

SEROQUEL® (quetiapine fumarate) Tablets
Product Monograph/Clinical Executive Summary
Manufacturer: AstraZeneca Pharmaceuticals LP, Wilmington, DE
Classification: Psychotropic agent belonging to the dibenzothiazepine chemical class
Please refer to the SEROQUEL Prescribing Information for complete product information

Indications

SEROQUEL is indicated for the treatment of depressive episodes associated with bipolar disorder, acute manic episodes associated with bipolar I disorder (as monotherapy or adjunct therapy to lithium [Li] or divalproex [DVP]), maintenance treatment of bipolar I disorder as adjunct therapy to Li or DVP, and for the treatment of schizophrenia.¹

Clinical Characteristics

- Symptom improvement observed by week 1 in acute bipolar depression, mania, and schizophrenia trials:
 - SEROQUEL showed greater improvement in depressive symptoms associated with bipolar I or II disorder, with or without a rapid cycling course, versus placebo as measured by Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 1 and continuing through Week 8. SEROQUEL demonstrated statistically significant improvement versus placebo in Hamilton Rating Scale for Depression (HAM-D), and Hamilton Rating Scale for Anxiety (HAM-A) scores at week 1 and through week 8.^{2,3,4}
 - SEROQUEL in combination with Li or DVP showed significantly greater improvement of manic symptoms within a week versus Li or DVP alone,⁵ and as early as day 4 in mania monotherapy trials as measured by the Young Mania Rating Scale (YMRS).⁶ Statistically significant improvement was seen with SEROQUEL versus placebo in all 11 YMRS items at day 21 and through day 84 in these monotherapy trials.⁶
 - SEROQUEL showed significant improvement in Brief Psychiatric Rating Scale (BPRS) total score at week 1 versus placebo in schizophrenia trials.⁷ SEROQUEL also showed significant improvement across a broad spectrum of schizophrenia symptoms, as measured by the BPRS, including anergia, thought disturbance, activation, hostility, and anxiety/depressive symptoms.⁸
- In two long-term trials (mean duration of exposure was 213 days for SEROQUEL and 152 days for placebo), SEROQUEL, as adjunct therapy to Li or DVP, was superior to placebo plus Li or DVP in increasing the time to recurrence of any mood event (manic, depressed, or mixed) using criteria including the MADRS and YMRS. Patients treated with SEROQUEL plus Li or DVP had a risk reduction of 70% (hazard ratio 0.30) relative to those treated with placebo plus Li or DVP for time to recurrence of a mood event. The proportion of patients who relapsed when treated with SEROQUEL plus Li or DVP was 19.3% versus 50.4% of patients on placebo plus Li or DVP. The treatment effect was present for both manic and depressed episodes and was independent of any specific subgroup.^{1,9,10,11}
- In bipolar depression clinical trials, SEROQUEL 300 mg showed improvements over placebo in overall quality of life and satisfaction related to various areas of functioning.¹

Safety

- SEROQUEL has the following boxed warnings: **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder and other psychiatric disorders. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis or for use in patients under the age of 18 years.**¹
- Warnings and precautions for SEROQUEL include (see Full Prescribing Information for complete information):¹
 - **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.
 - **Hyperlipidemia:** Increases in cholesterol and triglycerides have been reported in clinical trials.
 - **Weight Gain:** Weight gain has been reported in clinical trials.
 - **Neuroleptic Malignant Syndrome (NMS):** Potentially fatal symptom complex has been reported with antipsychotic drugs, including quetiapine.
 - **Tardive Dyskinesia** may develop acutely or chronically.
 - **Orthostatic Hypotension:** Associated dizziness, tachycardia and syncope especially during the initial dose titration period.
 - **Leukopenia, Neutropenia and Agranulocytosis:** have been reported with atypical antipsychotics including SEROQUEL. 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 at the first sign of a decline in WBC in absence of other causative factors.
 - **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.
 - **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.
- The most commonly observed adverse reactions (incidence \geq 5% and twice placebo) associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, hyperlipidemia, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, hyperglycemia, nasal congestion, ALT increased, and dyspepsia.¹
- In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar maintenance with mean exposure of 213 days for SEROQUEL and 152 days for placebo, the exposure-adjusted rate of hyperglycemia (glucose \geq 126 mg/dL more than 8 hours since a meal) was 18 per 100 patient years (10.7% of patients) for SEROQUEL vs. 9.5 for placebo (4.6% in patients). In short-term (\leq 12

weeks) clinical trials including SEROQUEL and SEROQUEL XR, patients with a fasting blood glucose ≥ 126 mg/dL or a non fasting blood glucose ≥ 200 mg/dL was 3.5% for quetiapine vs. 2.1% for placebo. In a trial designed to evaluate glycemic status, at week 24, the incidence of a post-glucose challenge glucose level ≥ 200 mg/dL was 1.7% and the incidence of a fasting blood glucose level ≥ 126 mg/dL was 2.6% in SEROQUEL-treated patients.¹

