FINAL PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAME (and dosage form):

Seroquel® XR 50; Seroquel® XR 150; Seroquel® XR 200; Seroquel® XR 300; Seroquel® XR 400 (Tablet)

COMPOSITION:

50 mg XR prolonged-release tablet:

Each tablet contains quetiapine fumarate equivalent to 50 mg of quetiapine free base.

150 mg XR prolonged-release tablet:

Each tablet contains quetiapine fumarate equivalent to 150 mg of quetiapine free base.

200 mg XR prolonged-release tablet:

Each tablet contains quetiapine fumarate equivalent to 200 mg of quetiapine free base.

300 mg XR prolonged-release tablet:

Each tablet contains quetiapine fumarate equivalent to 300 mg of quetiapine free base.

400 mg XR prolonged-release tablet:

Each tablet contains quetiapine fumarate equivalent to 400 mg of quetiapine free base.

Contains sugar (lactose monohydrate).

List of excipients:

Microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hydroxypropyl methycellulose, polyethylene glycol 400, titanium dioxide and iron oxide.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Central nervous system depressants: Miscellaneous structures

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to dopamine D_2 receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic $alpha_1$ receptors, with a lower affinity at adrenergic $alpha_2$ and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

In animal models, quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance.

It also reverses the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2 receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor super-sensitivity after chronic administration.

Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Pharmacokinetic properties:

Quetiapine is absorbed and extensively metabolised following oral administration.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the SEROQUEL XR C_{max} and AUC of 44-52% and 20-22%, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. This increase in exposure is not clinically significant, and therefore SEROQUEL XR can be taken with or without food.

Quetiapine is approximately 83% bound to plasma proteins.

Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine does not differ between men and women.

SEROQUEL XR achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}). SEROQUEL XR displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for SEROQUEL XR administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate (SEROQUEL tablets) administered twice daily.

When SEROQUEL XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (SEROQUEL) administered twice daily, the area under the quetiapine plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13% lower. When SEROQUEL XR administered once daily is compared to the same total daily dose of the immediate release formulation of quetiapine

(SEROQUEL) administered once daily, the quetiapine XR AUC is equivalent; and C_{max} is 59% lower. The AUC and C_{max} for the metabolite norquetiapine are 37% and 18% lower than the SEROQUEL, respectively.

The mean clearance of quetiapine in the elderly is approximately 30-50% lower than that seen in adults aged 18-65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73m^2), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5% excreted in the urine.

Metabolism:

Quetiapine is extensively metabolised by the liver with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean plasma clearance of quetiapine is reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis). Since quetiapine is extensively metabolised by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5-50 fold higher than those observed at a dose range of 300-800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of SEROQUEL XR with other medicines will result in clinically significant medicine inhibition of cytochrome P450 mediated metabolism of the other medicine.

INDICATIONS:

SEROQUEL XR is indicated for the treatment of:

- Schizophrenia
- Preventing relapse in stable schizophrenic patients who have been maintained on SEROQUEL XR
- Bipolar disorder including:
    - Manic episodes associated with bipolar disorder
    - Depressive episodes associated with bipolar disorder
    - Preventing recurrence in the maintenance treatment of bipolar disorder (manic, mixed or depressive episodes) as monotherapy or in combination with mood stabilisers
- Major depressive disorder
- Preventing relapse in stable major depressive disorder patients who have been maintained on SEROQUEL XR.

CONTRA-INDICATIONS:

SEROQUEL XR is contra-indicated in patients who are hypersensitive to any component of this product.

WARNINGS:

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine.

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 (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic

was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

INTERACTIONS:

Given the primary central nervous system effects of quetiapine, SEROQUEL XR should be used with caution in combination with other centrally acting medicines and alcohol.

Caution should be exercised when SEROQUEL XR is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see "*Side-effects and Special precautions*").

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of quetiapine and thioridazine caused increases in clearance of quetiapine.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine.

This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence, in each patient, consideration for a higher dose of SEROQUEL XR, depending on clinical response, should be considered. The safety of doses above 800 mg/day has not been established in the clinical trials.

Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of SEROQUEL XR may be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL XR and phenytoin, and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc). The dose of SEROQUEL XR may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of SEROQUEL XR given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of SEROQUEL XR of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%.

The mean half-life of SEROQUEL XR increased from 2,6-6,8 hours, but the mean T_{max} was unchanged. Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of SEROQUEL XR and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors).

