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 ***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 Psychoses. (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----------

Indications and Usage, Schizophrenia (1.1), 12/2009
Indications and Usage, Bipolar Disorder (1.2), 12/2009
Indications and Usage, Major Depressive Disorder (MDD), Adjunctive Treatment with Antidepressants (1.3), 12/2009
Dosage and Administration, Schizophrenia (2.1), 12/2009
Dosage and Administration, Bipolar Disorder (2.2), 12/2009
Dosage and Administration, Major Depressive Disorder (MDD), Adjunctive Treatment with Antidepressants (2.3), 12/2009
Warnings and Precautions, Hyperglycemia (5.4), 12/2009
Warnings and Precautions, Hyperlipidemia (5.5), 12/2009
Warnings and Precautions, Weight Gain (5.6), 12/2009
Warnings and Precautions, Increases in Blood Pressure (Children and Adolescents) (5.9), 12/2009
Warnings and Precautions, Hypothyroidism (5.13), 01/2009
Warnings and Precautions, Hyperprolactinemia (5.14), 01/2009
Warnings and Precautions, Potential for Cognitive and Motor Impairment (5.16), 12/2009
Warnings and Precautions, Suicide (5.20), 12/2009

------ - ----------INDICATIONS AND USAGE----------

SEROQUEL XR is an atypical antipsychotic indicated for the:

Treatment of schizophrenia (1.1)

- Adults: Efficacy was established with SEROQUEL XR in one 6-week and one maintenance trial in patients with schizophrenia as well as in three 6-week trials with SEROQUEL in patients with schizophrenia (14.1)

Acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex (1.2)

- Adults: Efficacy was established with SEROQUEL XR in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder as well as two 12-week monotherapy trials and one 3-week adjunctive trial with SEROQUEL in patients with manic episodes associated with bipolar I disorder (14.2)

Acute treatment of depressive episodes associated with bipolar I disorder (1.2)

- Adults: Efficacy was established with SEROQUEL XR in one 8-week trial in patients with bipolar I or II disorder as well as two 8-week trials with SEROQUEL in patients with bipolar I or II disorder (14.2)

Maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex (1.2)

- Adults: Efficacy was established with SEROQUEL in two maintenance trials in patients with bipolar I disorder (14.2)

Adjunctive treatment of major depressive disorder (MDD) (1.3)

- Adults: Efficacy as an adjunct to antidepressants was established in two 6-week trials in patients with MDD who had an inadequate response to an antidepressant alone (14.3)

---------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 (approx. 300 calories). SERQOUEL XR should be administered once daily, preferably in the evening.

Indication	Dosing Instructions*	Recommended Dose / Dose
Schizophrenia-(2.1)	Day 1: 300 mg/day Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day.	400-800 mg/day
Schizophrenia Maintenance (Monotherapy) (2.1)	400 mg/day to 800 mg/day	400-800 mg/day
Bipolar Mania-Acute monotherapy or as an adjunct to lithium or divalproex (2.2)	Day 1: 300 mg. Day 2: 600 mg. Day 3: between 400 mg and 800 mg	400– 800 mg/day
Depressive Episodes Associated with Bipolar Disorder (2.2)	Day 1: 50 mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day
Bipolar I Disorder-Maintenance Treatment as an adjunct to lithium or divalproex (2.2)	400 mg/day to 800 mg/day	400-800 mg/day
Major Depressive Disorder, Adjunctive Therapy with Antidepressants (2.3)	Day 1 and 2: 50 mg Day 3 and 4: 150 mg	150-300 mg/day

*After initial dosing, adjustments can be made upwards or downwards, if necessary, within the dose range depending upon the clinical response and tolerance of the patient.

----------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 Psychoses**: Antipsychotic drugs, including quetiapine, are associated with an increased risk of death; causes of death are variable. (5.1)
- **Suicidality and Antidepressant Drugs:** Increased the risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. (5.2)
- **Neuroleptic Malignant Syndrome (NMS):** Manage with immediate discontinuation and close monitoring. (5.3)
- **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 diabetes or risk factors for diabetes should undergo blood glucose testing before and during treatment. (5.4)
- **Hyperlipidemia:** Undesirable alterations in lipids have been observed. Increases in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol have been reported in clinical trials. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment. (5.5)
- **Weight Gain:** Patients should receive regular monitoring of weight. (5.6)
- **Tardive Dyskinesia:** Discontinue if clinically appropriate. (5.7)
- **Orthostatic Hypotension**: Associated dizziness, tachycardia and syncope may occur especially during the initial dose titration period. Use in caution in patients with known cardiovascular or cerebrovascular disease. (5.8)
- **Increased Blood Pressure in Children and Adolescents:** Blood pressure should be measured at the beginning of, and periodically during treatment in children and adolescents. SEROQUEL XR has not been evaluated in pediatric patients. (5.9)
- **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. (5.10)
- **Cataracts:** Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment. (5.11)
- **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**

Most common adverse reactions (incidence ≥5% and twice placebo) in decreasing frequency are: somnolence, dry mouth, , constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, 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 X

[FULL PRESCRIBING INFORMATION: CONTENTS*

* SECTIONS OR SUBSECTIONS OMITTED FROM THE FULL PRESCRIBING INFORMATION ARE NOT LISTED.

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 XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL XR is not approved for use in pediatric patients [see *Warnings and Precautions* (5.2)].

1 INDICATIONS AND USAGE

1.1 Schizophrenia

SEROQUEL XR is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL XR in schizophrenia was established in one 6-week and one maintenance trial in adults with schizophrenia as well by

extrapolation from three 6-week trials in adults with schizophrenia treated with SEROQUEL *[see Clinical Studies (14.1)]*.

1.2 Bipolar Disorder

SEROQUEL XR is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex. The efficacy of SEROQUEL XR in manic or mixed episodes of bipolar I disorder was established in one 3-week trial in adults with manic or mixed episodes associated with bipolar I disorder as well by extrapolation from two 12-week monotherapy and one 3-week adjunctive trial in adults with manic episodes associated with bipolar I disorder treated with SEROQUEL *[see Clinical Studies (14.2)]*.

SEROQUEL XR is indicated for the acute treatment of depressive episodes associated with bipolar disorder. The efficacy of SEROQUEL XR was established in one 8-week trial in adults with bipolar I or II disorder as well as extrapolation from two 8-week trials in adults with bipolar I or II disorder treated with SEROQUEL *[see Clinical Studies (14.2)]*.

SEROQUEL XR is indicated for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or divalproex. Efficacy was extrapolated from two maintenance trials in adults with bipolar I disorder treated with SEROQUEL. The effectiveness of monotherapy for the maintenance treatment of bipolar disorder has not been systematically evaluated in controlled clinical trials *[see Clinical Studies (14.2)]*.

1.3 Adjunctive Treatment of Major Depressive Disorder (MDD)

SEROQUEL XR is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD. The efficacy of SEROQUEL XR as adjunctive therapy to antidepressants in MDD was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant treatment *[see Clinical Studies (14.3)]*.

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

Dose Selection—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 mg/day – 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—A maintenance trial in adult patients with schizophrenia treated 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 mg/day to 800 mg/day for 16 weeks. 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

Bipolar Mania

Usual Dose for Acute Monotherapy or Adjunct Therapy (with lithium or divalproex)

Dose Selection—When used as 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

Depressive Episodes Associated with Bipolar Disorder

Usual Dose—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

DOCKET ALARM

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