



**Bipolar
depression
doesn't just
affect you.**

**It can
consume
you.**

SEROQUEL XR is an option proven effective for treating bipolar depression.

It's easy to feel like you're fading into the background when you're living with bipolar depression. SEROQUEL XR has been proven to work alone to effectively treat bipolar depression. And for many people, it's just one pill, once a day. Bipolar depression doesn't have to consume you. Talk to your doctor. Understand your options. And discuss whether XR—SEROQUEL XR—is right for you. To learn more, visit seroquelXR.com

Important Safety Information About SEROQUEL XR

Elderly patients with dementia-related psychosis (having lost touch with reality due to confusion and memory loss) treated with this type of medicine are at an increased risk of death, compared to placebo (sugar pill). SEROQUEL XR is not approved for treating these patients.

Antidepressants have increased the risk of suicidal thoughts and actions in some children, teenagers, and young adults. Patients of all ages starting treatment should be watched closely for worsening of depression, suicidal thoughts or actions, unusual changes in behavior, agitation, and irritability. Families and caregivers should watch patients daily and report these symptoms immediately to the physician. SEROQUEL XR is not approved for patients under the age of 18 years.

- High blood sugar and diabetes have been reported with SEROQUEL XR and medicines like it. If you have diabetes or risk factors such as obesity or a family history of diabetes, ask your doctor about checking your blood sugar before starting SEROQUEL XR and regularly throughout treatment. If you develop symptoms of high blood sugar or diabetes, such as excessive thirst or hunger, increased urination, or weakness, contact your doctor. Complications from diabetes can be serious and even life threatening.
- Increases in triglycerides and in LDL (bad) cholesterol and decreases in HDL (good) cholesterol have been reported with SEROQUEL XR. Your doctor should check your cholesterol levels before you start SEROQUEL XR and during therapy.
- Weight gain has been reported with SEROQUEL XR. Your doctor should check your weight regularly.
- A rare, but potentially fatal, side effect reported with SEROQUEL XR and medicines like it is neuroleptic malignant syndrome (NMS). Tell your doctor if you have very high fever; rigid muscles; shaking; confusion; sweating; changes in pulse, heart rate, or blood pressure; or muscle pain and weakness because treatment should be stopped if you have NMS.
- Another serious side effect reported with SEROQUEL XR and medicines like it is tardive dyskinesia (TD)—uncontrollable movements of the face, tongue, or other parts of the body. TD may become permanent, and the risk of TD is believed to increase as the length of time on and the amount of these medications increase. While TD can develop in patients taking low doses for short periods, this is much less common. There is no known treatment for TD, but it may go away partially or completely if treatment is stopped.
- Before starting treatment, tell your doctor if you have high prolactin levels or have a history of, or are at risk for, seizures or a low white blood cell (WBC) count. An eye exam for cataracts is recommended at the beginning of treatment and every 6 months thereafter.

- Other risks include feeling dizzy or lightheaded upon standing, or having trouble swallowing. Tell your doctor if you experience any of these.
- Suicidal thoughts or actions may occur; tell your doctor if you have thoughts about death or suicide.
- Since drowsiness has been reported with SEROQUEL XR, you should not participate in activities such as driving or operating machinery until you know that you can do so safely. Avoid drinking alcohol while taking SEROQUEL XR because SEROQUEL XR increases the effects of alcohol. Avoid becoming overheated or dehydrated while taking SEROQUEL XR.
- Common side effects: The most common side effects are drowsiness, dry mouth, increases in cholesterol and triglycerides, constipation, upset stomach, dizziness, a sudden drop in blood pressure upon standing, weight gain, increased hunger, tiredness, increases in blood sugar, difficulty speaking, and stuffy nose.

This is not a complete summary of safety information. Please discuss the full Prescribing Information for prescription SEROQUEL XR with your health care provider.

Indications

SEROQUEL XR is a once-daily tablet approved to treat acute depressive episodes in bipolar disorder; acute manic or mixed episodes in bipolar disorder alone or when added to lithium or divalproex; and long-term maintenance of bipolar disorder when added to lithium or divalproex.

