

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022047Orig1s000**

**LABELING**

**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.

- Atypical antipsychotic drugs are associated with an increased risk of death (5.1)
- Causes of death are variable (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychoses (5.1)

**INDICATIONS AND USAGE**

SEROQUEL XR is an atypical antipsychotic agent indicated for:

- The treatment of schizophrenia (1)

**DOSAGE AND ADMINISTRATION**

**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. 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).

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

None

**WARNINGS AND PRECAUTIONS**

- Increased Mortality in Elderly Patients with Dementia Related Psychoses:** Atypical antipsychotic drugs, including quetiapine, are associated with an increased risk of death; causes of death are variable.
- 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. (5.2)
- Neuroleptic Malignant Syndrome (NMS):** Potentially fatal symptom complex has been reported with antipsychotic drugs, including quetiapine. (5.3)
- Orthostatic hypotension:** Associated dizziness, tachycardia and syncope especially during the initial dose titration period. (5.4)
- Tardive Dyskinesia** may develop acutely or chronically (5.5)

- Cataracts:** Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination should be done when starting treatment and at 6 months intervals during chronic treatment (5.6).
- Hyperlipidemia (5.9)**
- The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy (5.16)
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS.**

**ADVERSE REACTIONS**

Most common adverse reactions (incidence ≥ 5% and greater than placebo) are dry mouth, constipation, dyspepsia, sedation, somnolence, dizziness, and orthostatic hypotension. (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:** For the initial dosing in the elderly use the immediate release formulation of SEROQUEL instead of SEROQUEL XR. Consider a lower starting dose (25mg/day immediate release formulation), slower titration, and careful monitoring during the initial dosing period in the elderly (2.2 and 8.5).
- Hepatic Impairment:** For the initial dosing in patients with hepatic impairment, use the immediate release formulation of SEROQUEL instead of SEROQUEL XR. Lower starting doses (25 mg/day immediate release formulation) and slower titration may be needed (2.2, 8.7, 12.3).
- Pregnancy and Lactation:** Quetiapine should be used only if the potential benefit justifies the potential risk (8.1) Breast feeding is not recommended (8.3).
- Pediatric Use:** Safety and effectiveness have not been established.

**SEE 17 FOR PATIENT COUNSELING INFORMATION**  
**Revised 5/2007**

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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 atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL XR is not approved for the treatment of patients with Dementia-Related Psychosis.

## **1 INDICATIONS AND USAGE**

SEROQUEL XR is indicated for the 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. In addition, the efficacy of SEROQUEL XR was demonstrated in 1 short-term (6-week) controlled trial of schizophrenic inpatients and outpatients [see *Clinical Studies* (14)].

The effectiveness of SEROQUEL XR in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see *Dosage And Administration* (2.3)].

## **2. DOSAGE AND ADMINISTRATION**

### **2.1 Usual Dose**

SEROQUEL XR should be administered once daily, preferably in the evening.<sup>4</sup>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)]. 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.

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)].

## 2.2 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* (8.7,8.8) and *Clinical Pharmacology* (12)]. When indicated, dose escalation should be performed with caution in these patients.

For those patients who require less than 200 mg per dose of SEROQUEL XR during the initial titration, use the immediate release formulation.

Elderly patients should be started on SEROQUEL immediate release formulation 25 mg/day and the dose can be increased in increments of 25-50 mg/day depending on the response and tolerance of the individual patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose [*see Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets* 2.5)].

Patients with hepatic impairment should be started on SEROQUEL immediate release formulation 25 mg/day. The dose can be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerance of the patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose [*see Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets* 2.5)].

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)].

### 2.3 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, it is recommended that responding patients be continued on SEROQUEL XR, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 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

Schizophrenic patients who are currently being treated with divided doses of SEROQUEL (immediate release formulation, eg. 2 to 3 times per day) 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 with schizophrenia 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 with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia 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

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 atypical 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 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 antipsychotics, 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.

### 5.3 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 (e.g., 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.

### 5.4 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  $\alpha_1$ -adrenergic antagonist properties. Syncope was reported in 0.3% (3/951) of the patients treated with SEROQUEL XR, compared with 0.3% (1/319) on placebo. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo.

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.

## 5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. 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, quetiapine 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 quetiapine, drug discontinuation should be

considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

## 5.6 Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). 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.

## 5.7 Seizures

During clinical trials with SEROQUEL XR, seizures occurred in 0.1% (1/951) of patients treated with SEROQUEL XR compared to 0.9% (3/319) on placebo. During clinical trials with SEROQUEL, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo. As with other antipsychotics quetiapine 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.

