

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEROQUEL XR safely and effectively. See full prescribing information for SEROQUEL XR.

SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets

Initial U.S. Approval: 1997

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS See full prescribing information for complete boxed warning.

- Antipsychotic drugs are associated with an increased risk of death (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychosis (5.1)

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS See full prescribing information for complete boxed warning.

- Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders (5.2)

RECENT MAJOR CHANGES

BOXED WARNING, Increased Mortality in Elderly Patients With Dementia-Related Psychosis, 08/2008
Warnings and Precautions, Increased Mortality in Elderly Patients with Dementia-Related Psychosis (5.1), 08/2008

Indications and Usage, Bipolar Disorder (1.2), 10/2008
Dosage and Administration, Bipolar Disorder (2.2), 10/2008
Warnings and Precautions, Hyperglycemia (5.3), 01/2009
Warnings and Precautions, Hyperlipidemia (5.4), 01/2009
Warnings and Precautions, Weight Gain (5.5), 01/2009
Warnings and Precautions, Hypothyroidism (5.12), 01/2009
Warnings and Precautions, Hyperprolactinemia (5.13), 01/2009
Warnings and Precautions, Increases in Blood Pressure (Children and Adolescents) (5.14), 01/2009
Adverse Reactions (6.1), 01/2009

INDICATIONS AND USAGE

SEROQUEL XR is an atypical antipsychotic agent indicated for the treatment of:

- Schizophrenia (1.1)
- Bipolar Disorder (1.2)
 - depressive episodes associated with bipolar disorder
 - manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex
 - maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

DOSAGE 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. (2)

Schizophrenia: SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg. The effective dose range for SEROQUEL XR is 400 – 800 mg per day depending on the response and tolerance of the individual patient. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. Individual dosage adjustments may be necessary. (2.1)

Bipolar Depression: Usual Dose for Acute Treatment - administer once daily in the evening starting with 50 mg per day and increasing doses to reach 300 mg per day by day 4 (2.2)

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 (2.2)

Bipolar Maintenance: Continue treatment at the dosage required to maintain symptom remission (2.2)

DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets: 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- **Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Antipsychotic drugs, including quetiapine, are associated with an increased risk of death; causes of death are variable. (5.1)
- **Suicidality and Antidepressant Drugs:** Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. (5.2)
- **Hyperglycemia and Diabetes Mellitus (DM):** Ketoacidosis, hyperosmolar coma and death have been reported in patients treated with atypical antipsychotics, including quetiapine. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with DM risk factors should undergo blood glucose testing before and during treatment. (5.3)
- **Hyperlipidemia:** Increases in cholesterol and triglycerides have been reported in clinical trials. (5.4)
- **Weight Gain:** Weight gain has been reported in clinical trials. (5.5)
- **Neuroleptic Malignant Syndrome (NMS):** Manage with immediate discontinuation and close monitoring. (5.6)
- **Tardive Dyskinesia:** Discontinue if clinically appropriate. (5.7)
- **Orthostatic Hypotension:** Associated dizziness, tachycardia and syncope especially during the initial dose titration period. Use in caution in patients with known cardiovascular or cerebrovascular disease. (5.8)
- **Leukopenia, Neutropenia and Agranulocytosis:** have been reported with atypical antipsychotics including SEROQUEL XR. Patients with a pre-existing low white cell count (WBC) or a history of leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months of treatment and should discontinue SEROQUEL XR at the first sign of a decline in WBC in absence of other causative factors. (5.9)
- **Cataracts:** Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination should be done when starting treatment and at 6-month intervals during chronic treatment. (5.10)
- **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high risk patients should accompany drug therapy. (5.20)
- See Full Prescribing Information for additional **WARNINGS** and **PRECAUTIONS**.

