PROPOSED CLEAN PACKAGE INSERT

SCHEDULING STATUS: **S 5**

PROPRIETARY NAME AND DOSAGE FORM:

Seroquel® 25, Seroquel® 100, Seroquel® 200, Seroquel® 300 (Tablet)

COMPOSITION:

25 mg tablet:

Each tablet contains quetiapine fumarate 28,78 mg equivalent to 25 mg of quetiapine free base.

100 mg tablet:

Each tablet contains quetiapine fumarate 115,13 mg equivalent to 100 mg of quetiapine free base.

200 mg tablet:

Each tablet contains quetiapine fumarate 230,26 mg equivalent to 200 mg of quetiapine free base.

300 mg tablet:

Each tablet contains quetiapine fumarate 345,39 mg equivalent to 300 mg of quetiapine free base.

Contains sugar (lactose monohydrate).

List of excipients:

Calcium hydrogen phosphate, ferric oxide, lactose monohydrate, macrogol, magnesium stearate, methylhydroxypropylcellulose, microcrystalline cellulose**,** povidone, sodium starch glycollate, and titanium dioxide.

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 which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin ($5HT_2$) receptors in the brain than it does for dopamine D_1 and D_2 receptors in the brain. Quetiapine also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors, but no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors. In animal models, quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance.

Quetiapine does not produce sustained elevations in prolactin in man.

Quetiapine, when given twice a day, maintains $5HT_2$ and D_2 receptor occupancy for up to 12 hours after dosing.

Pharmacokinetic properties:

Quetiapine is absorbed and extensively metabolised following oral administration. The principal human plasma metabolites do not have significant pharmacological activity. The bioavailability of quetiapine is not significantly affected by administration with food.
The elimination half-life of quetiapine is approximately 7 hours. Quetiapine is approximately 65 % - 83 % bound to plasma proteins.

The pharmacokinetics of quetiapine are variable but do not differ significantly between men and women.

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/1,73 m^2) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects.

Quetiapine is extensively metabolised with the parent compound accounting for less than 5 % of unchanged drug-related material in the urine or faeces, following the administration of radio-labelled quetiapine. Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10-50 fold higher than those observed in the usual effective dose range of 300 to 450 mg/day in humans.

INDICATIONS:

SEROQUEL is indicated for the treatment of schizophrenia. SEROQUEL is also indicated for the treatment of manic episodes associated with a bipolar disorder. Safety and efficacy beyond 12 weeks has not been demonstrated.

CONTRAINDICATIONS:

SEROQUEL is contraindicated in patients who are hypersensitive to any component of this medicine.

Pregnancy and lactation, as safety has not been demonstrated.

Safety and efficacy in children and adolescents have not been demonstrated.

Advanced liver and renal function impairment, as safety has not been demonstrated.

WARNINGS AND 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 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.

Neutropenia and agranulocytosis:

Severe neutropenia (<0,5 X 10^9/L) without infection has been uncommonly reported in short-term placebo controlled monotherapy clinical trials with SEROQUEL. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with SEROQUEL during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate. SEROQUEL should be discontinued in patients with a neutrophil count <1,0 X 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 X 10^9/L). (see SIDE EFFECTS)

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 SEROQUEL.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as SEROQUEL, 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 such as SEROQUEL, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as SEROQUEL, should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as SEROQUEL, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Lipids:

Increases in triglycerides and cholesterol, and decreases in HDL have been observed with SEROQUEL (see SIDE EFFECTS). Lipid changes should be managed as clinically appropriate.

Metabolic factors:

In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed. Changes in these parameters should be managed as clinically appropriate.

Pancreatitis:

Pancreatitis has been reported in clinical trials and during the postmarketing experience. Among the post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see WARNINGS AND SPECIAL PRECAUTIONS: *Lipids*), gallstones, and alcohol consumption.

Concomitant illness:

SEROQUEL should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. SEROQUEL may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients. In patients who have a history of or are at risk of sleep apnoea, and are receiving concomitant central nervous system (CNS) depressants, SEROQUEL should be used with caution.

QT prolongation:

In clinical trials, SEROQUEL was not associated with a persistent increase in QTc intervals. However, caution should be exercised when SEROQUEL is prescribed with drugs known to prolong the QTc interval, especially in the elderly.