PREGNANCY AND LACTATION:

SEROQUEL XR is contra-indicated during pregnancy and lactation, as safety has not been demonstrated.

The degree to which quetiapine is excreted into human milk is unknown. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking SEROQUEL XR.

DOSAGE AND DIRECTIONS FOR USE:

SEROQUEL XR should be administered once daily, with or without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia:

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400-800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of manic episodes associated with bipolar disorder:

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400-800 mg per day, depending on the clinical response and tolerability of the patient.

For the treatment of depressive episodes associated with bipolar disorder:

SEROQUEL XR should be administered once daily in the evening.

SEROQUEL XR should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). SEROQUEL XR can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with SEROQUEL at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group during short-term treatment.

For preventing recurrence in maintenance treatment of bipolar disorder:

Patients who have responded to SEROQUEL XR in combination therapy to a mood stabiliser (lithium or valproate) for acute treatment of bipolar disorder should continue on SEROQUEL XR therapy at the same dose. The SEROQUEL XR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 400-800 mg/day. Patients who have responded to SEROQUEL XR for acute treatment of bipolar disorder should continue on SEROQUEL XR therapy at the same dosing regimen.

SEROQUEL XR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300-800 mg/day.

For the treatment of major depressive disorder:
SEROQUEL XR should be administered once daily in the evening.

Initial dosing should begin at 50 mg on Day 1 and 2, increased to 150 mg on Day 3 and 4. Further adjustments can be made upwards or downwards within the recommended dose range of 50-300 mg depending upon the clinical response and tolerability of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient.

Switching from SEROQUEL immediate-release tablets:
For more convenient dosing, patients who are currently being treated with divided doses of SEROQUEL immediate release (SEROQUEL tablets) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly:
SEROQUEL XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of SEROQUEL XR may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30-50% in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance of the individual patient.

In elderly patients with major depressive disorder initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8 and then up to 300 mg depending on clinical response and tolerability.

Children and adolescents:

The safety and efficacy of SEROQUEL XR have not been evaluated in children and adolescents.

Renal and hepatic impairment:

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolised by the liver. Therefore, SEROQUEL XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

The most commonly reported adverse drug reactions (ADRs) with SEROQUEL XR are somnolence, dizziness, dry mouth, asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

Weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema; have been associated with SEROQUEL XR.

System Organ Class	Frequency	Event
Gastrointestinal disorders	Very common (≥ 10%)	Dry mouth
	Common (≥ 1% - < 10%)	Constipation; Dyspepsia
	Uncommon (≥ 0,1% - < 1%)	Dysphagia[9]
Nervous system disorders	Very common (≥ 10%)	Dizziness [6, 16]; Somnolence [2, 16]
	Common (≥ 1% - < 10%)	Syncope[6, 16]; Extrapyramidal symptoms[1,16]; Dysarthria
	Uncommon (≥ 0,1% - < 1%)	Seizure[1]; Restless legs syndrome;

System Organ Class	Frequency	Event
		Tardive dyskinesia
Blood and lymphatic system disorders	Common (≥ 1% - < 10%)	Leukopenia
	Uncommon (≥ 0,1% - < 1%)	Eosinophilia
Cardiac disorders	Common (≥ 1% - < 10%)	Tachycardia[6]
Eye disorders	Common (≥ 1% - < 10%)	Blurred vision
Metabolism and nutrition disorders	Common (≥ 1% - < 10%)	Increased appetite
Psychiatric disorders	Common (≥ 1% - < 10%)	Abnormal dreams and nightmares
Respiratory, thoracic, and mediastinal disorders	Common (≥ 1% - < 10%)	Rhinitis
Vascular disorders	Common (≥ 1% - < 10%)	Orthostatic hypotension[1, 6, 16]
Renal and urinary disorders	Common (≥ 1% - < 10%)	Urinary tract infection[18]
Immune system disorders	Uncommon (≥ 0,1% - < 1%)	Hypersensitivity[7]
	Rare (≥ 0,01% - < 0,1%)	Anaphylactic reaction[19]
Reproductive system and breast disorders	Rare (≥ 0,01% - < 0,1%)	Priapism; Galactorrhoea
General disorders and administration site conditions	Very common (≥ 10%)	Headache[18]; Withdrawal (discontinuation) symptoms[1, 10]
	Common (≥ 1% - < 10%)	Asthenia; Peripheral oedema; Irritability
	Rare (≥ 0,01% - < 0,1%)	Neuroleptic malignant syndrome[1]
Investigations	Very common (≥ 10%)	Elevations in serum triglyceride levels[11]; Elevations in total cholesterol (predominantly LDL cholesterol)[12]; Decreases in HDL Cholestrol[17]; Weight gain[4]
	Common (≥ 1% - < 10%)	Elevations in serum transaminases (ALT, AST)[5]; Decreased neutrophil count[3]; Increased blood glucose to hyperglycaemic level[8]; Elevations