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$ and twice placebo) are somnolence, dry mouth, hyperlipidemia, constipation, dyspepsia, dizziness, orthostatic hypotension, weight gain, increased appetite, fatigue, hyperglycemia, dysarthria and nasal congestion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **P450 3A Inhibitors:** May decrease the clearance of quetiapine. Lower doses of quetiapine may be required. (7.1)
- **Hepatic Enzyme Inducers:** May increase the clearance of quetiapine. Higher doses of quetiapine may be required with phenytoin or other inducers. (7.1)
- **Centrally Acting Drugs:** Caution should be used when quetiapine is used in combination with other CNS acting drugs. (7)
- **Antihypertensive Agents:** Quetiapine may add to the hypotensive effects of these agents. (7)
- **Levodopa and Dopamine Agents:** Quetiapine may antagonize the effect of these drugs. (7)

USE IN SPECIFIC POPULATIONS

- **Geriatric Use:** Consider a lower starting dose (50 mg/day), slower titration, and careful monitoring during the initial dosing period in the elderly. (2.3 and 8.5)
- **Hepatic Impairment:** Lower starting dose (50 mg/day) and slower titration may be needed. (2.3, 8.7, 12.3)
- **Pregnancy:** Limited human data. Based on animal data, may cause fetal harm. (8.1)
- **Nursing Mothers:** Caution should be exercised when administered to a nursing woman. (8.3)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)

SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised: 07/2009

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FULL PRESCRIBING INFORMATION

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 seventeen placebo-controlled trials (modal duration of 10 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 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (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* (5.1)].

SUICIDALITY 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 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* (5.2)].

1 INDICATIONS AND USAGE**1.1 Schizophrenia**

SEROQUEL XR is indicated for the acute and maintenance treatment of schizophrenia. The efficacy of SEROQUEL XR in schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of SEROQUEL. [see *Clinical Studies* (14.1)].

1.2 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

The efficacy of SEROQUEL XR in bipolar disorder was established, in part, on the basis of extrapolation from the established effectiveness of SEROQUEL [see *Clinical Studies* (14.2)].

2 DOSAGE AND ADMINISTRATION

SEROQUEL XR tablets should be swallowed whole and not split, chewed or crushed. It is recommended that SEROQUEL XR be taken without food or with a light meal (approximately 300 calories) [see *Clinical Pharmacology* (12.3)].

2.1 Schizophrenia**Usual Dose for Acute Treatment**

SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg/day. Patients should be titrated within a dose range of 400 – 800 mg/day depending on the response and tolerance of the individual patient [see *Clinical Studies* (14.1)]. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Maintenance Treatment

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, a longer-term schizophrenia study with SEROQUEL XR has shown this drug to be effective in delaying time to relapse in patients who were stabilized on SEROQUEL XR at doses of 400 to 800 mg/day for 16 weeks [see *Clinical Studies* (14.1)]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see *Clinical Studies* (14.1)].

2.2 Bipolar Disorder**Depressive Episodes Associated with Bipolar Disorder****Usual Dose for Acute Treatment**

SEROQUEL XR should be administered once daily in the evening to reach 300 mg/day by Day 4.

Recommended Dosing Schedule

| Day | Day 1 | Day 2 | Day 3 | Day 4 |
|-------------|-------|--------|--------|--------|
| SEROQUEL XR | 50 mg | 100 mg | 200 mg | 300 mg |

Bipolar Mania**Usual Dose for Acute Monotherapy or Adjunct Therapy**

(with lithium or divalproex)

SEROQUEL XR should be administered once daily in the evening starting with 300 mg on Day 1 and 600 mg on Day 2. SEROQUEL XR can be adjusted between 400 mg and 800 mg beginning on Day 3 depending on the response and tolerance of the individual patient.

Recommended Dosing Schedule

| Day | Day 1 | Day 2 | Day 3 |
|-------------|--------|--------|------------------|
| SEROQUEL XR | 300 mg | 600 mg | 400 mg to 800 mg |

Maintenance Treatment for Bipolar Disorder

While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, maintenance of efficacy in Bipolar I Disorder was demonstrated with SEROQUEL (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase [see *Clinical Studies* (14.2)]. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see *Clinical Studies* (14.2)].

2.3 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* (8.5, 8.7) and *Clinical Pharmacology* (12)]. 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.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital [see *Drug Interactions* (7.1)].

2.4 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.

2.5 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.

2.6 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.

3 DOSAGE FORMS AND STRENGTHS

50 mg extended-release tablets
150 mg extended-release tablets
200 mg extended-release tablets
300 mg extended-release tablets
400 mg extended-release tablets

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS**5.1 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 *Boxed Warning*].