Dysphagia:

Dysphagia (see SIDE EFFECTS) and aspiration have been reported with SEROQUEL. SEROQUEL should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction:

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with SEROQUEL (see SIDE EFFECTS). This includes fatal reports inpatients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation.

Seizures:

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

Tardive dyskinesia and Extrapyramidal Symptoms (EPS):

There is a potential for SEROQUEL to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of SEROQUEL should be considered.

In placebo-controlled clinical trials of adult patients with 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 SEROQUEL 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, the incidence of EPS was higher in SEROQUEL treated patients than in placebo treated patients (see SIDE EFFECTS).

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome has been associated with SEROQUEL treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic

instability, and increased creatine phosphokinase. In such an event, SEROQUEL should be discontinued and appropriate medical treatment given.

Cardiomyopathy and Myocarditis:

Cardiomyopathy and myocarditis have been reported in clinical trials and during the postmarketing experience. Treatment with SEROQUEL should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Withdrawal:

Acute withdrawal symptoms such as insomnia, nausea, and vomiting have been described after abrupt cessation of antipsychotic drugs including SEROQUEL. Gradual withdrawal over a period of at least one to two weeks is advisable. (see SIDE EFFECTS)

Misuse and abuse:

Cases of misuse and abuse have been reported. Caution may be needed when prescribing SEROQUEL to patients with a history of alcohol or drug abuse.

Elderly patients with dementia:

SEROQUEL is not approved for the treatment of patients with dementia-related psychosis. In a meta-analysis of atypical antipsychotic drugs, 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 SEROQUEL treatment and death in elderly patients with dementia.

Anticholinergic (muscarinic) effects:

Norquetiapine, an active metabolite of SEROQUEL, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to adverse drugs reactions (ADRs) reflecting anticholinergic effects when SEROQUEL is used at recommended doses, when used concomitantly with other medications having anticholinergic effects, and in the setting of overdose. SEROQUEL should be used with caution in patients receiving medications having anticholinergic (muscarinic) effects. SEROQUEL should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma. (see INTERACTIONS and SIDE EFFECTS)

Effects on ability to drive and use machines:

SEROQUEL 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.

INTERACTIONS:

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

Caution should be exercised when SEROQUEL concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see WARNINGS AND SPECIAL PRECAUTIONS).

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see WARNINGS AND SPECIAL PRECAUTIONS).

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

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

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

SEROQUEL did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. In a multiple dose trial in patients to assess the pharmacokinetics of SEROQUEL given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of SEROQUEL. This increase in clearance reduced systemic SEROQUEL exposure (as measured by AUC) to an average of 13 % of the exposure during administration of SEROQUEL 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, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of SEROQUEL is 750 mg/day, for the treatment of schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder. 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 SEROQUEL with another microsomal enzyme inducer, phenytoin, also caused increases in clearance of SEROQUEL. Increased doses of SEROQUEL may be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of SEROQUEL may need to be reduced if phenytoin, 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 SEROQUEL. The pharmacokinetics of SEROQUEL was not altered following co-administration with cimetidine a known P450 enzyme inhibitor. The pharmacokinetics of SEROQUEL 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 given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of SEROQUEL of 235 % and 522 %, respectively, with a corresponding decrease in mean oral clearance of 84 %. The mean half-life of SEROQUEL increased from 2,6 to 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 SEROQUEL should be reduced during concomitant use of SEROQUEL and potent CYP3A4 inhibitors (such as azole antifungal, macrolide antibiotics and protease inhibitors).

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken SEROQUEL. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

PREGNANCY AND LACTATION:

SEROQUEL is contraindicated during pregnancy and lactation, as safety has not been demonstrated.

DOSAGE AND DIRECTIONS FOR USE:

SEROQUEL should be administered twice daily, with or without food.

Adults:

For the treatment of schizophrenia the total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the effective dose range of 300-450 mg/day. However this may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range 150-750 mg/day.

For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4).
Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on the clinical response and tolerability of the individual patient, within the range of 200-800 mg/day. The usual effective dose is in the range of 400-800 mg/day.

Elderly:
SEROQUEL should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on SEROQUEL 25 mg/day. The dose should be increased daily, in increments of 25-50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Renal and hepatic impairment:
The oral clearance of SEROQUEL is reduced by approximately 25 % in patients with renal or hepatic impairment. SEROQUEL is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment.

Patients with renal or hepatic impairment should be started on SEROQUEL 25 mg/day. The dose should be increased daily in increments of 25-50 mg, to an effective dose.

SIDE EFFECTS:

The most commonly reported adverse drug reactions (ADRs) with SEROQUEL 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.

Frequency	**System Organ Class**	**Event**
Very common (≥ 10 %)	Nervous system disorders	Dizziness[a,e,p]; Somnolence[b,p] Extrapyramidal symptoms[a,p]
	Gastrointestinal disorders	Dry mouth
	General disorders and administration site conditions	Withdrawal (discontinuation) symptoms[a,j]
	Investigations	Elevations in serum triglyceride levels[a,k] Elevations in total cholesterol (predominantly LDL cholesterol)[a,l] Decreases in HDL cholesterol[a,q] Weight gain[c] Decreased haemoglobin[r]

Frequency	**System Organ Class**	**Event**
Common (≥ 1 % - < 10 %)	Blood and lymphatic system disorders	Leucopenia[a,w]
	Cardiac disorders	Tachycardia[a,e] Palpitations
	Eye disorders	Vision blurred[s]
	Gastrointestinal disorders	Constipation; Dyspepsia Vomiting[u]
	General disorders and administration site conditions	Asthenia; Peripheral oedema Irritability Pyrexia
	Investigations	Elevations in serum transaminases (ALT, AST)[d] Elevations in gamma-GT levels[d] Neutrophils count decreased[a,g] Eosinophils increased[v]

Frequency	**System Organ Class**	**Event**
		Blood glucose increased to hyperglycaemic level[a,h] Elevations in serum prolactin[o] Decreases in Total T_4[t] Decreases in Free T_4[t] Decreases in Total T_3[t] Increases in TSH[t]
	Nervous system disorders	Dysarthria Syncope[a,e,p]
	Metabolism and nutrition disorders	Increased appetite
	Respiratory, thoracic, and mediastinal disorders	Dyspnoea[s] Rhinitis
	Vascular disorders	Orthostatic hypotension[a,e,p]
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥ 0,1 % - < 1 %)	Cardiac disorders	Bradycardia[x]

Frequency	**System Organ Class**	**Event**
	Gastrointestinal disorders	Dysphagia[a,i]
	Immune system disorders	Hypersensitivity (angioedema, anaphylaxis[f], urticaria/rash)
	Investigations	Platelet count decreased[n] Decreases in Free T_3[t]
	Nervous system disorders	Seizure[a] Restless legs syndrome Tardive dyskinesia[a]
	Renal and urinary disorders	Urinary retention
Rare (0,01 % - < 0,1 %)	General disorders and administration site conditions	Neuroleptic malignant syndrome[a] Hypothermia
	Hepatobiliary disorders	Hepatitis (with or without jaundice)
	Investigations	Elevations in blood creatinine phosphokinase[m] Agranulocytosis[y]

Frequency	System Organ Class	Event
	Psychiatric disorders	Somnambulism and other related events
	Reproductive system and breast disorders	Priapism Galactorrhoea
	Gastrointestinal disorders	Intestinal obstruction/Ileus
Not known	General disorders and administration site conditions	Neonatal withdrawal[z]

[a]See *"Warnings and Special precautions"*.

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

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

[d] Asymptomatic elevations (shift from normal to ≥ 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in patients administered SEROQUEL. These elevations were usually reversible on continued SEROQUEL treatment.

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

[f] The inclusion of anaphylactic reaction is based on post-marketing reports.

[g] In all short-term placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥ 1,5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <1,5 X 10^9/L, was 1,9 % in patients treated with quetiapine compared to 1,5 % in placebo-treated patients. The incidence >0,5 - <1,0 x 10^9/L was 0,2 % in patients treated with

quetiapine and 0,2 % 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/L, among patients with a baseline neutrophil count ≥1,5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <0,5 X 10^9/L was 0,21 % in patients treated with quetiapine and 0 % in placebo treated patients.

[h] Fasting blood glucose ≥126 mg/dL or a non fasting blood glucose ≥200 mg/dL on at least one occasion.

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

[j] 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.