System Organ Class	Frequency	Event
		in serum prolactin[15]
	Uncommon (≥ 0,1% - < 1%)	Elevations in gamma-GT levels[5]; Platelet count decreased[14]
	Rare (≥ 0,01% - < 0,1%)	Elevations in blood creatine phosphokinase[13]

[1] See "*Special precautions"*.

[2] Somnolence may occur, usually during the first 2 weeks of treatment and generally resolves with the continued administration of SEROQUEL XR.

[3] In all placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥ 1,5 X 10^9/litre, the incidence of at least 1 occurrence of neutrophil count < 1,5 X 10^9/litre, was 1,72% in patients treated with SEROQUEL compared to 0,73% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count < 1,0 x 10^9/litre, among patients with a baseline neutrophil count ≥ 1,5 X 10^9/litre, the incidence of at least 1 occurrence of neutrophil count < 0,5 X 10^9/litre was 0,21% in patients treated with SEROQUEL and 0% in placebo treated patients and the incidence ≥ 0,5 - < 1,0 X 10^9/litre was 0,75% in patients treated with SEROQUEL and 0,11% in placebo-treated patients.

[4] Based on ≥ 7% increased in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

[5] Elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in patients administered SEROQUEL XR. These elevations were usually reversible on continued SEROQUEL XR treatment.

[6] SEROQUEL XR may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.

[7] Manifestations of hypersensitivity may include angioedema and urticaria/rash.

[8] Fasting blood glucose ≥ 7,0 mmol/litre or a non-fasting blood glucose ≥ 11,1 mmol/litre on at least 1 occasion.

[9] An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

[10] In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12,1% for quetiapine and 6,7% for placebo. The aggregated incidence of the individual adverse events (e.g. insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 5,3 % in any treatment group and usually resolved after 1 week post-discontinuation.

[11] Triglycerides ≥ 200 mg/dl on at least 1 occasion (patients ≥ 18 years of age).

[12] Cholesterol ≥ 240 mg/dl on at least 1 occasion (patients ≥ 18 years of age).

[13] Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

[14] Platelets ≤ 100 x 10^9/litre on at least 1 occasion.

[15] Prolactin levels (patients ≥ 18 years of age): > 20 µg/litre males; > 30 µg/litre females at any time.

[16] May lead to falls.

[17] HDL cholesterol: < 40 mg/dl for males; < 50 mg/dl for females at any time.

[18] Since the incidence rates for these events were only slightly higher in SEROQUEL XR treated patients than in placebo-treated patients, causality between these adverse events and SEROQUEL XR is not established. Thus, these adverse events were not necessarily causally related to treatment with SEROQUEL XR.

[19] Based on post-marketing reports.

Thyroid level:

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2-4 weeks of quetiapine treatment, with no further reduction during long-term treatment.

There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment.

Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with any indication that quetiapine causes clinically relevant hypothyroidism.

Extrapyramidal symptoms:

The following clinical trials (monotherapy and combination therapy) included treatment with SEROQUEL and SEROQUEL XR.

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7,8% for quetiapine and 8,0% for placebo; bipolar mania: 11,2% for quetiapine and 11,4% for placebo. In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8,9% for quetiapine compared to 3,8% for placebo, though the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5,4% for

SEROQUEL XR and 3,2% for placebo. In a short-term placebo controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9,0% for SEROQUEL XR and 2,3% for placebo. In long-term studies of schizophrenia, bipolar disorder and major depressive disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

Special precautions:

Suicide/suicidal thoughts or clinical worsening:

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which SEROQUEL XR is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant medicines in approximately 4 400 children and adolescents and 77 000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old.

Neutropenia:

Severe neutropenia (< 0,5 X 10^9/litre) has been uncommonly reported in SEROQUEL clinical trials. Most cases of severe neutropenia have occurred within the first 2 months of starting therapy with SEROQUEL XR. There was no apparent dose relationship. Possible risk factors

for neutropenia include pre-existing low white cell count (WBC) and history of medicine induced neutropenia. SEROQUEL XR should be discontinued in patients with a neutrophil count < 1,0 X 10^9/litre. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 X 10^9/litre) (see "*Side-effects"*).