5.2 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. 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 1000 patients treated) are provided in Table 1.

Table 1

| Age Range | Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated |
|-----------|---|
| | Increases Compared to Placebo |
| <18 | 14 additional cases |
| 18-24 | 5 additional cases |
| | Decreases Compared to Placebo |
| 25-64 | 1 fewer case |
| ≥65 | 6 fewer cases |

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 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.

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 mixed/manic 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.

5.3 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 anti-

psychotics, including quetiapine. 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 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 (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.

Adults: In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar maintenance, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +5.0 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 precluded from calorie intake from fluids 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).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with quetiapine and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥ 126 mg/dL or a non fasting blood glucose ≥ 200 mg/dL was 3.5% for quetiapine and 2.1% for placebo. The mean change in glucose from baseline was 2.70 mg/dL for quetiapine and 1.06 mg/dL for placebo.

In a 24-week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥ 200 mg/dL was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥ 126 mg/dL was 2.6%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in 2 hour glucose from baseline was -1.8 mg/dL for quetiapine.

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 (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL compared to placebo was -0.75 mg/dL versus -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 3.62 mg/dL versus -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.

5.4 Hyperlipidemia

Adults: In clinical trials with SEROQUEL XR the percentage of patients with the following changes in cholesterol and triglycerides have been reported [see **Adverse Reactions** (6.3)].

Percentage of Patients with Shifts from Normal Baseline to Clinically Significant Levels

| | Cholesterol ≥ 240 mg/dL | Triglycerides ≥ 200 mg/dL |
|--|------------------------------|--------------------------------|
| Schizophrenia (6 weeks duration) | | |
| SEROQUEL XR | 9% | 18% |
| Placebo | 9% | 5% |
| Bipolar Depression (8 weeks duration) | | |
| SEROQUEL XR | 7% | 8% |
| Placebo | 3% | 8% |
| Bipolar Mania (3 weeks duration) | | |
| SEROQUEL XR | 7% | 15% |
| Placebo | 4% | 6% |

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 changes in cholesterol and triglycerides have been reported.

Percentage of Patients with Shifts from Normal Baseline to Clinically Significant Levels

| | Cholesterol ≥ 240 mg/dL | Triglycerides ≥ 200 mg/dL |
|--|------------------------------|--------------------------------|
| Schizophrenia (13-17 years, 6 weeks duration) | | |
| SEROQUEL | 12% | 17% |
| Placebo | 2% | 8% |
| Bipolar Mania (10-17 years, 3 weeks duration) | | |
| SEROQUEL | 10% | 22% |
| Placebo | 3% | 13% |

5.5 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 (6 weeks duration) | Bipolar Mania (3 weeks duration) | Bipolar Depression (8 weeks duration) |
|-------------|----------------------------------|----------------------------------|---------------------------------------|
| SEROQUEL XR | 10% | 5.1% | 8.2% |
| Placebo | 5% | 0% | 0.8% |

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 (23%) compared to placebo (6%).

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, one in bipolar mania and one in schizophrenia, reported increases in weight are included in the table 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 (6 weeks duration) | Bipolar Mania (3 weeks duration) |
|----------|----------------------------------|----------------------------------|
| SEROQUEL | 21% | 12% |
| Placebo | 7% | 0% |

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL. 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; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

5.6 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 (rhabdomyolysis) and acute renal failure.

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

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

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

5.7 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.

5.8 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% (4/1239) of the patients treated with SEROQUEL XR, compared with 0.3% (2/619) on placebo. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, 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.

5.9 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 $<1000/\text{mm}^3$) should discontinue SEROQUEL XR and have their WBC followed until recovery [see **Adverse Reactions** (6.2)].

5.10 Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies [see **Animal Toxicology** (13.2)]. 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 or shortly thereafter, and at 6-month intervals during chronic treatment.

5.11 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, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo. As with other antipsychotics, 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.