## 5.8 Hypothyroidism

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 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of these patients with TSH increases needed replacement thyroid treatment.

## 5.9 Cholesterol and Triglyceride Elevations

In schizophrenia clinical trials, SEROQUEL XR treated patients had increases from baseline in mean cholesterol and triglycerides of 4% and 15%, respectively compared to decreases from baseline in mean cholesterol and triglycerides of 2% and 6% for placebo treated patients. In schizophrenia clinical trials, SEROQUEL treated patients had increases from baseline in mean cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients.

## 5.10 Hyperprolactinemia

An elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL XR as compared with placebo. Increased prolactin levels with quetiapine were observed in rat toxicity studies, and were associated with an increase in mammary gland neoplasia in rats. [see *Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)]. 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 contemplated in a patient with previously detected breast cancer.

## 5.11 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 6-week placebo controlled schizophrenia trials were approximately 1% 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 SEROQUEL.

## 5.12 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 and sedation were reported in 12% and 13% of patients on SEROQUEL XR respectively compared to 4% and 7% of placebo patients. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% 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.

#### 5.13 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  $\alpha$ -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.

#### 5.14 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.

#### 5.15 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.

#### 5.16 Suicide

The possibility of a suicide attempt is inherent in schizophrenia; 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, as measured by the Columbia Analysis of Suicidal Behavior, was low in Seroquel XR treated patients (0.6%) and similar to placebo (0.9%).

### 5.17 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* (5.4)].

### 5.18 Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine. 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 951 patients exposed to SEROQUEL XR for the treatment of schizophrenia in placebo controlled trials. This experience corresponds to approximately 82.9 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 event 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 trials.

#### Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Short-Term, Placebo-Controlled Trials

Table 1 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 1. Treatment-Emergent Adverse Experience Incidence in 6-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia<sup>1</sup>**

<b>Body System/Preferred Term</b>	<b>SEROQUEL XR (n=951)</b>	<b>PLACEBO (n=319)</b>
<b>Gastrointestinal Disorders</b>		
Dry mouth	12%	1%
Constipation	6%	5%
Dyspepsia	5%	2%
<b>Nervous System Disorders</b>		
Sedation	13%	7%
Somnolence	12%	4%
Dizziness	10%	4%
<b>Vascular Disorders</b>		
Orthostatic hypotension	7%	5%

<sup>1</sup>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.

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 dry mouth (12%), somnolence (12%), dizziness (10%), and dyspepsia (5%).

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 that have historically been associated with the use of SEROQUEL and not listed elsewhere in the label

The following adverse reactions have also been reported with SEROQUEL: anaphylactic reaction, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels and restless legs syndrome.

#### Extrapyramidal Symptoms:

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.

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.

## 6.2 Vital Signs and Laboratory Studies

### Vital Sign Changes:

Quetiapine is associated with orthostatic hypotension [see *Warnings And Precautions* (5)].

### Weight Gain:

In schizophrenia trials with SEROQUEL XR, the proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight was 10% for SEROQUEL XR compared to 5% for placebo. 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%).

### Laboratory Changes:

An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in ALT and increases in both total cholesterol and triglycerides [see *Warnings and Precautions* (5)]. In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed.

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.

### ECG Changes:

0.8% of SEROQUEL XR patients, and no 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 decrease of 1 beat per minute for placebo. This is consistent with the rates of 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)*].

### 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 were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, cardiomyopathy hyponatremia, myocarditis rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Stevens-Johnson syndrome (SJS).

## 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 (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) [*see Dosage and Administration* (2)].

#### Divalproex

Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) 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 bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

#### Cimetidine

Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). 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 is indicated when SEROQUEL XR is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

#### Fluoxetine, Imipramine, Haloperidol, and Risperidone

Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) 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 tid 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 bid) was administered with quetiapine (150 mg bid). The mean oral clearance of

total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

#### Lithium

Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

#### Antipyrine

Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C: The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m<sup>2</sup> basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m<sup>2</sup> basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m<sup>2</sup> basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m<sup>2</sup> basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## 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 in milk of treated animals during lactation. It is not known if SEROQUEL XR is excreted in human milk. It is recommended that women receiving SEROQUEL XR should not breast feed.

## 8.4 Pediatric Use

The safety and effectiveness of SEROQUEL XR in pediatric patients have not been established.

## 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 Use in Special Populations (2.2) 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 *Dosing and Administration* (2.2) 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, (e.g., development of tolerance, increases in dose, drug-seeking behaviour).

