ATTACHMENT A

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SEROQUEL® *(quetiapine fumarate)* Tablets

Initial US 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

Warnings and Precautions, Hyperglycemia (5.4), 1/2011
Warnings and Precautions, Hyperlipidemia (5.5), 1/2011
Warnings and Precautions, Weight Gain (5.6), 1/2011
Warnings and Precautions, QT prolongation (5.12), 6/2011
Warnings and Precautions, Hypothyroidism (5.14), 1/2011
Warnings and Precautions, Withdrawal (5.23), 05/2010

INDICATIONS AND USAGE

SEROQUEL is an atypical antipsychotic indicated for the:

Treatment of schizophrenia (1.1)

- Adults: Efficacy was established in three 6-week clinical trials in patients with schizophrenia (14.1)
- Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1)

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

- Adults: Efficacy was established in two 12-week monotherapy trials and in one 3-week adjunctive trial in patients with manic episodes associated with bipolar I disorder (14.2)
- Children and Adolescents (ages 10-17): Efficacy was established in one 3-week monotherapy trial in patients with manic episodes associated with bipolar I disorder (14.2)

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

- Adults: Efficacy was established in two 8-week trials in patients with bipolar I or II disorder (14.2)

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

- Adults: Efficacy was established in two maintenance trials in adults (14.2)

DOSAGE AND ADMINISTRATION

SEROQUEL can be taken with or without food.

Indication	Dosing Instructions*	Recommended Dose / Dose Range
Schizophrenia-Adults (2.1)	Day 1: 25 mg twice daily. Increase in increments of 25 mg-50 mg divided two or three times on Days 2 and 3 to range of 300-400 mg by Day 4. Further adjustments can be made in increments of 25–50 mg twice a day, in intervals of not less than 2 days.	150-750 mg/day
Schizophrenia-Adolescents (13-17 years) (2.1)	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day.	400-800 mg/day
	Based on response and tolerability, may be administered three times daily.	
Bipolar Mania-Adults Monotherapy or as an adjunct to lithium or divalproex (2.2)	Day 1: Twice daily dosing totaling 100 mg. Day 2: Twice daily dosing totaling 200 mg. Day 3: Twice daily dosing totaling 300 mg. Day 4: Twice daily dosing totaling 400 mg. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.	400– 800 mg/day
Bipolar Mania-Children and Adolescents (10 to 17 years), Monotherapy	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-600 mg/day. Based on response and tolerability, may be administered three times daily.	400-600 mg/day
Bipolar Depression-Adults	Administer once daily at bedtime. Day 1: 50 mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day
Bipolar I Disorder Maintenance Therapy- Adults	Administer twice daily totaling 400-800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized.	

*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

25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- **Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Atypical 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)

5.12 QT Prolongation

In clinical trials quetiapine was not associated with a persistent increase in QT intervals. However, the QT effect was not systematically evaluated in a thorough QT study. In post marketing experience, there were cases reported of QT prolongation in patients who overdosed on quetiapine [*see Overdosage (10.1)*], in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval [*see Drug Interactions (7)*].

The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrythmics (e.g., quinidine, procainamide) or Class III antiarrythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g. cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

5.13 Seizures

During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.14 Hypothyroidism

Adults: Clinical trials with quetiapine demonstrated dose-related decreases in thyroid hormone levels. The reduction in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range was maximal in the first six weeks of treatment and maintained without adaptation or progression during more chronic therapy. 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. Some patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies,