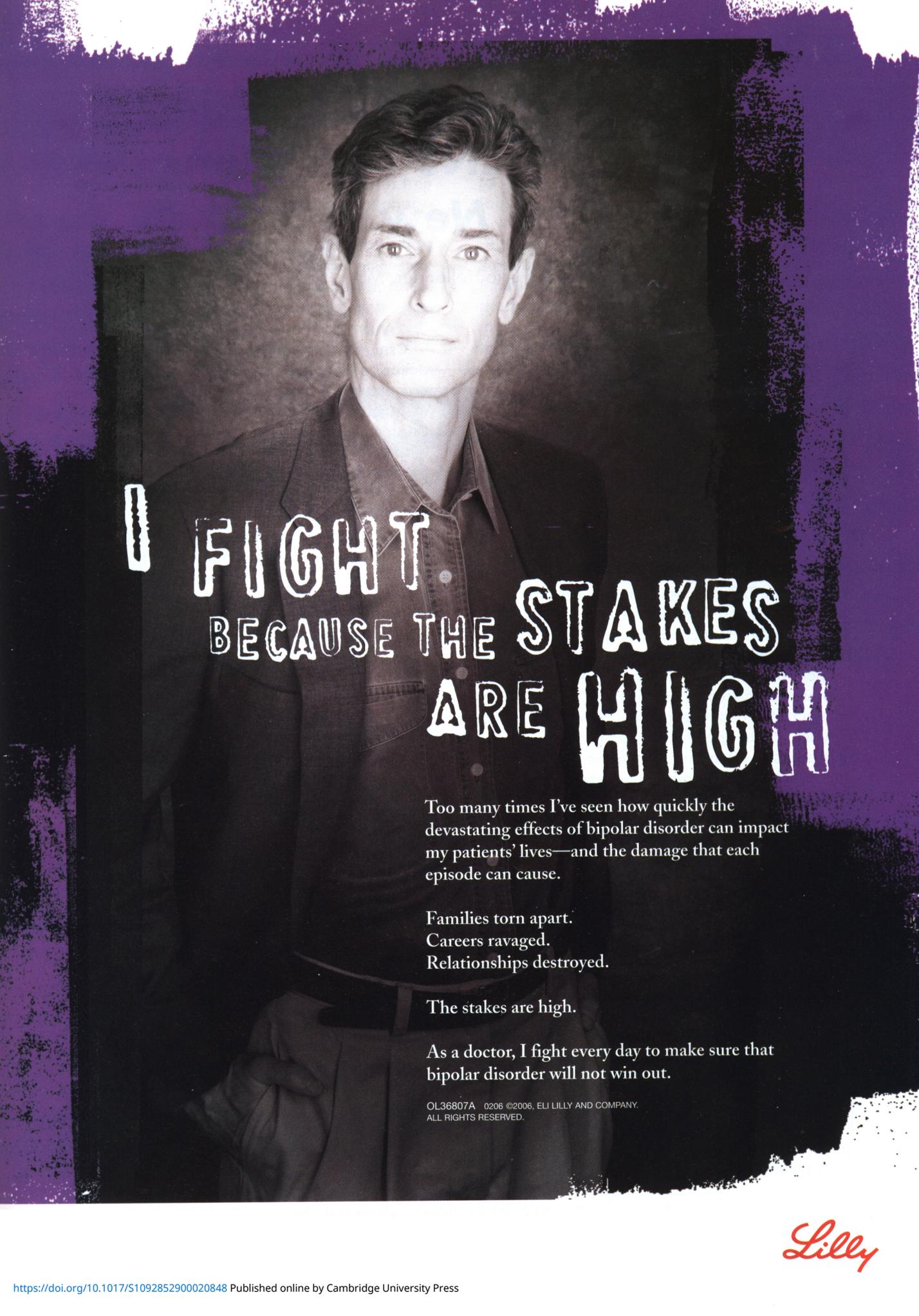
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MISSION

CNS Spectrums' editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.

This month's issue of *CNS Spectrums*, as well as a host of educational resources, enduring materials, and archived issues, is available at www.cnsspectrums.com.



**FIGHT
BECAUSE THE STAKES
ARE HIGH**

Too many times I've seen how quickly the devastating effects of bipolar disorder can impact my patients' lives—and the damage that each episode can cause.

Families torn apart.
Careers ravaged.
Relationships destroyed.

The stakes are high.

As a doctor, I fight every day to make sure that bipolar disorder will not win out.

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