SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of drug Product**
   Quitide 200; Quetiapine 200 mg film-coated tablets

   Quitide 300; Quetiapine 300 mg film-coated tablets

2. **Qualitative and quantitative compositions:**

   Quetiapine 200 mg
   Each tablet contains 200 mg of quetiapine as quetiapine fumarate
   Quetiapine 300 mg
   Each tablet contains 300mg of quetiapine as quetiapine fumarate

   Excipient with known effect:
   Quetiapine 200 mg: Each tablet contains of lactose 41.333 mg (as lactose monohydrate)
   Quetiapine 300 mg: Each tablet contains 62.00 mg of lactose (as lactose monohydrate)
   For the full list of excipients, see section 6.1.

3. **Pharmaceutical form:**
   Film-coated tablet

   Quetiapine Fumarate Tablets 200 mg: White, round, biconvex, film-coated tablets Imprinted with “E 55” on one side and plain on the other side.

   Quetiapine Fumarate Tablets 300 mg: White, Capsule shaped, biconvex, film-coated tablets Imprinted with “E 56” on one side and plain on the other side.

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:

   Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

   Adults:
   For the treatment of schizophrenia:
   For the treatment of schizophrenia, Quetiapine Fumarate Tablets 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 Fumarate Tablets 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 Fumarate Tablets 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. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder:
For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

Elderly:
As with other antipsychotics, Quetiapine Fumarate Tablets 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.

Paediatric population:
Quetiapine Fumarate Tablets 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.

Renal impairment
Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolised by the liver. Therefore, Quetiapine Fumarate Tablets should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 25mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

Method of administration
Quetiapine can be administered with or without food.

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

As Quetiapine fumarate tablets has several indications, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Paediatric population
Quetiapine is not recommended for use in children and adolescents below 18 years of age. Certain adverse events may be 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). Changes in thyroid function tests may be 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 development are not known

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania and bipolar depression.

Suicide/suicidal thoughts or clinical worsening
Depression in bipolar disorder 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.

In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of Quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which Quetiapine 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 episodes. The same precautions observed when treating patients with major depressive episodes 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. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). A population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other antidepressants.

Metabolic risk
Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycaemia) and lipids, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate.

Extrapyramidal symptoms
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder.

The use of Quetiapine has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive dyskinesia
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.

Somnolence and dizziness
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation.
For treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension
Quetiapine treatment has been associated with orthostatic hypotension and related dizziness which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Sleep apnoea syndrome

Sleep apnoea syndrome may be reported in patients using Quetiapine. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, Quetiapine should be used with caution.

Seizures
There was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

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

Severe neutropenia and agranulocytosis
Most cases of severe neutropenia may be occurred within a couple of months of starting therapy with Quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include preexisting low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count <1.0 x 109/L.

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy, or sore throat) at any time during Quetiapine therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Anti-cholinergic (muscarinic) effects
Norquetiapine, an active metabolite of Quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when Quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose.
Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects.
Quetiapine 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.

Interactions
Concomitant use of Quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases Quetiapine plasma concentrations, which could affect the efficacy of Quetiapine therapy. 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).

Weight
Weight gain may be reported in patients who have been treated with Quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines.

Hyperglycaemia
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma may be reported rarely, including some fatal cases. In some cases, a prior increase in body weight may be reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol may be observed with Quetiapine. Lipid changes should be managed as clinically appropriate.

QT prolongation
Quetiapine was not associated with a persistent increase in absolute QT intervals. As with other antipsychotics, caution should be exercised when Quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when Quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Cardiomyopathy and myocarditis
Cardiomyopathy and myocarditis may be reported with Quetiapine. However, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable.

Elderly patients with dementia-related psychosis
Quetiapine is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.
In a meta-analysis of atypical antipsychotics, 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.

Elderly patients with Parkinson's disease (PD)/parkinsonism
A population-based retrospective study of quetiapine for the treatment of patients with MDD, showed an increased risk of death during use of quetiapine in patients aged >65 years. This association was not present when patients with PD were removed from the analysis. Caution should be exercised if quetiapine is prescribed to elderly patients with PD

Dysphagia
Dysphagia has been reported with Quetiapine. Quetiapine 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 Quetiapine. This includes fatal reports in patients 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. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Quetiapine and preventive measures undertaken.