5.12 Hypothyroidism

Adults: In SEROQUEL XR clinical trials, 0.5% (4/806) of patients on SEROQUEL XR vs. 0% (0/262) on placebo experienced decreased free thyroxine and 2.7% (21/786) on SEROQUEL XR vs. 1.2% (3/256) on placebo experienced increased TSH; however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. No patients had reactions of 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. Generally, these changes were of no clinical

significance and TSH was unchanged in most patients and levels of TBG were unchanged. In nearly all cases, cessation of 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 patients did experience TSH increases in monotherapy 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 to potentially clinically important thyroid function values at any time for SEROQUEL 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 treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

5.13 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 µg/L males; >26 µg/L females at any time) was 13.4% for SEROQUEL compared to 4% for placebo in males and 8.7% for SEROQUEL 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 [see **Carcinogenesis, Mutagenesis, Impairment of Fertility** (13.1)].

5.14 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 and 5.5% for placebo; the incidence of increases at any time in diastolic blood pressure (≥ 10 mmHg) was 40.6% for SEROQUEL and 24.5% for placebo.

5.15 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 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.

5.16 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. 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.

5.17 Priapism

One case of priapism 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 priapism, and it is possible that quetiapine may share this capacity. Severe priapism may require surgical intervention.

5.18 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.

5.19 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.

5.20 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.

5.21 Use in Patients with Concomitant Illness

Clinical experience with SEROQUEL XR in patients with certain concomitant systemic illnesses [see **Pharmacokinetics** (12.3)] 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** (5.8)].

5.22 Withdrawal

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

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. This experience corresponds to approximately 143.1 patient-years. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, body weights, laboratory analyses, and ECG results.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized event categories. In the tables and tabulations that follow, standard MedDRA terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

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 (6.4% 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 at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Short-Term, Placebo-Controlled Trials

Table 2 enumerates 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.

Table 2: Treatment-Emergent Adverse Reaction Incidence in 6-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia¹

| Body System/Preferred Term | SEROQUEL XR (n=951) | PLACEBO (n=319) |
|-----------------------------------|------------------------|--------------------|
| Gastrointestinal Disorders | | |
| Dry Mouth | 12% | 1% |
| Constipation | 6% | 5% |
| Dyspepsia | 5% | 2% |
| Nervous System Disorders | | |
| Somnolence ² | 25% | 10% |
| Dizziness | 10% | 4% |
| Vascular Disorders | | |
| Orthostatic Hypotension | 7% | 5% |

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

² Somnolence combines adverse reaction terms somnolence and sedation.

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%).

Table 3 enumerates 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 ≥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.

Table 3: Treatment-Emergent Adverse Reactions in an 8-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Depression¹

| Body System/Preferred Term | SEROQUEL XR (n=137) | PLACEBO (n=140) |
|---|------------------------|--------------------|
| Gastrointestinal Disorders | | |
| Dry Mouth | 37% | 7% |
| Constipation | 8% | 6% |
| Dyspepsia | 7% | 1% |
| General Disorders and Administration Site Conditions | | |
| Fatigue | 6% | 2% |
| Investigations | | |
| Weight Gain | 7% | 1% |
| Metabolism and Nutrition Disorder | | |
| Increased Appetite | 12% | 6% |
| Nervous System Disorders | | |
| Somnolence ² | 52% | 13% |
| Dizziness | 13% | 11% |

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

² Somnolence combines adverse reaction terms somnolence and sedation.

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 (52%), dry mouth (37%), increased appetite (12%), weight gain (7%), dyspepsia (7%), and fatigue (6%).

Table 4 enumerates 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 ≥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.

Table 4: Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Mania¹

| Body System/Preferred Term | SEROQUEL XR (n=151) | PLACEBO (n=160) |
|---|------------------------|--------------------|
| Gastrointestinal Disorders | | |
| Dry Mouth | 34% | 7% |
| Constipation | 10% | 3% |
| Dyspepsia | 7% | 4% |
| General Disorders and Administration Site Conditions | | |
| Fatigue | 7% | 4% |
| Investigations | | |
| Weight Gain | 7% | 1% |
| Nervous System Disorders | | |
| Somnolence ² | 50% | 12% |
| Dizziness | 10% | 4% |
| Dysarthria | 5% | 0% |
| Respiratory, Thoracic and Mediastinal Disorders | | |
| Nasal Congestion | 5% | 1% |

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

² Somnolence combines adverse reaction terms somnolence and sedation.

