1.NAME OF THE MEDICINAL PRODUCT

SAQUIN SR PROLONGED-RELEASE TABLETS 50mg
SAQUIN SR PROLONGED-RELEASE TABLETS 150mg
SAQUIN SR PROLONGED-RELEASE TABLETS 200mg
SAQUIN SR PROLONGED-RELEASE TABLETS 300mg
SAQUIN SR PROLONGED-RELEASE TABLETS 400mg

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

SAQUIN SR PROLONGED-RELEASE TABLETS 50mg contains 50 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 14 mg lactose (anhydrous) per tablet
SAQUIN SR PROLONGED-RELEASE TABLETS 150mg contains 150 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 42 mg lactose (anhydrous) per tablet
SAQUIN SR PROLONGED-RELEASE TABLETS 200mg contains 200 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 56 mg lactose (anhydrous) per tablet
SAQUIN SR PROLONGED-RELEASE TABLETS 300mg contains 300 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 85 mg lactose (anhydrous) per tablet
SAQUIN SR PROLONGED-RELEASE TABLETS 400mg contains 400 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 113 mg lactose (anhydrous) per tablet

3.PHARMACEUTICAL FORM

Prolonged-release tablet

50 mg: a white to off white, round biconvex tablet, 7.1 mm in diameter and 3.2 mm in thickness, engraved with “50” on one side.

150 mg: a white to off white, oblong biconvex tablet, 13.6 mm in length, 6.6 mm in width and 4.2 mm in thickness, engraved with “150” on one side.

200 mg: a white to off white, oblong biconvex tablet, 15.2 mm in length, 7.7 mm in width and 4.8 mm in thickness, engraved with “200” on one side.

300 mg: a white to off white, oblong biconvex tablet, 18.2 mm in length, 8.2 mm in width and 5.4 mm in thickness, engraved with “300” on one side.

400 mg: a white to off white, oval biconvex tablet, 20.7 mm in length, 10.2 mm in width and 6.3 mm in thickness, engraved with “400” on one side.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

Saquin SR is indicated for:
- Treatment of Schizophrenia
- Treatment of bipolar disorder:

- For the treatment of manic episodes associated with bipolar I disorder
- For the treatment of depressive episodes associated with bipolar disorder
- For the prevention of recurrence in maintenance treatment of bipolar disorder (manic, mixed or depressive episode) as monotherapy or in combination with lithium or valproate

- Add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of quetiapine.

4.2 Posology and method of administration

Posology
SAQUIN SR should be administered once daily, with or without food. The tablets should be swallowed whole and not split, chewed or crushed
Adults:
For the treatment of schizophrenia
The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2 .The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary. The safety of doses above 800 mg/day have not been evaluated.

For the treatment of manic episodes associated with bipolar disorder:
SAQUIN SR should be administered once daily in the evening.
The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient.

For the treatment of depressive episodes associated with bipolar disorder
Saquin SR should be administered once daily in the evening. SAQUIN SR should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). SAQUIN SR can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

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

For preventing recurrence in maintenance treatment of bipolar disorder (manic, mixed or depressive episode) as monotherapy or in combination with lithium or valproate
Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.
Patients who have responded to SAQUIN SR in monotherapy for acute treatment of bipolar disorder should continue on SAQUIN SR therapy at the same dosing regimen. Saquin SR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day.
Patients who have responded to SAQUIN SR in combination therapy to a mood stabilizer (lithium or valproate) for acute treatment of bipolar disorder should continue on SAQUIN SR therapy at the same dose. The SAQUIN SR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 400 mg to 800 mg/day.

For add-on treatment of major depressive episodes in MDD
When treating recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.
Saquin SR should be administered once daily in the evening. Saquin SR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine) and at 50 mg/day in short-term monotherapy trials.
There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.
Patients who have not responded to SAQUIN SR after 6 weeks treatment for MDD should have treatment re-evaluated.

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

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

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1- 3, increasing to 100 mg/day on Day 4 ,150 mg/day on Day 8 and then up to 300 mg/day depending on clinical response and tolerability.