- In schizophrenia clinical trials for SEROQUEL (6 weeks), the percentage of patients with shifts from normal baseline to clinically significant levels of cholesterol (≥ 240 mg/dL) and triglycerides (≥ 200 mg/dL) were 16% and 23%, respectively, for SEROQUEL, and 7% and 16%, respectively, for placebo. In the 8-week bipolar depression trials, the percentage of shifts for cholesterol and triglycerides were 9% and 14%, respectively, for SEROQUEL and 6% and 9%, respectively, for placebo.¹
- No discontinuations due to weight gain were observed in short-term SEROQUEL pivotal trials.^{3,4,5,6,12,13,14} In schizophrenia trials the proportions of patients with a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials (up to 12 weeks), the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in 3-week mania adjunct therapy trials the proportion of patients meeting the same weight gain criterion were 13% compared to 4% for placebo. In 8-week bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo.¹
- In acute mania, schizophrenia, and bipolar maintenance trials, SEROQUEL showed an extrapyramidal symptom (EPS) profile similar to placebo.^{1,5,6,9,12,13} In the bipolar depression trials, the incidence of adverse reactions potentially related to EPS was 12% for SEROQUEL and 6% in placebo group. In these studies, the incidences of the individual EPS adverse reactions were generally low and did not exceed 4% in any treatment group.¹
- During clinical trials with quetiapine, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% of patients treated with quetiapine compared to 2.6% on placebo.¹

Dosing¹

- **Bipolar depression:** SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by day 4. In clinical trials, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for days 1-4, respectively; patients receiving 600 mg increased to 400 mg on day 5 and 600 mg on day 8 (week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg however; no additional benefit was seen in the 600 mg group.
- **Bipolar mania:** SEROQUEL should be initiated in BID doses totaling 100 mg/day on day 1, increased by 100 mg/day (in BID divided doses) increments to 400 mg/day on day 4, with further dosage adjustment up to 800 mg/day by day 6 (in increments of no more than 200 mg/day). The majority of patients responded to doses between 400-800 mg/day.
- **Bipolar maintenance:** Continue treatment at the dosage required to maintain symptom remission.
- **Schizophrenia:** SEROQUEL should generally be administered with an initial dose of 25 mg BID, with increases of 25-50 mg BID/TID on days 2 or 3, as tolerated, to a target dose range of 300-400 mg/day by day 4, given BID-TID. Efficacy was demonstrated in a dose range of 150-750 mg/day.

Dosage Strengths¹

SEROQUEL is available in 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg tablets.

References

¹ SEROQUEL Prescribing Information.

² Data on file, 267578, AstraZeneca LP.

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⁵ Yatham LN, Paulsson B, et al. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol*. 2004;24(6):599-606.

⁶ Vieta E, Mullen J, Brecher M, et al. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomized, placebo-controlled studies. *Curr Med Res and Opin*. 2005;21:923-934.

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⁸ Buckley PF. Efficacy of quetiapine for the treatment of schizophrenia: a combined analysis of three placebo-controlled trials. *Curr Med Res Opin*. 2004;20:1357-1363.

⁹ Brecher M, Liu S, Paulsson B. Quetiapine in the maintenance treatment of bipolar I disorder: combined data from two long-term, phase III studies [poster]. Presented at: the 3rd Biennial Conference of the International Society for Bipolar Disorders; January 27-28, 2008; Delhi, India; January 30, 2008; Agra, India.

¹⁰ Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord*. 2008;109(3):251-263.

¹¹ Suppes T, Vieta E, Liu S, et al. Maintenance treatment for patients with bipolar I disorder: Results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry*. 2009. In Press. doi:10.1177/appi.ajp.2008.08020189.

¹² Arvanitis LA, Miller BG, et al. Multiple fixed doses of 'SEROQUEL' (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Soc Biol Psychiatry*. 1997;42:233-246.

¹³ Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry*. 1997;54(6):549-557.

¹⁴ Data on file, 266268, AstraZeneca LP.