## 1.3 Product information

### 1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

**National Agency for Food & Drug Administration & Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R) Directorate**

# SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

## 1. NAME OF THE MEDICINAL PRODUCT

**XYTAL-200 & 300** QUETIAPINE TABLETS USP 200 & 300 MG

## 2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each film coated tablet contains:
Quetiapine fumarate USP
Eq. to Quetiapine.....200 mg
Excipients.....Q.S
Color: Titanium Dioxide BP

Each film coated tablet contains:
Quetiapine fumarate USP
Eq. to Quetiapine.....300 mg
Excipients.....Q.S
Color: Titanium Dioxide BP

## 3. PHARMACEUTICAL FORM

Oral Film coated tablets

## 4. Clinical particulars

### 4.1 Therapeutic indications

Quetiapine is indicated for:

- Treatment of schizophrenia
- Treatment of bipolar disorder
- For the treatment of moderate to severe manic episodes in bipolar disorder
- For the treatment of major depressive episodes in bipolar disorder
- For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

### 4.2 Posology and method of administration

**Route of Administration:** Oral

**Posology**
**Adults:**
**For the treatment of schizophrenia**
For the treatment of schizophrenia, Quetiapine should be administered twice a day. The total daily dose for the first four 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 usual effective dose of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

**For the treatment of moderate to severe manic episodes in bipolar disorder**
For the treatment of manic episodes associated with bipolar disorder, Quetiapine should be administered twice a day. The total daily dose for the first four 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 clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day.

**For the treatment of major depressive episodes in bipolar disorder**

Quetiapine should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

**Elderly:** occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product.
Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated.

## 4.4 Special warnings and precautions for use

Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults, certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents. Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural As with other antipsychotics, Quetiapine should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30-50% in elderly subjects when compared to younger patients. Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

## 4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol. Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects. Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is

contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.
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, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).
The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).
The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%.
The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.
The pharmacokinetics of lithium were not altered when co-administered with quetiapine.
In a 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel XL in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).
The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.
Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.
Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval. There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

## 4.6 Pregnancy and Lactation

**Pregnancy**
***First trimester***

The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

***Third trimester***

Neonates exposed to antipsychotics (including Quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

**Breast-feeding**

Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Quetiapine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

**Fertility**

The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans

**4.7 Effects on ability to drive and use machines**

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

**4.8 Undesirable effects**

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥10%) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of ADRs associated with quetiapine therapy, are tabulated below (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

**Table 1 ADRs associated with quetiapine therapy**

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

| **very common** ≥ 1/10 | **common** ≥ 1/100 to < 1/10 | **uncommon** ≥ 1/1,000 to < 1/100 | **rare** ≥ 1/10,000 to <1/1,000 | **very rare** < 1/10,000 | **not known** frequency cannot be estimated from available data |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | | |
| Decreased haemoglobin | Leucopenia, decreased neutrophil count, eosinophils increased | Neutropenia, Thrombocytopenia, Anaemia, platelet count | Agranulocytosis | | |

| | | | | | |
|---|---|---|---|---|---|
| | | decreased | | | |
| **Immune system disorders** | | | | | |
| | | Hypersensitivity (including allergic skin reactions) | | Anaphylactic reaction | |
| **Endocrine disorders** | | | | | |
| | Hyperprolactinaemia, decreases in total $T_4$ , decreases in free $T_4$ , decreases in total $T_3$ , increases in TSH | Decreases in free $T_3$ , Hypothyroidism | | Inappropriate antidiuretic hormone secretion | Anaphylactic reaction |
| **Metabolism and nutrition disorders** | | | | | |
| Elevations in serum triglyceride levels Elevations in total cholesterol (predominantly LDL cholesterol) Decreases in HDL cholesterol , Weight gain | Increased appetite, blood glucose increased to hyperglycaemic levels | Hyponatraemia, Diabetes Mellitus, Exacerbation of pre-existing diabetes | Metabolic syndrome | | |
| **Psychiatric disorders** | | | | | |
| | Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour | | Somnambulism and related reactions such as sleep talking and sleep related eating disorder | | |
| **Nervous system disorders** | | | | | |
| Dizziness, somnolence, headache, Extrapyramidal symptoms | Dysarthria | Seizure, Restless legs syndrome, Tardive dyskinesia, Syncope Confusional state | | | |
| **Eye disorders** | | | | | |
| | Vision blurred | | | | |
| **Cardiac disorders** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | Tachycardia, Palpitations | QT prolongation, Bradycardia | | | cardiomyopathy and myocarditis |
| **Vascular disorders** | | | | | |
| | Orthostatic hypotension | | Venous thromboembolism[1] | | Stroke |
| **Respiratory, thoracic and mediastinal disorder** | | | | | |
| | Dyspnoea | Rhinitis | | | |
| **Gastrointestinal disorders** | | | | | |
| Dry mouth | Constipation, dyspepsia, vomiting | Dysphagia | Pancreatitis, Intestinal obstruction/Ileus | | |
| **Hepatobiliary disorders** | | | | | |
| | Elevations in serum alanine aminotransferase (ALT) Elevations in gamma-GT levels | Elevations in serum aspartate aminotransferase (AST) | Jaundice, Hepatitis | | |
| **Skin and subcutaneous tissue disorders** | | | | | |
| | | | | Angioedema, Stevens-Johnson syndrome | Toxic Epidermal Necrolysis, Erythema Multiforme, Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Cutaneous vasculitis |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| | | | | Rhabdomyolysis | |
| **Renal and urinary disorders** | | | | | |
| | | Urinary retention | | | |
| **Pregnancy, puerperium and perinatal conditions** | | | | | |
| | | | | | Drug withdrawal |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | syndrome neonatal |
| **Reproductive system and breast disorders** | | | | | |
| | | Sexual dysfunction | Priapism, galactorrhoea, breast swelling, menstrual disorder | | |
| **General disorders and administration site conditions** | | | | | |
| Withdrawal (discontinuation) symptoms | Mild asthenia, peripheral oedema, irritability, pyrexia | | Neuroleptic malignant syndrome, hypothermia | | |
| **Investigations** | | | | | |
| | | | Elevations in blood creatine phosphokinase | | |