Lipids:
Increases in triglycerides and cholesterol, and decreases in HDL have been observed in clinical trials with SEROQUEL XR (see "*Side-effects*"). Lipid changes should be managed as clinically appropriate.

Concomitant illness:
SEROQUEL XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. SEROQUEL XR may induce orthostatic hypotension especially during the initial dose-titration period.

Dysphagia (see "*Side-effects*") and aspiration have been reported with SEROQUEL XR. Although a causal relationship with aspiration pneumonia has not been established, SEOQUEL XR should be used with caution in patients at risk for aspiration pneumonia.

Seizures:
Caution is recommended when treating patients with a history of seizures.

Tardive dyskinesia and extrapyramidal symptoms:
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medicines including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see "*Side-effects*").

In placebo-controlled clinical trials for schizophrenia and bipolar mania the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical

antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients. In short-term, placebo-controlled clinical trials for bipolar depression and major depressive disorder the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (see "*Side-effects*").

Neuroleptic malignant syndrome:
Neuroleptic malignant syndrome has been associated with SEROQUEL XR treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, SEROQUEL XR should be discontinued and appropriate medical treatment given.

QT prolongation:
In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose. As with other antipsychotics, caution should be exercised when SEROQUEL XR is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when SEROQUEL XR is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e. the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesaemia (see "*Interactions*").

Withdrawal:
Acute withdrawal symptoms such as insomnia, nausea, and vomiting have been described after abrupt cessation of antipsychotic medicines, including SEROQUEL XR. Gradual withdrawal over a period of at least 1-2 weeks is advisable.

Elderly patients with dementia:
SEROQUEL XR is not approved for the treatment of dementia-related psychosis. In a meta-analysis of atypical antipsychotic medicines, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo controlled quetiapine studies in the same patient population (n = 710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was

5,5% versus 3,2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Interactions:
Concomitant use of SEROQUEL XR with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of SEROQUEL XR may need to be considered if used concomitantly with a hepatic enzyme inducer.

During concomitant administration of medicines, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of SEROQUEL XR should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

Effect on ability to drive and use machines:
SEROQUEL XR may cause somnolence, which may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported 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 post marketing experience, there have been very rare reports of overdose of SEROQUEL XR alone resulting in death or coma.

In post marketing experience, there were cases reported of QT prolongation with overdose (see "*Side-effects and Special precautions*").

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See "*Side-effects and Special precautions: Concomitant illness*").

In general, reported signs and symptoms were those resulting from an exaggeration of the medicine's known pharmacological effects, i.e. drowsiness, sedation, tachycardia and hypotension.

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Close medical supervision and monitoring should be continued until the patient recovers.

IDENTIFICATION:

SEROQUEL XR 50:

Peach, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 50' on one side and plain on the other.

SEROQUEL XR 150:

White, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 150' on one side and plain on the other.

SEROQUEL XR 200:

Yellow, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 200' on one side and plain on the other.

SEROQUEL XR 300:

Pale yellow, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 300' on one side and plain on the other.

SEROQUEL XR 400:

White, film-coated, capsule-shaped, biconvex, intagliated tablet with 'XR 400' on one side and plain on the other.

PRESENTATION:

The tablets are packed into opaque PVC/PCTFE aluminium foil blister strips containing 10 tablets. The blisters are packed in cartons of 10, 60 or 100 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30°C.

Keep out of reach of children.

Do not remove the blisters from the outer carton until required for use.

REGISTRATION NUMBERS:

SEROQUEL XR 50: 42/2.6.5/0573

SEROQUEL XR 150: 44/2.6.5/0973

SEROQUEL XR 200: 42/2.6.5/0574

SEROQUEL XR 300: 42/2.6.5/0575

SEROQUEL XR 400: 42/2.6.5/0576

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

03 June 2011

Ref: Seroquel XR 50-150-200-300-400 mg Tablets – EPI (02-02-2011)

CDS: August 2009

Seroquel XR 50 NAMIBIA: NS3 Reg. No.: 11/2.6.5/0215	Seroquel XR 150 NAMIBIA: NS3 Reg. No.: 11/2.6.5/0216	Seroquel XR 200 NAMIBIA: NS3 Reg. No.: 11/2.6.5/0217
Seroquel XR 300 NAMIBIA: NS3 Reg. No.: 11/2.6.5/0218	Seroquel XR 400 NAMIBIA: NS3 Reg. No.: 11/2.6.5/0219	