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 at an Incidence of 5% or More Among SEROQUEL XR Treated Patients 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=94) 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 and 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 elsewhere in the label:

abnormal dreams and nightmares, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels, restless legs syndrome, and elevations in serum creatine phosphokinase (not associated with NMS).

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.

Four methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) Barnes Akathisia Rating Scale (BARS) Global Assessment Score, (3) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (4) use of anticholinergic medications to treat emergent EPS.

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 (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 SAS total score and BARS 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 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, dystonia, hypertonia) 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, dystonia, restlessness, and cogwheel 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 12.9% for SEROQUEL and 5.3% 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 and 1.1% for placebo.

Increased Appetite

Adults: Data on increased appetite appear in Table 3 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.

6.2 Vital Signs and Laboratory Values

Hyperglycemia, hyperlipidemia, weight gain and orthostatic hypotension have been reported with quetiapine [see **Warnings and Precautions** (5.3, 5.4, 5.5 and 5.8)].

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 1.5% 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% (2/1349) 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** (5.9)].

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. The incidence of adverse reactions of tachycardia was 3% for SEROQUEL XR compared to 1% for placebo. 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. The slight tendency for tachycardia may be related to quetiapine's potential for inducing orthostatic changes [see **Warnings and Precautions** (5.8)].

6.3 Post Marketing Experience

The following adverse reactions were identified during post approval use of SEROQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction which was 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, cardiomyopathy hyponatremia, 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 reported.

7 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 psychotic 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.

7.1 The Effect of Other Drugs on Quetiapine**Phenytoin**

Coadministration of quetiapine (250 mg three times/day) and phenytoin (100 mg three times/day) 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, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate) [see **Dosage and Administration** (2)].

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 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 (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, Haloperidol, and Risperidone

Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg twice daily), haloperidol (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.

7.2 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.

Antipyrene

Administration of multiple daily doses up to 750 mg/day (on a three times daily 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.

8 USE IN SPECIFIC POPULATIONS**8.1 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, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are limited published data on the use of quetiapine for treatment of schizophrenia and other psychiatric disorders during pregnancy. In a prospective observational study, 21 women exposed to quetiapine and other psychoactive medications during pregnancy delivered infants with no major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (one study of 36 women, 6 case reports). Due to the limited number of exposed pregnancies, these postmarketing data do not reliably estimate the frequency or absence of adverse outcomes.

When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no increase in the incidence of major malformations in fetuses at doses up to 2.4 times the maximum recommended human dose for schizophrenia (MRHD, 800 mg/day on a mg/m² basis); however, there was evidence of embryo-fetal toxicity. In rats, delays in skeletal ossification occurred at 0.6 and 2.4 times the MRHD and in rabbits at 1.2 and 2.4 times the MRHD. At 2.4 times the MRHD, there was an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit fetuses and decreased fetal weights in both species. Maternal toxicity (decreased body weights and/or death) occurred at 2.4 times the MRHD in rats and at 0.6-2.4 times the MRHD (all doses) in rabbits.

In a peri/postnatal reproductive study in rats, no drug-related effects were observed when pregnant dams were treated with quetiapine at doses 0.01, 0.12, and 0.24 times the MRHD. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3.0 times the MRHD.

8.2 Labor and Delivery

The effect of SEROQUEL XR on labor and delivery in humans is unknown.

8.3 Nursing Mothers

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

In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 µg/L. The estimated infant dose ranged from 0.09% to 0.43% of the weight-adjusted maternal dose. Based on a limited number (N=8) of mother/infant pairs, calculated infant daily doses range from less than 0.01 mg/kg (at a maternal daily dose up to 100 mg quetiapine) to 0.1 mg/kg (at a maternal daily dose of 400 mg).

8.4 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 (5) and Adverse Reactions (6)].**8.5 Geriatric Use**

Sixty-eight patients 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 [see **Dosing in Special Populations (2.3) and Pharmacokinetics (12.3)**].

8.6 Renal Impairment

Clinical experience with SEROQUEL XR in patients with renal impairment [see **Clinical Pharmacology (12.3)**] is limited.