[k] Triglycerides ≥ 200 mg/dL (patients ≥ 18 years of age) or ≥ 150 mg/dL (patients <18 years of age) on at least one occasion.

[l] Cholesterol ≥240 mg/dL (patients ≥18 years of age) or ≥ 200 mg/dL (patients <18 years of age) on at least one occasion.

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

[n] Platelets ≤100 x 10^9/L on at least one occasion.

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

[p] May lead to falls.

[q] HDL cholesterol: <40 mg/dL males; <50 mg/dL females at any time.

[r] Decreased haemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 11 % of quetiapine patients in all trials including open label extensions. In short term placebo controlled trials, decreased haemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 8,3 % of quetiapine patients compared to 6,2 % of placebo patients.

[s] These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.

[t] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T4, free T4, total T3 and free T3 are defined as <0,8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.

[u] Based upon the increased rate of vomiting in elderly patients (≥65 years of age).

[v] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as ≥ 1 x 10^9 cells/L at any time.

[w] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤ 3X10^9cells/L at any time.

[x] May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with SEROQUEL.

[y] Based on the frequency of patients during all SEROQUEL clinical trials with severe neutropenia (<0,5 x 10^9/L) and infection.

[z] See “*Pregnancy and lactation*”.

Thyroid Levels

SEROQUEL 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 to 4 weeks of SEROQUEL 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 SEROQUEL 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 SEROQUEL causes clinically relevant hypothyroidism.

The following adverse events seen in clinical trials are not drug related and their frequencies are unknown: headache, abdominal pain, back pain, chest pain, hypertension, diarrhoea, myalgia, anxiety, dry eyes, ear pain and urinary tract infection.

Extrapyramidal symptoms (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity and tremor) occur at an incidence similar to placebo and are not dose related.

SEROQUEL may cause prolongation of the QTc interval (see "*Warnings and Special Precautions"*).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In clinical trials, experience with SEROQUEL in overdosage is limited. In postmarketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death or coma.

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 SEROQUEL. Treatment is symptomatic and supportive.

IDENTIFICATION:

SEROQUEL 25:

Peach, round, bi-convex, film-coated tablet intagliated with SEROQUEL 25.

SEROQUEL 100:

Yellow, round, bi-convex, film-coated tablet intagliated with SEROQUEL 100.

SEROQUEL 200:

White, round, bi-convex, film-coated tablet intagliated with SEROQUEL 200.

SEROQUEL 300:

White, capsule-shaped, film-coated tablet intagliated with SEROQUEL on one side and 300 on the other

PRESENTATION:

The tablets are packed into PVC aluminium foil blister strips.

SEROQUEL 25: Packs of 6 or 100 tablets.

SEROQUEL 100: Packs of 60; 90 or 100 tablets.

SEROQUEL 200: Packs of 60; 90 or 100 tablets.

SEROQUEL 300: Packs of 60, 90 or 100 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep out of reach of children.

REGISTRATION/APPLICATION NUMBER(S):

SEROQUEL 25: 32/2.6.5/0589

SEROQUEL 100: 32/2.6.5/0590

SEROQUEL 200: 32/2.6.5/0591

SEROQUEL 300: 36/2.6.5/0070

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

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West, Bryanston

Johannesburg, 2191

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date on registration certificate:

13 June 2008

AstraZeneca Logo

Seroquel is a registered trade mark of the AstraZeneca group of companies.

Ref: Seroquel 25-100-200-300 mg Tablets – EPI (29-11-2017)

CDS: 21 September 2016

Inclusion of Namibia + Botswana registration details (01-03-2011)

Seroquel 25 NAMIBIA: NS3 Reg. No.: 10/2.6.5/0586	Seroquel 100 NAMIBIA: NS3 Reg. No.: 10/2.6.5/0587	Seroquel 200 NAMIBIA: NS3 Reg. No.: 10/2.6.5/0588	Seroquel 300 NAMIBIA: NS3 Reg. No.: 10/2.6.5/0580

Seroquel 25 BOTSWANA: S2 Reg. No.: BOT 1101819	Seroquel 100 BOTSWANA: S2 Reg. No.: BOT 1101820	Seroquel 200 BOTSWANA: S2 Reg. No.: BOT 1101821	Seroquel 300 BOTSWANA: S2 Reg. No.: BOT 1101947