July 31, 2009

Mr. Bob Faller
ID State Medicaid Program
3232 Elder St
Boise, ID 83705

Dear Mr. Faller:

Your Regional Scientific Manager, Jen Kammerer, has forwarded your request regarding SEROQUEL® (quetiapine fumarate) Tablets / SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets. The following information is attached for your review:

- **SEROQUEL - CLINICAL EXECUTIVE SUMMARY**
- **SEROQUEL XR - CLINICAL EXECUTIVE SUMMARY**

The attached information is supplied to you as a professional courtesy in response to your request. These materials may include information that is not found in the currently approved prescribing information for SEROQUEL & SEROQUEL XR. The enclosed information is intended to provide pertinent data in response to your request and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for SEROQUEL & SEROQUEL XR. Prescribing information for SEROQUEL & SEROQUEL XR may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933.

Thank you for your interest in SEROQUEL & SEROQUEL XR. If we may be of further assistance to you, please contact AstraZeneca at 1-800-236-9933.

Sincerely,

*Marian Quan, Pharm.D.*

Sr. Medical Information Manager

**Tel** 800 236 9933
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AstraZeneca

**SEROQUEL XR® (quetiapine fumarate) Extended-Release 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 XR Prescribing Information for complete product information**

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## Indications

SEROQUEL XR is indicated for acute depressive episodes associated with bipolar disorder, acute manic or mixed 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 acute and maintenance treatment of schizophrenia.[1]

## Clinical Characteristics

- SEROQUEL XR, dosed once daily, has comparable bioavailability to an equivalent total daily dose of SEROQUEL (quetiapine fumarate) (immediate release tablets) administered in divided doses, twice daily at steady-state.[1]
- Patients can achieve a dose within the recommended range as early as the second day of treatment for schizophrenia and bipolar mania, and as early as day 4 for bipolar depression.[1]
- SEROQUEL XR is effective in both acute bipolar depression and bipolar mania; and it is approved for the maintenance treatment of bipolar disorder as an adjunct therapy:
  - SEROQUEL XR is the only atypical FDA-approved for acute depressive, manic, and mixed episodes of bipolar disorder as monotherapy[2]
  - In an 8-week, randomized, double-blind, placebo-controlled study in outpatients with bipolar I or II disorder, with or without rapid cycling (N=280), SEROQUEL XR (300 mg/day) showed significantly greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) total score compared with placebo from week 1 through week 8 ($p<0.001$). The mean change in MADRS total score at week 8 was -17.4 vs. -11.9, for SEROQUEL XR and placebo, respectively ($p<0.001$).[1,3]
  - In a 3-week randomized, double-blind, placebo-controlled study of patients with manic or mixed episodes associated with bipolar I disorder, with or without psychotic features (N=316), SEROQUEL XR (400-800 mg/day, flexibly dosed) was superior to placebo in the reduction of Young Mania Rating Scale (YMRS) from baseline to endpoint (-14.34 vs. -10.52, respectively; $p<0.001$). The differences were statistically significant as early as day 4 ($p<0.001$).[1,4]
- SEROQUEL XR demonstrated efficacy across a broad range of acute schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) total, subscales, and cluster scores; and a reduction in the risk of relapse in the longer-term:
  - In a 6-week, randomized, double-blind clinical study of inpatients and outpatients with schizophrenia (N=573), SEROQUEL XR doses of 400 mg, 600 mg and 800 mg once daily were superior to placebo in improvement in the PANSS total score from baseline to Day 42.[1,5] Mean improvements in PANSS positive subscale, general psychopathology subscale, and hostility and aggression cluster scores were statistically significant for all SEROQEUL XR groups vs. placebo. Mean improvements in PANSS negative subscale and depression cluster scores versus placebo were statistically significant for SEROQUEL XR 600 and 800 mg/day.[5]
  - In a longer-term study, clinically stable schizophrenia outpatients (N=171) who remained stable following 16 weeks of open-label treatment with SEROQUEL XR were randomized to continue SEROQUEL XR (400-800 mg/day) or to receive placebo.[1,6] Patients treated with SEROQUEL XR experienced a significantly longer time to relapse vs. placebo. The relative risk of relapse in patients treated with SEROQUEL XR was significantly reduced by 84% (hazard ratio 0.16) compared with patients receiving placebo. Fewer patients experienced relapse in the SEROQUEL XR group (10.7%) compared with patients in the placebo group (41.4%). The mean randomized study duration with SEROQUEL XR was 120 days and the maximum time was 270 days.[6]