Children and adolescents:
Saquin SR is not indicated for use in children and adolescents below 18 years of age.

Renal and hepatic impairment:
The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver. Therefore, SAQUIN SR should be used with caution in patients with known hepatic impairment.
Patients with hepatic or renal impairment should be started on 50 mg/day. The dose should be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
As Saquin SR is indicated for the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with MDD, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.
Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy.

Children and adolescents (10 to 17 years of age) Quetiapine is not recommended for use in children and adolescents below 18 years of age. Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials in children and adolescent patients, the same special warnings and special precautions for use that appear above for adults should be considered for pediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate.

Long-term safety data including growth, maturation, and behavioral development, beyond 26 weeks of treatment with Quetiapine , is not available for children and adolescents (10 to 17 years of age).

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 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.
An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4400 children and adolescents and 77000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine.

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

Tardive Dyskinesia and Extrapyramidal Symptoms (EPS):
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment.
In placebo-controlled clinical trials for schizophrenia and bipolar mania the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients.
In short-term, placebo-controlled clinical trials for bipolar depression and major depressive disorder, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients.

Seizures:
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. 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.

Neutropenia and agranulocytosis:
Severe neutropenia (neutrophil count <0.5 X 109/L) without infection has been uncommonly reported in short-term placebo controlled monotherapy clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine 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.
Quetiapine 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).

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 may substantially decreases systemic exposure to quetiapine. Depending on clinical response, higher doses of quetiapine may need to be considered if quetiapine is used concomitantly with a hepatic enzyme inducer.
During concomitant administration of drugs, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of quetiapine should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients

Weight:
Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines.

Increases in blood glucose and hyperglycaemia
Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation.

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with atypical antipsychotics, including Quetiapine Assessment of the association between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Some epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in the patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Appropriate clinical monitoring is advised for patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) and those who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics. Patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine. Lipid changes should be managed as clinically appropriate.

QT Prolongation
QT interval
In clinical trials, quetiapine was not associated with a persistent increase in QTc intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (see OVERDOSAGE), in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients, including children and adolescents, with cardiovascular disease or family history of QT prolongation. Particularly in the elderly, the use of quetiapine should be avoided in combination with neuroleptics and drugs that are known to prolong QTc including Class Ia antiarrhythmics (e.g. disopyramide) or Class III antiarrhythmics (e.g. amiodarone, sotalol), antipsychotic medications (e.g. ziprasidone, chlorpromazine, haloperidol), antibiotics (e.g. moxifloxacin, erythromycin), or any other class of medications known to prolong the QTc interval (e.g. citalopram, pentamidine, methadone).

Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsades de pointes and/or sudden death, including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesmia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Cardiomyopathy and Myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are potentially life-threatening adverse drug reactions that have been reported during quetiapine exposure. SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, vomiting, have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable.

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

Elderly patients with dementia-related psychosis
SAQUIN SR 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 quetiapine treatment and death in elderly patients with dementia.

Dysphagia
Dysphagia and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, 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.

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.

Concomitant illness
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.
Quetiapine 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 for sleep apnea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

Lactose
Saquin SR prolonged-release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

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 a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co–administration of ketoconazole resulted in an increase in mean C_{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half–life of quetiapine increased from 2.6 to 6.8 hours. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors).

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. Quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. The safety of doses above 800 mg/day has not been established in the clinical trials. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin, and other hepatic enzyme inducers (eg, barbiturates, rifampicin etc). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (eg, 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 antipsychotic risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.

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

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN)) and quetiapine fumarate.Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

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 and lactation
The safety and efficacy of quetiapine during human pregnancy have not been established. Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast feeding should therefore be advised to avoid breast feeding while taking quetiapine.