**Paediatric population**

The same ADRs described above for adults should be considered for children and adolescents. The following table summarises ADRs that occur in a higher frequency category in children and adolescent patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

**Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not identified in the adult population**

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

| **Very Common (>1/10)** | **Common (>1/100, <1/10),** |
|---|---|
| **Endocrine disorders** | |
| Elevations in prolactin | |
| **Metabolism and nutritional disorders** | |
| Increased appetite | |
| **Nervous system disorders** | |
| Extrapyramidal symptoms | |
| **Vascular disorders** | |
| Increases in blood pressure | |
| **Respiratory, thoracic and mediastina disorders** | |
| | Rhinitis |
| **Gastrointestinal disorders** | |
| Vomiting | |
| **General disorders and administration site conditions** | |
| | Irritability |

## 4.9 Overdose

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.
Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (see section 4.4, Orthostatic hypotension).

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, 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. Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered. In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade. Close medical supervision and monitoring should be continued until the patient recovers.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antipsychotics

ATC code: N05A H04

**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 $D_2$- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Seroquel's therapeutic efficacy as an antidepressant.

**Pharmacodynamic effects**

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electro physiologically, 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 supersensitivity 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 mesolimbic but not the 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.
Clinical efficacy:
Schizophrenia
In three placebo-controlled clinical trials, in patients with schizophrenia, using variable doses of quetiapine, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anti-cholinergics. A placebo-controlled trial evaluating fixed doses of quetiapine across the range of 75 to 750 mg/day showed no evidence of an increase in EPS or the use of concomitant anti-cholinergics. The long-term efficacy of Seroquel IR in prevention of schizophrenic relapses has not been verified in blinded clinical trials. In open label trials, in patients with schizophrenia, quetiapine was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response, suggesting some long-term efficacy.
Bipolar disorder
In four placebo-controlled clinical trials, evaluating doses of Seroquel up to 800 mg/day for the treatment of moderate to severe manic episodes, two each in monotherapy and as combination therapy to lithium or divalproex, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anti-cholinergics.
In the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. There are no data from long-term studies to demonstrate Seroquel's effectiveness in preventing subsequent manic or depressive episodes. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.
The mean last week median dose of Seroquel in responders was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.
In 4 clinical trials with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Seroquel IR 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg Seroquel IR and those who received 600 mg dose.
In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on Seroquel IR 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating Seroquel in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Seroquel was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Seroquel was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel XL in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

Clinical trials have demonstrated that Seroquel is effective in schizophrenia and mania when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study, which identified that for quetiapine, $5HT_2$- and $D_2$-receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Clinical safety

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). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XL 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 XL and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short-term, fixed-dose (50 mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

A 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel XL in adult patients with acute mania indicated that the combination of Seroquel XL with lithium leads to more adverse events (63% versus 48% in Seroquel XL in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the Seroquel XL with lithium add-on group (12.7%) compared to the Seroquel XL with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain (≥7%) at the end of treatment compared to patients in the placebo add-on group (4.7%).
Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.
In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.
In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 x $10^9$/L, the incidence of at least one occurrence of a shift to 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 of shifts to >0.5-<1.0 x $10^9$/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥1.5 x $10^9$/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x $10^9$/L was 2.9% and to <0.5 x $10^9$/L was 0.21% in patients treated with quetiapine.
Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism.
The reduction in total and free $T_4$ was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of 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.
Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of Seroquel (200-800 mg/day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in Seroquel (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.
Paediatric population
Clinical efficacy
The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo

controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Seroquel 400 mg/day and –6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Seroquel 400 mg/day and –9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XL in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

Clinical safety

In the short-term paediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain ≥ 7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 13.7% vs. 6.8% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended post treatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

Long-term safety

A 26-week open-label extension to the acute trials (n=380 patients), with Seroquel flexibly dosed at 400 - 800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see sections 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

## 5.2 Pharmacokinetic properties

**Absorption**

Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

**Distribution**
Quetiapine is approximately 83% bound to plasma proteins.

**Biotransformation**
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. 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.
Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.
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 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

**Elimination**
The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

**Pharmacokinetics in special populations**
Elderly
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Renal impairment
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 $m^2$), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients.

Paediatric population
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though $C_{max}$ in children was at the higher end of the range observed in adults. The AUC and $C_{max}$ for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12

years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

### 5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research: In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma $T_3$ levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts. (For cataracts/lens opacities). In an embryofetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown. In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Dibasic calcium phosphate
Microcrystalline cellulose PH-101
Lactose Monohydrate
Sodium Starch Glycolate (Type A)
Povidone K-30
Purified water
Magnesium stearate
Crosscarmellose Sodium
Colorezy White 17F580001
Isopropyl alcohol
Methylene chloride

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months for the date of manufacturing.

### 6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

**6.5 Nature and contents of container<and special equipment for use, administration or implantation>**

3X 10 Tablets Alu-Alu Blister Pack

**6.6 Special precautions for disposal <and other handling>**

None

**7. <APPLICANT/MANUFACTURER>**

**STALLION LABORATORIES PVT. LTD.**
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