## Safety

- SEROQUEL XR 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 XR is <u>not</u> 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 XR 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):* Manage with immediate discontinuation and close monitoring.
  - *Tardive Dyskinesia*: Discontinue if clinically appropriate.
  - *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.
  - *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.
  - *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 reported adverse reactions (incidence ≥ 5% and twice placebo) associated with the use of SEROQUEL XR in clinical trials were somnolence, dry mouth, hyperlipidemia, constipation, dyspepsia, dizziness, orthostatic hypotension, weight gain, increased appetite, fatigue, hyperglycemia, dysarthria, and nasal congestion.[1]
- In short-term (≤12 weeks) clinical trials that included SEROQUEL XR and SEROQUEL, 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 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 ≥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 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 XR (6 weeks), the percentage of patients with shifts from normal to clinically significant levels of cholesterol (≥240 mg/dL) and triglycerides (≥200 mg/dL) were 9% and 18%, respectively, for SEROQUEL XR, and 9% and 5%, respectively, for placebo. In the 8-week bipolar depression trial, the percentage of shifts for cholesterol and triglycerides were 7% and 8%, respectively, for SEROQUEL XR and 3% and 8%, respectively, for placebo. In the 3-week bipolar mania trial, the percentage of shifts for cholesterol and triglycerides were 7% and 15%, respectively, for SEROQUEL XR and 4% and 6%, respectively, for placebo.[1]
- No discontinuations due to weight gain were observed in SEROQUEL XR short-term schizophrenia or bipolar disorder pivotal trials.[4,7,8] In schizophrenia trials with SEROQUEL XR, the percentage of patients with a weight gain of ≥7% was 10% for SEROQUEL XR and 5% for placebo. In the bipolar depression clinical trial, the percentage of patients with a weight gain ≥7% was 8.2% for SEROQUEL XR compared to 0.8% for placebo. In the acute mania trial, the incidences were 5.1% compared to 0%, respectively.[1]
- In schizophrenia trials, the incidences of any adverse reactions potentially related to extrapyramidal symptoms (EPS) symptoms were 8% for SEROQUEL XR, 8% for SEROQUEL, and 5% for placebo. In the bipolar depression trial, the incidence was 4.4% for SEROQUEL XR and 0.7% for placebo. In the bipolar mania trial, the incidence was 6.6% for SEROQUEL XR and 3.8% for placebo.[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]

## Dosing[1]

- SEROQUEL XR should be taken without food or with a light meal (approximately 300 calories). It should be swallowed whole and not split, chewed, or crushed.
- *Bipolar depression:* SEROQUEL XR should be administered once daily in the evening to reach 300 mg/day by day 4. The recommended dosing schedule is 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4.
- *Bipolar mania:* 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.
- *Bipolar maintenance:* Continue treatment at the dosage required to maintain symptom remission.
- *Schizophrenia*: 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 individual response and tolerance. Dose increases of 300 mg/day can be made (maximum daily dose 800 mg/day).
- Patients who are currently being treated with divided doses of SEROQUEL (immediate release formulation) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily.

## Dosage Strengths

SEROQUEL XR is available in 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg tablets.

## References


[1] SEROQUEL XR Prescribing Information
[2] Data on file, 272661, AstraZeneca LP.
[3] Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression [poster]. Presented at: the 8th Annual International Review of Bipolar Disorders Conference; April 14-16, 2008; Copenhagen, Denmark.
[4] Cutler A, Datto C, Nordenhem A, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar mania [poster]. Presented at: the 8th Annual International Review of Bipolar Disorders Conference; April 14-16, 2008; Copenhagen, Denmark.
[5] Kahn RS, Schulz SC, Palazov V, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68:832-842.
[6] Peuskens J, Trivedi J, Malyarov S, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: A randomized, placebo-controlled trial in clinically stable patients. *Psychiatry 2007*. 2007; 4(11):34-50.
[7] In House Data, AstraZeneca LP. Quetiapine extended-release for the treatment of schizophrenia-Summary of Clinical Safety. June, 2006
[8] In House Data, AstraZeneca LP, D144CC00002.