Non-teratogenic effects
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

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 are somnolence, dizziness, 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

SOC	Very Common (≥10%)	Common (≥1%-<10%)	Uncommon (≥0.1%-<1%)	Rare (≥0.01%-<0.1%)	Very Rare (<0.1%)	Not known
Blood and lymphatic system disorders		Leukopenia [1,25]				
Immune system disorders			Hypersensitivity		Anaphylactic reaction [6]	
Metabolism and nutritional disorders		Increased appetite				
Psychiatric disorders		Abnormal dreams and nightmares		Somnambulism and other related events		
Nervous system disorders	Dizziness [1,5,17] Somnolence[2,17] Extrapyramidal symptoms [1,16]	Dysarthria	Seizure [1] Restless legs syndrome Tardive dyskinesia [1] Syncope[1,5,17] Confusional state			
Cardiac disorders		Tachycardia [1,5] Palpitations [21]	Bradycardia [26] QT prolongation [16,19]			
Eye disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension [1,5,17]				
Respiratory, thoracic and mediastinal disorder		Dyspnea[21]	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation Dyspepsia Vomiting[23]	Dysphagia[1,9]	Intestinal obstruction/ Ileus		Bezoar [30]
Hepato-biliary disorders				Hepatitis with or without jaundice [29]		
Skin and subcutaneous tissue disorders						Drug reaction with

						eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP) Erythema multiforme (EM) Cutaneous vasculitis
Musculoskeletal and connective tissue disorders					Rhabdomyolysis	
Renal and urinary disorders			Urinary retention			
Reproductive system and breast disorders				Priapism, Galactorrhoea		
General disorders and administration site conditions	Withdrawal (discontinuation)symptoms [1,10]	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome [1] Hypothermia		Neonatal withdrawal [28]
Investigations	Elevations in serum triglyceride levels[11] Elevations in total cholesterol (predominantly LDL cholesterol)[12] Decreases in HDL cholesterol[1,18] Weight gain[3] Decreased haemoglobin[20]	Elevations in serum alanine aminotransferase (ALT)[4] Elevations in gamma-GT levels [4] Neutrophil count decreased [1,7] Eosinophils increased [24] Blood glucose increased to hyperglycaemic level [1,8] Elevations in serum prolactin [15] Decreases in Total T4 [22]	Elevations in serum aspartate aminotransferase (AST) [4] Platelet count decreased [14] Decreases in free T3 [22]	Elevations in blood creatine phosphokinase [13] Agranulocytosis[27]		

		Decreases in Free T4 [22] Decreases in Total T3 [22] Increases in TSH [22]				

[1] See Special warnings and special precautions for use.
[2] Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
[3] Based on ≥7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment.
[4] Asymptomatic elevations (shift from normal to ≥ 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
[5] As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.
[6] The inclusion of anaphylactic reaction is based on post-marketing reports.
[7] 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. 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 109/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 and the incidence ≥0.5 - <1.0 X 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients.
[8] Fasting blood glucose ≥126mg/dL or a non-fasting blood glucose ≥200mg/dL on at least one occasion.
[9] An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
[10] In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (eg, insomnia, nausea, headache, diarrhea, vomiting, dizziness, and irritability) did not exceed 5.3 % in any treatment group and usually resolved after 1 week post-discontinuation.
[11] Triglycerides ≥200 mg/dL (patients ≥18 years of age) or ≥150 mg/dL (patients <18 years of age) on at least one occasion.
[12] Cholesterol ≥240 mg/dL (patients ≥18 years of age) or ≥ 200 mg/dL (patients <18 years of age) on at least one occasion.
[13] Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
[14] Platelets ≤100 x 10^9/L on at least one occasion.
[15] Prolactin levels (patients ≥18 years of age): > 20 µg/L males; > 30 µg/L females at any time
[16] See text below
[17] May lead to falls
[18] HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
[19] Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
[20] 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. In the long-term randomised withdrawal trials, the time to onset of decreased haemoglobin is variable and the trend in the incidence of decreased haemoglobin declines with longer exposure.
[21] These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.
[22] Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 X LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
[23] Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
[24] 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 10^9cells/L at any time.
[25] 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.
[26] 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 quetiapine.
[27] Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (<0.5 x 10^9/L) and infection.
[28] See section 'Pregnancy and lactation'.
[29] SERM Clinical Overview, 2014-March. Hepatic Events. GEL locator: [CNS.000-377-593].
[30] Observed only in overdose. See section 'Overdose'.