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For a free doctor conversation guide, visit seroquelXR.com or call 1-866-331-3010.

If you're without prescription coverage and can't afford your medication, AstraZeneca may be able to help. For more information, please visit seroquelXR.com

Bipolar depression doesn't have to consume you.

Once-daily
SEROQUEL XR[®]
quetiapine fumarate
extended-release tablets

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AstraZeneca 

Please read this summary carefully and then ask your doctor about SEROQUEL XR. No advertisement can provide all the information needed to determine if a drug is right for you. This advertisement does not take the place of careful discussions with your doctor. Only your doctor has the training to weigh the risks and benefits of a prescription drug.

SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets

BRIEF SUMMARY: This summary provides important information about SEROQUEL XR. For more information, please ask your doctor about the full prescribing information and discuss it with him or her. The full Prescribing Information is available at www.SEROQUELXR.com or by calling 1-800-236-9903.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seven placebo-controlled trials (total duration of 18 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 18-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.5% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis (see Warnings and Precautions).

SUCIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24. There was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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 XR is not approved for use in pediatric patients (see Warnings and Precautions).

INDICATIONS AND USAGE

Bipolar Disorder

SEROQUEL XR is indicated for the treatment of:

- acute depressive episodes associated with bipolar disorder
- acute manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or divalproex therapy and
- maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

DOSEAGE AND ADMINISTRATION

SEROQUEL XR Tablets should be swallowed whole and not split, chewed or crushed. SEROQUEL XR should be taken without food or with a light meal.

Bipolar Depression: Usual Dose for Acute Treatment - administer once daily in the evening starting with 50 mg per day and increasing twice to reach 300 mg per day by Day 4.

Bipolar Mania: Usual Dose for Acute Monotherapy or Adjunct Therapy (with lithium or divalproex) - administer once daily in the evening starting with 300 mg on day 1, 600 mg on day 2 and adjust between 400 mg - 800 mg per day thereafter depending on the clinical response and tolerance of the individual patient.

Bipolar Maintenance: Continue treatment at the dosage required to maintain symptom remission.

Dosing in Special Populations: Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see Use in Specific Populations). When indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on SEROQUEL XR 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the response and tolerance of the individual patient.

Patients with hepatic impairment should be started on SEROQUEL XR 50 mg/day. The dose can be increased daily in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance of the patient.

Re-initiation of Treatment in Patients Previously Discontinued:

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting therapy of patients who have been off SEROQUEL XR for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off SEROQUEL XR for less than one week, gradual dose escalation may not be required and the maintenance dose may be reinitiated.

Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets

Patients who are currently being treated with SEROQUEL (immediate release formulation) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Switching from Antipsychotics

There are no systematically collected data to specifically address switching patients from other antipsychotics to SEROQUEL XR, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate SEROQUEL XR therapy in place of the next scheduled injection. The need for continuing existing extrapyramidal syndrome medication should be re-evaluated periodically.

CONTRAINDICATIONS

Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL XR (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis (see **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 medication, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24. There was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are as follows: <18 years of age—14 additional cases compared to placebo; 18-24 years of age—5 additional cases compared to placebo; 25-64 years of age—1 fewer case compared to placebo; ≥65 years of age—6 fewer cases compared to placebo.

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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.

Families and caregivers of 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 healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mania/mixed episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately 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.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketonuria or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increase in 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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions 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 (e.g., 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.

Adults: In a 2-8 week placebo-controlled randomized withdrawal clinical trial for bipolar maintenance, mean exposure of 213 days for SEROQUEL (846 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +6.0 mg/dL for quetiapine and -0.05 mg/dL for placebo. The exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dL) for patients more than 8 hours since a meal (however, some patients may not have been excluded from eating intake from meals during fasting period) was 18.0 per 100 patient years for SEROQUEL (10.7% of patients; n=556) and 9.5 for placebo per 100 patient years (4.6% of patients; n=581).

