

SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets

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 (eg, development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

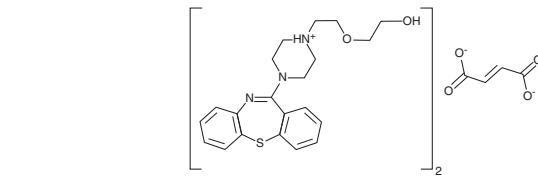
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. 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 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 Overdose

In case of acute overdose, 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 overdose of SEROQUEL XR. Similarly, it is reasonable to expect that the α -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 initiated. 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 β stimulation may worsen hypotension in the setting of quetiapine-induced α blockade. In cases of severe extrapyramidal symptoms, anticholinergic agents and medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

SEROQUEL XR (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-cibenzo [b,f] [1,1d]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 $C_{24}H_{26}N_{10}O_5 \cdot S_2 \cdot C_4H_2O_4$ and 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 50 mg (peach), 150 mg (white), 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 (50, 200 and 300 mg tablets) are included in the film coating of specific strengths.

Each 50 mg tablet contains 58 mg of quetiapine fumarate equivalent to 50 mg quetiapine. Each 150 mg tablet contains 174 mg of quetiapine fumarate equivalent to 150 mg quetiapine. Each 200 mg tablet contains 230 mg of quetiapine fumarate equivalent to 200 mg quetiapine. Each 300 mg tablet contains 345 mg of quetiapine fumarate equivalent to 300 mg quetiapine. Each 400 mg tablet contains 461 mg of quetiapine fumarate equivalent to 400 mg quetiapine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of quetiapine is unknown; however, it is believed that the drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D₂) and serotonin type 2 (5HT₂) receptor antagonism, with the metabolite N-desalkyl quetiapine (norquetiapine) having similar activity at D₂, but greater activity at 5HT_{2A} receptors than the parent drug. Quetiapine's efficacy in bipolar depression may partly be explained by the high affinity and potent inhibitory effects that norquetiapine exhibits for the norepinephrine transporter.

Antagonism at receptors other than dopamine and serotonin with similar or greater affinities may explain some of the other effects of quetiapine and norquetiapine: antagonism at histamine H₁ receptors may explain the somnolence, antagonism at adrenergic α_1 receptors may explain the orthostatic hypotension, and antagonism at muscarinic M₁ receptors may explain the anticholinergic effects.

12.2 Pharmacodynamics

Quetiapine and norquetiapine have affinity for multiple neurotransmitter receptors including dopamine D₁ and D₂, serotonin 5HT_{1A} and 5HT_{2A}, histamine H₁, muscarinic, and adrenergic α_1 and α_2 receptors. Quetiapine differs from norquetiapine in having no appreciable affinity for muscarinic M₁ receptors whereas norquetiapine has high affinity. Quetiapine and norquetiapine lack appreciable affinity for benzodiazepine receptors.

| Receptor Affinities (Ki, nM) for Quetiapine and Norquetiapine | Quetiapine | Norquetiapine |
|---|------------|---------------|
| Receptor | | |
| Dopamine D ₁ | 426 | 69.8 |
| Dopamine D ₂ | 628 | 489 |
| Serotonin 5HT _{1A} | 1040 | 191 |
| Serotonin 5HT _{2A} | 38 | 2.9 |
| Norepinephrine transporter | >10000 | 34.9 |
| Histamine H ₁ | 4.41 | 1.15 |
| Adrenergic α_1 b | 14.6 | 46.4 |
| Adrenergic α_2 | 617 | 1290 |
| Muscarinic | 1086 | 38.3 |
| Benzodiazepine | >10000 | >10000 |

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 norquetiapine, 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 norquetiapine are about 21-27% and 48-56%, 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 approximately 12 hours for norquetiapine 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 cytochromes 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_{max} 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_{max} 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 10x4 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 ¹⁴C-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 sulfidation 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 norquetiapine.

Age

Oral clearance of quetiapine was reduced by 40% in elderly patients (> 65 years, n = 9) compared to young patients (n = 15), and dosing adjustment may be necessary [see Dosage and Administration (2.3)].

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/1.73m², n=8) had a 25% lower mean oral clearance than normal subjects (CL_{CR} >30 mL/min/1.73m², n=8), but plasma quetiapine concentrations in the patients with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dose 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 (2.3)].

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 (2.3)].

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 for schizophrenia and bipolar mania (800 mg/day) on a mg/m² basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m² 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/m² basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. Mammary gland adenocarcinomas were statistically significant 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/m² 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-year 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 (5.12)].

Mutagenesis

The mutagenic potential of quetiapine was tested *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficient 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 mg/m² basis. Drug related effects included increases in the number of matings required for successful impregnation. These effects were not observed or observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m² basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m² 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 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m² basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m² basis.

13.2 Animal Toxicology and/or Pharmacology

Quetiapine caused a dose-related increase in pigment deposition in thyrocyd 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 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m² 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 mg/kg, or 4 times the maximum recommended human dose on a mg/m² 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 levels and the presence of cataracts in individual dogs. The appearance of delta 8 cholesterol 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 27 females at a dose of 225 mg/kg or 4.5 times the maximum recommended human dose on a mg/m² 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=570) 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.