Extrapyramidal symptoms
The following clinical trials (monotherapy and combination therapy) included treatment with Quetiapine and Quetiapine extended released.
In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo. In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group). In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for quetiapine extended released 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 quetiapine extended released and 2.3% for placebo. In two placebo-controlled short-term adjunct therapy clinical trials for the treatment of MDD utilising between 150 mg and 300 mg of quetiapine extended released, the incidence of any adverse reactions potentially related to EPS was 5.1% for quetiapine and 4.2% for placebo. In long-term studies of schizophrenia, bipolar disorder and major depressive disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

Thyroid levels
Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4: 3.4 % for quetiapine versus 0.6 % for placebo; free T_4: 0.7% for quetiapine versus 0.1% for placebo; total T_3: 0.54 % for quetiapine versus 0.0% for placebo and free T_3: 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T and TSH was 0.0 % for both quetiapine and placebo and 0.1% for quetiapine versus

0.0 % for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally 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. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. In eight patients, where TBG was measured, levels of TBG were unchanged.

Children and adolescents (10 to 17 years of age)
The same ADRs described above for adults should be considered for children and adolescents. The following table summarizes ADRs that occur in a higher frequency category in children and adolescents 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

SOC	Very Common (≥10%)	Common (1%-<10%)
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders		Syncope
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
Investigations	Elevations in serum prolactin[1] Increase in blood pressure[2]	

[1] Prolactin levels (patients < 18 years of age): >20 µg/L males; > 26 µg/L females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L
[2] Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

Weight gain in children and adolescents
In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty one percent of quetiapine-treated patients and 7% of placebo-treated patients gained ≥ 7 % of their body weight.
In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo treated patients gained ≥ 7 % of their body weight.
In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.
In one 8-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the mean increase in body weight was 1.4 kg in the quetiapine extended released group and 0.6 kg in the placebo group.

13.7 % of quetiapine extended released-treated patients and 6.8% of placebo-treated patients gained ≥ 7 % of their body weight.

Extrapyramidal symptoms in children and adolescent population:
In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) was generally low and did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo.
In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar depression in which efficacy was not established, the aggregated incidence of extrapyramidal symptoms was 1.1% for quetiapine extended released and 0.0% for placebo.

Post-market adverse reactions
Hepatic failure, including fatalities, has also been reported very rarely during the post-marketing period.

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

In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma.

In post marketing experience there were cases reported of QT prolongation with overdose.
Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

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

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. In this context, published reports in the setting of anti-cholinergic symptoms describe a reversal of severe CNS effects, including coma and delirium, with administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring.

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. Quetiapine overdose may lead to gastric bezoar formation and an appropriate diagnostic

imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass. Endoscopic pharmacobezoar removal has been performed successfully in many cases.

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 D1- and D2-receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic α_1- receptors and moderate affinity at adrenergic α_2 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). Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin 5HT1A receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine prolonged release'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 electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade.
In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2-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
The efficacy of Quetiapine extended released in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Quetiapine immediate-released -to- Quetiapine extended released switching study in clinically stable outpatients with schizophrenia.
The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Quetiapine extended released 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

In the 6-week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, ie, who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on Quetiapine immediate-released 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of Quetiapine extended released given once daily.
In a long-term study in stable schizophrenic patients who had been maintained on Quetiapine extended released for 16 weeks, Quetiapine extended released was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Quetiapine extended released treatment group compared to 68.2% for placebo. The mean dose was 669 mg.