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a placebo-controlled quetiapine monotherapy study of adolescent patients (13-17 years of age) with schizophrenia (8 weeks duration), the mean change in fasting glucose levels for SEROQUEL compared to placebo was -6.75 mg/dL vs. -1.70 mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescent patients (10-17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for quetiapine compared to placebo was 3.82 mg/dL vs. -1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level (< 100 mg/dL) or a baseline borderline fasting glucose level (≥ 100 mg/dL and < 126 mg/dL) had a treatment-emergent blood glucose level of ≥ 126 mg/dL.

Hyperlipidemia

Adults: In clinical trials with SEROQUEL XR the percentage of patients with the following shifts from normal baseline to clinically significant levels of cholesterol and triglycerides have been reported (see **Adverse Reactions**):

Schizophrenia (30 weeks duration):

9% of patients on SEROQUEL XR had cholesterol ≥ 240 mg/dL vs 9% of patients on placebo. 18% of patients on SEROQUEL XR had triglycerides ≥ 200 mg/dL vs 5% of patients on placebo.

Bipolar Depression Trial (6 weeks duration)
7% of patients on SEROQUEL XR had Cholesterol ≥ 240 mg/dL vs 3% of patients on placebo. 8% of patients on SEROQUEL XR had Triglycerides ≥ 200 mg/dL vs 8% of patients on placebo.

Bipolar Mania Trial (3 weeks duration)
7% of patients on SEROQUEL XR had Cholesterol ≥ 240 mg/dL vs 4% of patients on placebo. 15% of patients on SEROQUEL XR had Triglycerides ≥ 200 mg/dL vs 6% of patients on placebo.

Children and Adolescents:
Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In clinical trials with SEROQUEL, the percentage of patients with the following shifts from Normal Baseline to Clinically Significant Levels of cholesterol and triglycerides have been reported.

Schizophrenia Trial (13-17 years, 6 weeks duration)
12% of patients on SEROQUEL XR had Cholesterol ≥ 240 mg/dL vs 2% of patients on placebo. 17% of patients on SEROQUEL XR had Triglycerides ≥ 200 mg/dL vs 8% of patients on placebo.

Bipolar Mania Trial (13-17 years, 3 weeks duration)
10% of patients on SEROQUEL XR had Cholesterol ≥ 240 mg/dL vs 3% of patients on placebo. 22% of patients on SEROQUEL XR had Triglycerides ≥ 200 mg/dL vs 13% of patients on placebo.

Weight Gain
Adults: In clinical trials with SEROQUEL XR the following increases in weight have been reported.

Proportion of Patients with Weight Gain $\geq 7\%$ of Body Weight (Adults)
Schizophrenia Trial (6 weeks duration)
10% of patients on SEROQUEL XR vs 5% of patients on placebo.

Bipolar Mania Trial (3 weeks duration)
5.1% of patients on SEROQUEL XR vs 0% of patients on placebo.

Bipolar Depression Trial (6 weeks duration)
8.2% of patients on SEROQUEL XR vs 0.6% of patients on placebo.

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 significant greater incidence of weight gain for SEROQUEL XR (23%) compared to placebo (9%).

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In two clinical trials with SEROQUEL XR, one in bipolar mania and one in schizophrenia, reported increases in weight are included below. When treating pediatric patients with SEROQUEL XR for any indication, weight gain should be assessed against that expected for normal growth. The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group and in the bipolar mania trial it was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group.

Proportion of Patients with Weight Gain $\geq 7\%$ of Body Weight (Children and Adolescents)
Schizophrenia Trial (6 weeks duration)
21% of patients on SEROQUEL XR vs 7% of patients on placebo.

Bipolar Mania Trial (3 weeks duration)
12% of patients on SEROQUEL XR vs 0% of patients on placebo.

In an observational study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL XR. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients gained $\geq 7\%$ of their body weight, not adjusted for normal growth. In order to adjust for normal growth, over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change. 18.2% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

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 quetiapine. Rare cases of NMS have been reported with quetiapine. 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 (myoglobinuria) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs including quetiapine. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely. If antipsychotic treatment is withdrawn, antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL XR should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL XR, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

Orthostatic Hypotension
Quetiapine 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 0.3% (4/1339) of the patients treated with SEROQUEL XR, compared with 0.3% (2/619) on placebo. Syncope was reported in 1% (28/2265) of the patients treated with SEROQUEL XR, compared with 0.2% (2/954) on placebo. Orthostatic hypotension, dizziness, and syncope may lead to falls.

Quetiapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Leukopenia, Neutropenia and Agranulocytosis
In clinical trials and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including SEROQUEL XR. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1500/mm^3$) should discontinue SEROQUEL XR and have their WBC followed until recovery [see **Adverse Reactions**].

Cataracts
The development of cataracts was observed in association with quetiapine treatment in chronic dog studies. Lens changes have also been observed in patients during long-term quetiapine treatment, but a causal relationship to quetiapine use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment not shortly thereafter, and at 6-month intervals during chronic treatment.

Seizures
During clinical trials with SEROQUEL XR, seizures occurred in 0.1% (1/1239) of patients treated with SEROQUEL XR compared to 0.5% (3/619) on placebo. During clinical trials with SEROQUEL XR, seizures occurred in 0.5% (20/3480) of patients treated with SEROQUEL XR compared to 0.2% (2/954) on placebo. As with other antipsychotic quetiapine fumarate 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.

Hydroxydation
Adults: In SEROQUEL XR clinical trials, 0.5% (4/806) of patients on SEROQUEL XR vs. 0% (0/252) on placebo experienced decreased free thyroxine and 2.7% (2/1768) on SEROQUEL XR vs. 1.2% (3/256) on placebo experienced increased thyroid stimulating hormone (TSH); however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. In patients had reactions of hydroxydation. Clinical trials with SEROQUEL XR demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of thyroid binding globulin were unchanged. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL XR patients did experience TSH increases in monitoring studies. Six of these patients with TSH increases needed replacement thyroid treatment.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts in potentially clinically important thyroid function values at any time for SEROQUEL XR treated patients and placebo-treated patients for elevated TSH was 2.9% vs 0.7%, respectively, and for decreased total thyroxine was 2.8% vs 0%, respectively. Of the SEROQUEL XR treated patients with elevated TSH levels, 1 had simultaneous low free T4 levels 14 weeks at end of treatment.

Hyperprolactinemia
Adults: During clinical trials with quetiapine, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts in prolactin levels to a clinically significant value ($>20 \mu g/L$ males; $>26 \mu g/L$ females at any time) was 13.4% for SEROQUEL XR compared to 4% for placebo in males and 8.7% for SEROQUEL XR compared to 0% for placebo in females.

Like other drugs that antagonize dopamine D2 receptors, SEROQUEL XR elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

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 considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in carcinogenicity studies conducted in mice and rats. 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, but the available evidence is too limited to be conclusive.

Increases in Blood Pressure (Children and Adolescents)
Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure (>20 mmHg) was 15.2% for SEROQUEL XR and 5.5% for placebo; the incidence of increases at any time in diastolic blood pressure (≥ 10 mmHg) was 40.6% for SEROQUEL XR and 24.5% for placebo.

Transaminase Elevations
Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of placebo-controlled trials ranged between 1% and 2% for SEROQUEL XR compared to 2% for placebo. 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 XR compared to 1% for 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 quetiapine.

Potential for Cognitive and Motor Impairment
Somnolence was a commonly reported adverse event reported in patients treated with quetiapine especially during the 3-day period of initial dose titration. In schizophrenia trials, somnolence was reported in 24.7% of patients on SEROQUEL XR compared to 10.3% of placebo patients. In a bipolar depression clinical trial, somnolence was reported in 51.8% of patients on SEROQUEL XR compared to 12.9% of placebo patients. In a clinical trial for bipolar mania, somnolence was reported in 50.3% of patients on SEROQUEL XR compared to 11.9% of placebo patients.

patients. Since quetiapine 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 quetiapine therapy does not affect them adversely. Somnolence may lead to falls.