8.7 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 (2.3) and Clinical Pharmacology (12.3)**].

9 DRUG ABUSE AND DEPENDENCE**9.1 Controlled Substance**

SEROQUEL XR is not a controlled substance.

9.2 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).

10 OVERDOSAGE**10.1 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 13.6 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 sedation, 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 (5)**]. 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.

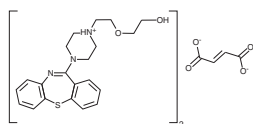
10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL XR. Similarly it is reasonable to expect that the α -adrenergic-blocking properties of bretylium 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.

11 DESCRIPTION

SEROQUEL XR (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [b,f] [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{24}H_{20}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL XR is supplied for oral administration as 50 mg (peach), 150 mg (white), 200 mg (yellow), 300 mg (pale yellow), and 400 mg (white). All tablets are capsule shaped and film coated.

Inactive ingredients for SEROQUEL XR are lactose monohydrate, microcrystalline cellulose, sodium citrate, hypromellose, and magnesium stearate. The film coating for all SEROQUEL XR tablets contain hypromellose, polyethylene glycol 400 and titanium dioxide. In addition, yellow iron oxide (50, 200 and 300 mg tablets) and red iron oxide (50 mg tablets) are included in the film coating of specific strengths.

Each 50 mg tablet contains 58 mg of quetiapine fumarate equivalent to 50 mg quetiapine. Each 150 mg tablet contains 173 mg of quetiapine fumarate equivalent to 150 mg quetiapine. Each 200 mg tablet contains 230 mg of quetiapine fumarate equivalent to 200 mg quetiapine. Each 300 mg tablet contains 345 mg of quetiapine fumarate equivalent to 300 mg quetiapine. Each 400 mg tablet contains 461 mg of quetiapine fumarate equivalent to 400 mg quetiapine.

12 CLINICAL PHARMACOLOGY**12.1 Mechanism of Action**

The mechanism of action of quetiapine is unknown; however, it is believed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) receptor antagonism, with the metabolite N-desalkyl quetiapine (norquetiapine) having similar activity at D_2 , but greater activity at $5HT_{2A}$ receptors, than the parent drug. Quetiapine's efficacy in bipolar depression may partly be explained by the high affinity and potent inhibitory effects that norquetiapine exhibits for the norepinephrine transporter.

Antagonism at receptors other than dopamine and serotonin with similar or greater affinities may explain some of the other effects of quetiapine and norquetiapine: antagonism at histamine H_1 receptors may explain the somnolence, antagonism at adrenergic α_1 receptors may explain the orthostatic hypotension, and antagonism at muscarinic M_1 receptors may explain the anticholinergic effects.

12.2 Pharmacodynamics

Quetiapine and norquetiapine have affinity for multiple neurotransmitter receptors including dopamine D_1 and D_2 , serotonin $5HT_{1A}$ and $5HT_{2A}$, histamine H_1 , muscarinic, and adrenergic α_1 and α_2 receptors. Quetiapine differs from norquetiapine in having no appreciable affinity for muscarinic M_1 receptors whereas norquetiapine has high affinity. Quetiapine and norquetiapine lack appreciable affinity for benzodiazepine receptors.

Receptor Affinities (K_i , nM) for Quetiapine and Norquetiapine

| Receptor | Quetiapine | Norquetiapine |
|----------------------------|------------|---------------|
| Dopamine D_1 | 428 | 99.8 |
| Dopamine D_2 | 626 | 489 |
| Serotonin $5HT_{1A}$ | 1040 | 191 |
| Serotonin $5HT_{2A}$ | 38 | 2.9 |
| Norepinephrine transporter | >10000 | 34.8 |
| Histamine H_1 | 4.41 | 1.15 |
| Adrenergic α_1 | 14.6 | 46.4 |
| Adrenergic α_2 | 617 | 1290 |
| Muscarinic | 1086 | 38.3 |
| Benzodiazepine | >10000 | >10000 |