Bipolar mania
In a clinical trial, Quetiapine extended released has been shown to be effective as monotherapy in reducing manic symptoms in patients with bipolar mania at doses between 400 and 800 mg/day. The effect of Quetiapine extended released was significant at Day 4 and was maintained through the end of the trial (Week 3).
In clinical trials, quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of quetiapine in responders, was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

Bipolar depression
In a clinical trial, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, Quetiapine extended released has been shown to be effective in patients with bipolar depression at doses of 300 mg/day. Quetiapine extended released was superior to placebo in reduction of MADRS total score. The antidepressant effect of Quetiapine extended released was significant at Day 8 (Week 1) and was maintained through the end of the trial (Week 8).
In four clinical trials, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, quetiapine has been shown to be effective in patients with bipolar depression at doses of 300 and 600 mg/day, however, no additional benefit was seen with the 600 mg dose during short-term treatment.
In all four studies, quetiapine was superior to placebo in reduction of MADRS total score. The antidepressant effect of quetiapine was significant at Day 8 (Week 1) and was maintained through the end of the studies (Week 8). Treatment with either quetiapine 300 or 600 mg at bedtime reduced depressive symptoms and anxiety symptoms in patients with bipolar depression. There were fewer episodes of treatment emergent mania with either dose of quetiapine than with placebo. In 3 out of 4 studies, for the 300 mg and 600 mg dose group, statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10 and in 2 out of 3 studies, for the 300 mg dose group, overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF).
In two bipolar depression clinical trials with quetiapine in adult patients, maintenance of antidepressant efficacy was evaluated. These trials included an 8-week placebo-controlled acute phase, followed by a placebo-controlled continuation phase of at least 26 weeks but up to 52-weeks in duration. Patients were required to be stable at the end of the acute phase in order to be in the randomized into continuation phase. In both trials, quetiapine was superior to placebo in increasing the time to recurrence of any mood event (depressed, mixed or manic). The risk reduction from the pooled trials was 49%. The risk of a mood event for quetiapine versus placebo was reduced by 41% for the 300-mg dose and by 55% for the 600-mg dose

Preventing recurrence in maintenance treatment of bipolar disorder
The efficacy of quetiapine in the monotherapy treatment for recurrence prevention was established in 1 placebo-controlled trial in 1226 patients who met DSM-IV criteria for Bipolar I Disorder. The trial included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilised on quetiapine for a minimum of 4 weeks in order to be randomized. In the randomization phase, patients either continued treatment with quetiapine (300 to 800 mg per day: average dose 546 mg per day) or were to receive lithium or placebo for up to 104 weeks. Quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed, or depressive), the primary endpoint. The risk reductions were 74%, 73%, and 75% for mood, manic and depressive events, respectively.

The efficacy of quetiapine in the combination treatment for recurrence prevention was established in 2 placebo-controlled trial in 1326 patients who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilised on quetiapine in combination with mood stabilizer (lithium or valproate) for a minimum of 12 weeks in order to be randomized. In the randomisation phase, patients either continued treatment with quetiapine (400 to 800 mg per day average dose 507 mg per day) in combination with mood stabiliser or received placebo in combination with mood stabiliser for up to 104 weeks. quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressive), the primary endpoint. The risk reductions were 70%, 67%, and 74% for mood, manic and depressive events, respectively.

Major depressive disorder
Two short-term (6 week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Quetiapine extended released 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).
Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (See below).
The following studies were conducted with Quetiapine extended released as monotherapy treatment, however Quetiapine extended released is only indicated for use as add-on therapy:
In three out of four short term (up to 8 weeks) monotherapy studies, in patients with major depressive disorder, Quetiapine extended released 50 mg, 150 mg and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (LS mean change vs. placebo of 2-4 points).
In a monotherapy relapse prevention study, patients with depressive episodes stabilised on open-label Quetiapine extended released treatment for at least 12 weeks were randomised to either Quetiapine extended released once daily or placebo for up to 52 weeks. The mean dose of Quetiapine extended released during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for Quetiapine extended released treated patients and 34.4% for placebo-treated patients.
In a short-term (9 week) study non-demented elderly patients (aged 66 to 89 years) with major depressive disorder, Quetiapine extended released dosed flexibly in the range of 50 mg to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study patients randomised to Quetiapine extended released received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The mean dose of Quetiapine extended released was 160 mg/day. Other than the incidence of extrapyramidal symptoms (See

Undesirable effects) the tolerability of Quetiapine extended released once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomized patients over 75 years of age was 19%.