Prison

The case of prazosin in a patient receiving quetiapine was reported prior to market introduction. While a causal relationship to use of quetiapine has not been established, other drugs with α -adrenergic blocking effects have been reported to induce prazosin, and it is possible that quetiapine may share this capacity. Severe prazosin may require surgical intervention.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL XR for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL XR 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 schizophrenia and bipolar disorder; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. In three, 6-week clinical studies in patients with schizophrenia (N=951), the incidence of treatment emergent suicidal ideation or suicide attempt was 0.6% in SEROQUEL XR treated patients and 0.9% in placebo-treated patients.

In an 8-week clinical study in patients with bipolar depression (N=137 for SEROQUEL XR and 140 for placebo), the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% for SEROQUEL XR treated patients and 1.4% for placebo.

In a 3-week clinical study in patients with bipolar mania (N=311, 151 for SEROQUEL XR and 160 for placebo), the incidence of treatment emergent suicidal ideation or suicide attempt was 1.3% for SEROQUEL XR compared to 3.8% for placebo.

Use in Patients with Concomitant Illness

Clinical experience with SEROQUEL XR in patients with certain concomitant systemic illnesses is limited. SEROQUEL XR 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 XR, caution should be observed in cardiac patients [see **Warnings and Precautions**].

Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotics including quetiapine fumarate. Gradual withdrawal is advised.

ADVERSE REACTIONS

Clinical Studies Experience

The information below is derived from a clinical trial database for SEROQUEL XR consisting of 1239 patients exposed to SEROQUEL XR for the treatment of schizophrenia and bipolar disorder in placebo-controlled trials.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials
There was no difference in the incidence and type of adverse reactions associated with discontinuation (8.4% for SEROQUEL XR vs 7.5% for placebo) in a pool of controlled schizophrenia trials. In a single clinical trial in patients with bipolar depression, 13% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 4% on placebo. In a single clinical trial in patients with bipolar mania, 4.6% of patients on SEROQUEL XR discontinued due to adverse reaction compared to 8.1% on placebo.

Adverse Reactions Occurring on or after Day 1 of Treatment in Short-Term, Placebo-Controlled Trials

The following is the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) in $\geq 5\%$ patients treated with SEROQUEL XR (doses ranging from 300 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

SEROQUEL XR (n=851) vs placebo (n=319): Dry Mouth 12% vs 1%, Constipation 6% vs 5%, Dyspepsia 5% vs 2%, Somnolence 25% vs 16%, Dizziness 10% vs 4%, and Orthostatic Hypotension 7% vs 5%.

¹ Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed, but included the following: headache, insomnia, and nausea. In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (25%), dry mouth (12%), dizziness (10%), and dyspepsia (5%).

The following is the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar depression (up to 8 weeks) in $\geq 5\%$ patients treated with SEROQUEL XR (300 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

SEROQUEL XR (N=137) vs placebo (n=140): Dry Mouth 37% vs 7%, Constipation 8% vs 6%, Dyspepsia 7% vs 1%, Fatigue 6% vs 2%, Weight Gain 7% vs 1%, Increased Appetite 12% vs 6%, Somnolence 22% vs 13%, and Dizziness 13% vs 1%.

¹ Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed, but included the following: headache and insomnia.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (22%), dry mouth (37%), increased appetite (12%), weight gain (7%), dyspepsia (7%), and fatigue (6%). The following is the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of bipolar mania (up to 3 weeks) in $\geq 5\%$ patients treated with SEROQUEL XR (doses ranging from 400 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in placebo-treated patients.

SEROQUEL XR (N=151) vs placebo (n=160): Dry Mouth 34% vs 7%, Constipation 10% vs 3%, Dyspepsia 7% vs 4%, Fatigue 7% vs 4%, Weight Gain 7% vs 1%, Somnolence 50% vs 12%, Dizziness 10% vs 4%, Dysarthria 5% vs 0%, and Nasal Congestion 5% vs 1%.

¹ Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed, but included the following: headache.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were somnolence (50%), dry mouth (34%), dizziness (10%), constipation (10%), weight gain (7%), dysarthria (5%), and nasal congestion (5%).