In a long-term trial, clinically stable adult outpatients (n=171) meeting DSM-IV criteria for schizophrenia who remained stable during the open label phase with flexible doses of SEROQUEL XR (400-800 mg/day) were randomized to placebo or to continue on their current SEROQUEL XR (400-800 mg/day) for observation for possible relapse during the double-blind continuation (maintenance) phase. Stabilization during the open label phase was defined as receiving a stable dose of SEROQUEL XR and having a CGI-S₄ and a PANSS score <60 from beginning to end of this open-label phase (with no increase of ≥ 10 points in PANSS total score). Relapse during the double-blind phase was defined in terms of a $\geq 30\%$ increase in the PANSS Total score, or CGI-Improvement score of ≥ 6 , or hospitalization due to increase in psychotic symptoms. Patients who received placebo or SEROQUEL XR experienced a statistically significant longer time to relapse than did patients on placebo.

14.2 Bipolar Disorder

Depressive Episodes Associated with Bipolar Disorder

The efficacy of SEROQUEL XR for the acute treatment of depressive episodes associated with bipolar disorder in patients who met DSM-IV criteria for bipolar disorder was established in one 8-week, randomized, double-blind, placebo-controlled study (N=280 outpatients). This study included patients with bipolar I and II disorder, and those with and without a rapid cycling course. Patients randomized to SEROQUEL XR were administered 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3 and 300 mg on Day 4 and after.

The primary rating instrument used to assess depressive symptoms was the Montgomery-Åsberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale with scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at week 8. SEROQUEL XR was superior to placebo in reduction of MADRS score at week 8.

The efficacy of SEROQUEL for the treatment of depressive episodes associated with bipolar disorder was established in 2 identical 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the MADRS. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score at week 8. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Bipolar Mania

The efficacy of SEROQUEL XR in the acute treatment of manic episodes was established in one 3-week, placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features (N=318). Patients were hospitalized for a minimum of 4 days at randomization. Patients randomized to SEROQUEL XR received 300 mg on Day 1 and 600 mg on Day 2. Afterwards, the dose could be adjusted between 400 mg and 800 mg per day.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptoms in a range from 0 (no manic features) to 60 (maximum score). SEROQUEL XR was superior to placebo in the reduction of the YMRS total score at week 3.

The efficacy of SEROQUEL in the treatment of acute manic episodes was also established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the YMRS score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=599) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In a 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS ≥ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score. The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Maintenance Therapy

The efficacy of SEROQUEL in the maintenance treatment of Bipolar I Disorder was established in 2 placebo-controlled trials in patients (n=1326) who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stable on SEROQUEL plus lithium or divalproex for at least 12 weeks in order to be randomized. On average, patients were stabilized for 15 weeks. In the randomized phase, patients continued treatment with lithium or divalproex and were randomized to receive either SEROQUEL (administered twice daily totaling 400 to 800 mg per day) or placebo. Approximately 50% of the patients had discontinued from the SEROQUEL group by day 280 and 50% of the placebo group had discontinued by day 117 of double-blind treatment. The primary endpoint in these studies was time to recurrence of a mood event (manic, mixed or depressed episode). A mood event was defined as medication initiation or hospitalization for a mood episode; YMRS score ≥ 20 or MADRS score ≥ 20 at 2 consecutive assessments; or study discontinuation due to a mood event. In both studies, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event. The treatment effect was present for both manic and depressed episodes. The effect of SEROQUEL was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

SEROQUEL XR 50 mg tablets (peach, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 50" 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.

150 mg Tablets (NDC 0310-0291) white, film-coated, capsule-shaped, biconvex, intagliated tablet with "XR 150" 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.

200 mg Tablets (NDC 0310-0292) yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 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 0310-0293) pale yellow, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 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 0310-0294) white, film coated, capsule-shaped, biconvex, intagliated tablet with "XR 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.

Stone SEROQUEL XR at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP:

17 PATIENT COUNSELING INFORMATION

Information for Patients

Hypertension and Diabetes Mellitus

Patients should be advised 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 [see Warnings and Precautions (5.3)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is not approved for elderly patients with dementia-related psychosis [see Warnings and Precautions (5.1)].

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be subtle. Such symptoms should be reported immediately to the prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk of suicidal thinking and action and indicate a need for very close monitoring and possible changes in the medication [see Warnings and Precautions (5.2)].

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should caution them in its appropriate use. A Patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or light-headed upon standing, which may lead to falls) especially during the period of initial dose titration, and also the risks of continuing treatment or increases in dose [see Warnings and Precautions (5.3)].

Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL XR [see Warnings and Precautions (5.6)].

Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation (which may lead to falls), 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 automatic) or operating machinery, until they are reasonably certain quetiapine fumarate therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine [see Warnings and Precautions (5.14)].

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 [see Use in Specific Populations (8.3)].

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 [see Warnings and Precautions (5.4)].


17.2 MEDICATION GUIDE

The primary rating instrument used to assess depressive symptoms in these studies was the MADRS. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score at week 8. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Medication Guide

SEROQUEL XR (SER-oh-kwell)

Generic name: quetiapine fumarate

| | |
|---|---------|
| Seroquel XR PI (for Bottles and Blister 3) | |
| Material No. 35284-00 | ■ Black |
| CR # 13145 | |
| Dimensions: 34" x 13.5" (flat size) | |
| Plate Date 1/09/09 10:10 am SZT AstraZeneca  | |

Notes to Printer:

Software: Adobe InDesign 3.0.1

Fonts: Helvetica Medium, Bold, Oblique, Bold Oblique; Times Roman; Symbol; OCRB

Barcode: The use of codes provided in artwork is optional; replace if code specifications do not meet press requirements.

8-digit 1 2 of 5
Magnification 38.8, Narrow Bar .0155, Ratio 2.5, Bar Adjust -.002, Encodation: 03528400

HRC: C37