Clinical safety

Suicide/suicidal thoughts or clinical worsening

In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events was 0.8% for both quetiapine (76/9327) and for placebo (37/4845).

In these trials of patients with schizophrenia the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥25 years of age, and 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients < 18 years of age.

In these trials of patients with bipolar mania the incidence of suicide related events was 0% for both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo 6/503 in patients ≥25 years of age, and 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients < 18 years of age.

In these trials of patients with bipolar depression the incidence of suicide related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24 and 1.8% for both quetiapine (19/1616) and placebo (11/622) in patients ≥25 years of age. There has been one trial conducted in patients 10-17 years of age in which efficacy was not established. The incidence of suicide related events was 1.0% (1/92) for quetiapine and 0% (0/100) for placebo. In this study there were two additional events in two patients that occurred during an extended post-treatment follow-up phase of the study; one of these patients was on quetiapine at the time of the event .

In these trials of patients with major depressive disorder the incidence of suicide related events was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo in patients 18-24 and 0.6% (11/1798) for quetiapine and 0.7% for placebo (7/1054) in patients ≥ 25 years of age. There have been no trials conducted in patients <18 years of age with major depressive disorder.

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of Quetiapine (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 Quetiapine compared with risperidone for patients with at least 21 months of exposure.

5.2 Pharmacokinetic properties

Absorption

Quetiapine is well absorbed following oral administration. Quetiapine prolonged release achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (Tmax). 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 and dose-proportional for doses up to 800 mg administered once daily. When quetiapine prolonged release administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate administered twice daily, the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (Cmax) are comparable.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the quetiapine prolonged release C_{max} and AUC of 44% to 52% and 20% to 22% respectively for the 50-mg and 300-mg tablets. In comparison, a light meal had no significant effect on the Cmax or AUC of quetiapine.

This increase in exposure is not clinically significant, and therefore quetiapine can be taken with or without food.

There are no clinically relevant differences in the observed apparent oral clearance (CL/F) and exposure of quetiapine between subjects with schizophrenia and bipolar disorder.

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.

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. Approximately 73% of a radiolabelled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Pre-clinical safety data
Acute toxicity studies
Quetiapine has low acute toxicity. Findings in mice and rats after oral (500 mg/kg) or intraperitoneal (100 mg/kg) dosing were typical of an effective neuroleptic agent and included decreased motor activity, ptosis, loss of righting reflex, fluid around the mouth and convulsions.

Repeat-dose toxicity studies
In multiple-dose studies in rats, dogs and monkeys, anticipated central nervous system effects of an antipsychotic drug were observed with quetiapine (eg, sedation at lower doses and tremor, convulsions or prostration at higher exposures).

Hyperprolactinaemia, induced through the dopamine D2 receptor antagonist activity of quetiapine or its metabolites, varied between species but was most marked in the rat, and a range of effects consequent to this were seen in the 12-month study, including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females.

Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey.
Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.
Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects.
Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/kg/day, nor in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man (See Pharmacodynamic properties).

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies.

Carcinogenicity studies
In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia.

In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Reproduction studies
Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.
Quetiapine had no teratogenic effects.

Mutagenicity studies
Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen.

Special populations

Gender
The pharmacokinetics of quetiapine does not differ between men and women.

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 m2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approximately 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 (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Methacrylic acid – ethyl acrylate copolymer (1:1), type A
Lactose anhydrous
Magnesium stearate
Crystalline Maltose
Talc

Coating
Methacrylic acid – ethyl acrylate copolymer (1:1), type A
Triethyl Citrate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
A cardboard box containing the appropriate number of white opaque PVC/PCTFE-Aluminium foil blisters and an instruction leaflet.

Tablet Strength	Carton (pack) contents	Blister
50mg, 150mg, 200mg,300mg and 400mg tablets	60 tablets	6 blisters of 10 tablets

6.6 Special precautions for disposal
No special requirements.

7. MANUFACTURER
Pharmathen International S.A
Industrial Park Sapes, Rodopi Prefecture,
Block No 5, Rodopi 69300, Greece.

8. **PRODUCT REGISTRANT**
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