Adverse Reactions Occurring on or after Day 1 of Treatment in Long-Term, Placebo-Controlled Trials

In a longer-term placebo-controlled trial, adult patients with schizophrenia who remained clinically stable on SEROQUEL XR during open-label treatment for at least 4 months were randomized to placebo (n=103) or to continue on their current SEROQUEL XR (n=84) for up to 12 months of observation for possible relapse; the adverse reactions reported were generally consistent with those reported in the short-term, placebo-controlled

trials. Insomnia (8.5%) and headache (7.4%) were the only adverse events reported by 5% or more patients.

Adverse Reactions that occurred in $< 5\%$ of patients and were considered drug-related (incidence greater than placebo) consistent with known pharmacology of drug class in order of decreasing frequency: heart rate increased, hypotension, weight increased, tremor, akathisia, increased appetite, blurred vision, postural dizziness, pyrexia, dysarthria, dystonia, drooling, syncope, tardive dyskinesia, dysphagia, leukopenia, and rash.

Adverse Reactions in clinical trials with quetiapine and not listed above are in the table:

Extrapyramidal Symptoms:
Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Adults: In placebo-controlled clinical trials with quetiapine, utilizing doses up to 800 mg per day, the incidence of any adverse reactions potentially related to EPS ranged from 8% to 11% for quetiapine and 4% to 11% for placebo. In three-arm placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 8% for SEROQUEL XR and 8% for SEROQUEL XR (without evidence of being dose related), and 5% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) was generally low and did not exceed 3% for any treatment group.

At the end of treatment, the mean change from baseline in Simpson-Angus Scale total score and Barnes Akathisia Rating Scale Global Assessment score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups. The incidence of extrapyramidal symptoms was consistent with that seen with the profile of SEROQUEL XR in schizophrenia patients.

In a placebo-controlled clinical trial for the treatment of bipolar depression utilizing 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 4.4% for SEROQUEL XR and 0.7% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) did not exceed 1.5% for any individual adverse reaction.

In a placebo-controlled clinical trial for the treatment of bipolar mania, utilizing the dose range of 400-800 mg/day of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 6.6% for SEROQUEL XR and 3.8% in the placebo group. In this study, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) did not exceed 2.0% for any adverse reaction.

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In a short-term placebo-controlled, monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.8% for SEROQUEL XR and 6.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term, placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% for SEROQUEL XR and 1.1% for placebo.

Increased Appetite:
Adults: Data on increased appetite appear earlier within this section and in "Adverse Reactions that occurred in $< 5\%$ of Patients" (both in this section).

Children and Adolescents: Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years. In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increased appetite was 7.6% for SEROQUEL compared to 2.4% for placebo. In a 26-week open-label study that enrolled patients from the above two pediatric trials, the incidence of increased appetite was 10% for SEROQUEL.

Vital Signs and Laboratory Values

Hyperpyrexia, hypotension, weight gain and orthostatic hypotension have been reported with quetiapine [see **Warnings and Precautions**].

Neutrophil Counts

In three-arm SEROQUEL XR placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9/L$, the incidence of at least one occurrence of neutrophil count $< 1.5 \times 10^9/L$ was 1.2% in patients treated with SEROQUEL XR and 1.5% for SEROQUEL compared to 0.8% in placebo-treated patients. In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $< 1.0 \times 10^9/L$ among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine compared to 0.1% (2/1348) in patients treated with placebo. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors [see **Warnings and Precautions**].

ECG Changes:
3.9% of SEROQUEL XR patients, and 3.4% of placebo patients, had tachycardia (> 120 bpm) at any time during the trials. SEROQUEL XR 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 for placebo. This is consistent with the rates for SEROQUEL XR. The incidence of adverse reactions of tachycardia was 2% for SEROQUEL XR compared to 1% for placebo. SEROQUEL XR 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. The slight tendency for tachycardia may be related to quetiapine's potential for inducing orthostatic changes [see **Warnings and Precautions**].

Post Marketing Experience
Adverse reactions reported since market introduction which were temporally related to SEROQUEL therapy includes anaphylactic reaction and galactorrhea.

Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomegaly/hypertrophy, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and decreased platelets.

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been noted.