12.3 Pharmacokinetics

Following multiple dosing of quetiapine up to a total daily dose of 800 mg, administered in divided doses, the plasma concentration of quetiapine and norquetiapine, the major active metabolite of quetiapine, were proportional to the total daily dose. Accumulation is predictable upon multiple dosing. Steady-state mean C_{max} and AUC of norquetiapine are about 21-27% and 46-56%, respectively of that observed for quetiapine. Elimination of quetiapine is mainly via hepatic metabolism. The mean-terminal half-life is approximately 7 hours for quetiapine and approximately 12 hours for norquetiapine within the clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. SEROQUEL XR is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption

Quetiapine fumarate reaches peak plasma concentrations approximately 6 hours following administration. SEROQUEL XR dosed once daily at steady-state has comparable bioavailability to an equivalent total daily dose of SEROQUEL administered in divided doses, twice daily. A high-fat meal (approximately 800 to 1000 calories) was found to produce statistically significant increases in the SEROQUEL XR C_{max} and AUC of 44% to 52% and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal (approximately 300 calories) had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that SEROQUEL XR be taken without food or with a light meal [see **Dosage and Administration (2)**].

Distribution

Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10 ± 4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination

Following a single oral dose of ^{14}C -quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively. The average dose fraction of free quetiapine and its major active metabolite is <5% excreted in the urine.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite and in the metabolism of its active metabolite norquetiapine.

Age

Oral clearance of quetiapine was reduced by 40% in elderly patients (> 65 years, $n = 9$) compared to young patients ($n = 12$), and dosing adjustment may be necessary [see **Dosage and Administration** (2.3)].

Gender

There is no gender effect on the pharmacokinetics of quetiapine.

Race

There is no race effect on the pharmacokinetics of quetiapine.

Smoking

Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency

Patients with severe renal impairment ($\text{CL}_{\text{cr}} = 10\text{--}30 \text{ mL/min/1.73m}^2$, $n = 8$) had a 25% lower mean oral clearance than normal subjects ($\text{CL}_{\text{cr}} > 80 \text{ mL/min/1.73m}^2$, $n = 8$), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency

Hepatically impaired patients ($n = 8$) had a 30% lower mean oral clearance of quetiapine than normal subjects. In 2 of the 8 hepatically impaired patients, AUC and C_{max} were 3 times higher than those observed typically in healthy subjects. 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** (2.3)].

Drug-Drug Interactions

In vitro enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole [see **Drug Interactions** (7.1) and **Dosage and Administration** (2.3)].

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam [see **Drug Interactions** (7.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose for schizophrenia and bipolar mania (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically 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/m^2 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.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. 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 **Warnings and Precautions** (5.13)].

Mutagenesis

The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did 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/m^2 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/m^2 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/m^2 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/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

13.2 Animal Toxicology and/or Pharmacology

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose-related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta 8 cholesterol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in 1 short-term, 6-week, fixed-dose, placebo-controlled trial of inpatients and outpatients with schizophrenia ($n = 573$) who met DSM-IV criteria for schizophrenia. SEROQUEL XR (once daily) was administered as 300 mg on Day 1, and the dose was increased to either 400 mg or 600 mg by Day 2, or 800 mg by Day 3. The primary endpoint was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment (Day 42). SEROQUEL XR doses of 400 mg, 600 mg and 800 mg once daily were superior to placebo in the PANSS total score at Day 42.

In a longer-term trial, clinically stable adult outpatients ($n = 171$) meeting DSM-IV criteria for schizophrenia who remained stable following 16 weeks of open-label treatment with flexible doses of SEROQUEL XR (400-800 mg/day) were randomized to placebo or to continue on their current SEROQUEL XR (400-800 mg/day) for observation for possible relapse during the double-blind continuation (maintenance) phase. Stabilization during the open-label phase was defined as receiving a stable dose of SEROQUEL XR and having a CGI-S ≤ 4 and a PANSS score ≤ 60 from beginning to end of this open-label phase (with no increase of ≥ 10 points in PANSS total score). Relapse during the double-blind phase was defined in terms of a $\geq 30\%$ increase in the PANSS Total score, or CGI-Improvement score of ≥ 6 , or hospitalization due to worsening of schizophrenia, or need for any other antipsychotic medication. Patients on SEROQUEL XR experienced a statistically significant longer time to relapse than did patients on placebo.