## 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 (5.4)*] 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

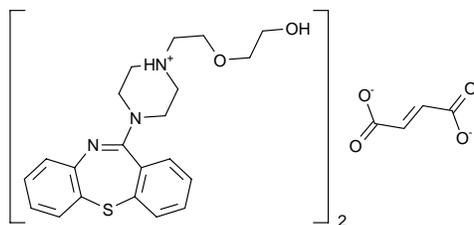
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or 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  $\alpha$ -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  $\beta$  stimulation may worsen hypotension in the setting of quetiapine-induced  $\alpha$  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<sup>®</sup> (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<sub>42</sub>H<sub>50</sub>N<sub>6</sub>O<sub>4</sub>S<sub>2</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> 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 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 (200 and 300 mg tablets) are included in the film coating of specific strengths.

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

## **12. CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

The mechanism of action of quetiapine, as with other drugs having efficacy in the treatment of schizophrenia, 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 ( $5HT_2$ ) antagonism by quetiapine and its active metabolite N-desalkyl quetiapine.

Antagonism at receptors other than dopamine  $D_2$  and serotonin  $5HT_2$  with similar or greater affinities may explain some of the other effects of quetiapine and N-desalkyl quetiapine; antagonism at histamine  $H_1$  receptors may explain the somnolence and antagonism at adrenergic  $\alpha_1$  receptors may explain the orthostatic hypotension observed with this drug.

### **12.2 Pharmacodynamics**

Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: serotonin  $5HT_{1A}$  and  $5HT_2$  ( $IC_{50s}=717$  &  $148nM$  respectively), dopamine  $D_1$  and  $D_2$  ( $IC_{50s}=1268$  &  $329nM$  respectively), histamine  $H_1$  ( $IC_{50}=30nM$ ), and adrenergic  $\alpha_1$  and  $\alpha_2$  receptors ( $IC_{50s}=94$  &  $271nM$ , respectively). Quetiapine has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors ( $IC_{50s}>5000$  nM).

### **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 N-desalkyl quetiapine, 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 N-desalkyl quetiapine 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 9 to 12 hours for N-desalkyl quetiapine 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<sub>max</sub> 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<sub>max</sub> 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 <sup>14</sup>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 N-desalkyl quetiapine .

### 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 ( $CL_{cr}=10-30$  mL/min/ $1.73m^2$ ,  $n=8$ ) had a 25% lower mean oral clearance than normal subjects ( $CL_{cr}>80$  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)*].

## 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)*].

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 (800 mg/day) on a mg/m<sup>2</sup> basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m<sup>2</sup> 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<sup>2</sup> basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis. Mammary gland adenocarcinomas were statistically significantly 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<sup>2</sup> 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-yr 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 (5.10)*].

### 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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{kg}$  even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25  $\text{mg}/\text{kg}$ , or 0.3 times the maximum human dose on a  $\text{mg}/\text{m}^2$  basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50  $\text{mg}/\text{kg}$ , or 0.6 times the maximum human dose on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{kg}$ , or 0.1 and 0.6 times the maximum human dose on a  $\text{mg}/\text{m}^2$  basis. The no effect dose in female rats was 1  $\text{mg}/\text{kg}$ , or 0.01 times the maximum human dose on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{kg}$  in rats, 75-750  $\text{mg}/\text{kg}$  in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{kg}$ , or 4 times the maximum recommended human dose on a  $\text{mg}/\text{m}^2$  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 cholestanol 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  $\text{mg}/\text{kg}$  or 5.5 times the maximum recommended human dose on a  $\text{mg}/\text{m}^2$  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.

## **15 REFERENCES**

None

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

- 200 mg Tablets (NDC 0310-0282) yellow, film coated, capsule-shaped, biconvex, intagliated tablet with “SR 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 “SR 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 “SR 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**

### **Hyperglycemia and Diabetes Mellitus**

Patients should be aware of the symptoms of hyperglycemia (high blood sugar, polydipsia, polyuria, polyphagia, and weakness) and be advised regarding the risk of 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.

#### **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Patients and caregivers should be advised that elderly patients with dementia-related psychoses 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.

#### **Orthostatic Hypotension**

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

#### **Interference with Cognitive and Motor Performance**

Patients should be advised of the risk of somnolence or sedation, 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.

#### **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.

#### **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.

#### **Heat Exposure and Dehydration**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

#### **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.

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Wilmington, DE 19850

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Rev. XX/XX

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