DRUG INTERACTIONS

The risks of using SEROQUEL XR in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL XR, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychiatric disorders, and alcoholic beverages should be limited while taking quetiapine.

Because of its potential for inducing hypotension, SEROQUEL XR may enhance the effects of certain antihypertensive agents.

SEROQUEL XR may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Quetiapine

Phenytoin
Coadministration of quetiapine (250 mg three times daily) and phenytoin (100 mg three times daily) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL XR may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, griseofulvin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate) [see **Dosage and Administration**].

Divalproex
Coadministration of quetiapine (150 mg twice daily) and divalproex (500 mg twice daily) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine

Thioridazine (200 mg twice daily) increased the oral clearance of quetiapine (300 mg twice daily) by 65%.

Cimetidine

Administration of multiple daily doses of cimetidine (400 mg three times daily for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg three times daily). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A4 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 (reduced dosage) is indicated when SEROQUEL XR is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, erythromycin, protease inhibitors).

Fluoxetine, Imipramine, Meprobamate, and Risperidone

Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg twice daily), meprobamate (7.5 mg twice daily), or risperidone (3 mg twice daily) with quetiapine (300 mg twice daily) 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 three times daily 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 twice daily) was administered with quetiapine (150 mg twice daily). The mean oral clearance of total valproic acid (administered as divalproex 500 mg twice daily) was increased by 11% in the presence of quetiapine (150 mg twice daily). The changes were not significant.

Lithium

Concomitant administration of quetiapine (250 mg three times daily) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipsychose

Administration of multiple daily doses up to 750 mg/day (ie, a three times daily schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipsychose or urinary recovery of antipsychose metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipsychose.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of SEROQUEL XR use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryos fetal toxicity occurred. 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 XR on labor and delivery in humans is unknown.

Nursing Mothers

SEROQUEL XR was excreted into human milk. Caution should be exercised when SEROQUEL XR is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of SEROQUEL XR have not been established in pediatric patients and SEROQUEL XR is not approved for patients under the age of 18 years [see **Warnings and Precautions** and **Adverse Reactions**].

Geriatric Use

Sixty-eight subjects in clinical studies with SEROQUEL XR were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL XR in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL XR, 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 quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients.

Renal Impairment

Clinical experience with SEROQUEL XR in patients with renal impairment is limited.

Hepatic Impairment

Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed [see **Dosage and Administration**].

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SEROQUEL XR is not a controlled substance.

Abuse

SEROQUEL XR 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 XR (eg, development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 15.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and orthostasis, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose [see **Warnings and Precautions**]. 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 XR 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, severe or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered to patients with acute overdose of SEROQUEL XR. Similarly it is reasonable to expect that the α -adrenergic-blocking properties of bethidolol might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL XR. 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 β stimulation may worsen hypotension in the setting of quetiapine-induced α -blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PATIENT COUNSELING INFORMATION

Information for Patients

(see Medication Guide or Full Prescribing Information)

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL XR and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicide Thoughts or Actions" is available for SEROQUEL 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.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL XR.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, aboulia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look 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 [see **Warnings and Precautions**].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is not approved for elderly patients with dementia-related psychosis [see **Warnings and Precautions**].

Hypertension and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should be monitored [see **Warnings and Precautions**].

Hypertension

Patients should be advised that elevations in total cholesterol, LDL, and triglycerides may occur [see **Warnings and Precautions**].

Weight Gain

Patients should be advised that they may experience weight gain [see **Warnings and Precautions**].

Neuroleptic Malignant Syndrome (NMS)

Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever [see **Warnings and Precautions**].

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing, which may lead to falls), especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [see **Warnings and Precautions**].

Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL XR [see **Warnings and Precautions**].

Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation (which may lead to falls), especially during the 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 machinery, until they are reasonably certain quetiapine therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine [see **Warnings and Precautions**].

Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine [see **Use in Specific Populations**].

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 [see **Warnings and Precautions**].

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see **Warnings and Precautions**].

This summary provides important information about SEROQUEL XR. For more information, please ask your doctor or health care provider about the full Prescribing Information and discuss it with them.

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