14.2 Bipolar Disorder

Depressive Episodes Associated with Bipolar Disorder

The efficacy of SEROQUEL XR for the acute treatment of depressive episodes associated with bipolar disorder in patients who met DSM-IV criteria for bipolar disorder was established in one 8-week, randomized, double-blind, placebo-controlled study ($N = 280$ outpatients). This study included patients with bipolar I and II disorder, and those with and without a rapid cycling course. Patients randomized to SEROQUEL XR were administered 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, and 300 mg on Day 4 and after.

The primary rating instrument used to assess depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 (no depressive features) to 60 (maximum score). The

primary endpoint was the change from baseline in MADRS score at week 8. SEROQUEL XR was superior to placebo in reduction of MADRS score at week 8.

The efficacy of SEROQUEL for the treatment of depressive episodes associated with bipolar disorder was established in 2 identical 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the MADRS. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score at week 8. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Bipolar Mania

The efficacy of SEROQUEL XR in the acute treatment of manic episodes was established in one 3-week, placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features (N=316). Patients were hospitalized for a minimum of 4 days at randomization. Patients randomized to SEROQUEL XR received 300 mg on Day 1 and 600 mg on Day 2. Afterwards, the dose could be adjusted between 400 mg and 800 mg per day.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptoms in a range from 0 (no manic features) to 60 (maximum score). SEROQUEL XR was superior to placebo in the reduction of the YMRS total score at week 3.

The efficacy of SEROQUEL in the treatment of acute manic episodes was also established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the YMRS score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In a 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS ≥ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score. The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Maintenance Therapy

The efficacy of SEROQUEL in the maintenance treatment of Bipolar I Disorder was established in 2 placebo-controlled trials in patients (n=1326) who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stable on SEROQUEL plus lithium or divalproex for at least 12 weeks in order to be randomized. On average, patients were stabilized for 15 weeks. In the randomization phase, patients continued treatment with lithium or divalproex and were randomized to receive either SEROQUEL (administered twice daily totaling 400 to 800 mg per day) or placebo. Approximately 50% of the patients had discontinued from the SEROQUEL group by day 280 and 50% of the placebo group had discontinued by day 117 of double-blind treatment. The primary endpoint in these studies was time to recurrence of a mood event (manic, mixed or depressed episode). A mood event was defined as medication initiation or hospitalization for a mood episode; YMRS score ≥ 20 or MADRS score ≥ 20 at 2 consecutive assessments; or study discontinuation due to a mood event.

In both studies, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event. The treatment effect was present for both manic and depressed episodes. The effect of SEROQUEL was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

- 50 mg Tablets (NDC 0310-0280) peach, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 50" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.
- 150 mg Tablets (NDC 0310-0281) white, film-coated, capsule-shaped, biconvex, intagliated tablet with "XR 150" on one side and plain on the other are supplied in

bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.

- 200 mg Tablets (NDC 0310-0282) yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 200" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.
- 300 mg Tablets (NDC 0310-0283) pale yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 300" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.
- 400 mg Tablets (NDC 0310-0284) white, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 400" on one side and plain on the other are supplied in bottles of 60 tablets and 500 tablets and hospital unit dose packages of 100 tablets.

Store SEROQUEL XR at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

[see Medication Guide]

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 Suicidal 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. The complete text of the Medication Guide is reprinted at the end of this document.

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, akathisia (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** (5.2)].

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** (5.1)].

Hyperglycemia 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** (5.3)].

Hyperlipidemia

Patients should be advised that elevations in total cholesterol, LDL and triglycerides may occur [see **Warnings and Precautions** (5.4)].

Weight Gain

Patients should be advised that they may experience weight gain [see **Warnings and Precautions** (5.5)].

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** (5.6)].

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** (5.8)].

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** (5.9)].

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** (5.16)].

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** (8.1 and 8.3)].

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** (5.21)].

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see **Warnings and Precautions** (5.18)].

17.2 Medication Guide

Medication Guide

SEROQUEL XR (SER-oh-kwell)

Generic name: quetiapine fumarate

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

Talk to you, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

- 1 Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- 2 Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
- 3 How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
 - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
 - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
 - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to AstraZeneca at 1-800-236-9933.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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