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides, gallstones, and alcohol consumption.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3.

Lactose
Quetiapine fumarate tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Misuse and abuse
Caution may be needed when prescribing Quetiapine to patients with a history of alcohol or drug abuse.

4.5 Interactions 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. 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.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when coadministered. 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 Fertility, 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 (see section 5.3). 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 (see section 5.3).

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.

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 to <1/10), uncommon (≥1/1,000) to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

SOC	Very Common	Common	Un Common	Rare	Very Rare	Not known
Blood and lymphatic system disorders	Decreased haemoglobin	Leucopenia decreased neutrophil count,	Neutropenia, Thrombocytopenia,	Agranulocytosis		

		eosinophils increased	Anaemia, platelet count 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	
Metabolism and Nutritional 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	Dizziness,	Dysarthria	Seizure, Restless			

Disorders	Somnolence, headache, Extra pyramidal symptoms		legs syndrome, Tardive dyskinesia, Syncope			
Cardiac disorders		Tachycardia, Palpitations	QT prolongation, Bradycardia			
Eye disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension		Venous thromboembolism		Stroke
Respiratory, thoracic and Mediastinal disorder		Dyspnoea	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting	Dysphagia	Pancreatitis, Intestinal obstruction /Ileus		
Hepato-biliary disorders		Elevations in serum Alanine amino transferase (ALT), Elevations in gamma-GT levels	Elevations in serum aspartate amino transferase (AST)	Jaundice, Hepatitis		
Skin and subcutaneous tissue disorders					Angioedema, Stevens-Johnson syndrome	Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Rash with Eosinophilia and Systemic

						Symptoms (DRESS)
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).

SOC	Very Common	Common
Endocrine disorders	Elevations in prolactin	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms	Syncope
Vascular disorders	Increases in blood pressure	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability

4.9 Overdosage

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 and 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.

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 delerium and agitation and a clear anticholinergic 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 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines
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 (5HT2) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Quetiapine Fumarate compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors, moderate affinity at adrenergic alpha2 receptors and moderate to high affinity at several muscarinic receptors. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Quetiapine Fumarate 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 behaviorally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

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.

5.2 Pharmacokinetics

Absorption
Quetiapine is well absorbed and extensively metabolized 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 metabolized 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.

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.

Special populations

Gender

The kinetics of quetiapine do not differ between men and women.

Elderly

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that 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/1.73m^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 metabolized by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients

Paediatric population

The AUC and Cmax 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

Tablet core: Calcium hydrogen Phosphate Dihydrate, Lactose Monohydrate, Cellulose Microcrystalline (Avicel PH 101) Sodium Starch Glycolate, Povidone (K-30), Cellulose Microcrystalline (Avicel PH 102), Silica Colloidal anhydrous, Talc, Magnesium Stearate.

Coating & Imprinting Ingredients:
For 200 mg & 300 mg strength: Hypromellose (6 CPS), Macrogol 400, Titanium Dioxide, Opacode S-1-17823 Black and Isopropyl Alcohol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage
Do not store above 30°C

6.5 Nature and contents of container
Clear opaque ALU/PVC Blister Pack
200 mg - 3 x 10's Tablets
300 mg - 3 x 10's Tablets

6.6 Special precautions for disposal and other handling
Any unused portion of this medicine or waste resulting from use of this medicinal product should be disposed as per local regulation; requirements.

7. Marketing Authorisation Holder

Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad,
Telangana State, INDIA.

Manufactured By:
Aurobindo Pharma Ltd., Unit-III,
Survey No. 313 & 314, Bachupally, Bachupally Mandal,
Medchal-Malkajgiri District,
Telangana State, INDIA.

8. Marketing authorisation number(s)
TAN 21 HM 0477

9. Date of first authorisation/renewal of the authorisation
Date of first authorization: November 26, 2021
Date of latest renewal: N/A

10. Date of revision of the text