

1. NAME OF THE MEDICINAL PRODUCT

Saquin SR Quetiapine 50 mg prolonged-release tablets
Saquin SR Quetiapine 200 mg prolonged-release tablets
Saquin SR Quetiapine 300 mg prolonged-release tablets
Saquin SR Quetiapine 400 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Saquin SR Quetiapine 50 mg prolonged-release tablets contains 50 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 14.21 mg lactose (anhydrous) per tablet

Saquin SR Quetiapine 200 mg prolonged-release tablets contains 200 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 56.84 mg lactose (anhydrous) per tablet

Saquin SR Quetiapine 300 mg prolonged-release tablets contains 300 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 85.26 mg lactose (anhydrous) per tablet

Saquin SR Quetiapine 400 mg prolonged-release tablets contains 400 mg quetiapine (as quetiapine fumarate)
Excipient with known effect: 113.68 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.

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 the treatment of schizophrenia.

Saquin SR is effective in preventing relapse in stable schizophrenic patients who have been maintained on Saquin SR.

Saquin SR is indicated for the treatment of moderate to severe manic episodes in the framework of bipolar disorder.

Saquin SR is indicated for the treatment of major depressive episodes in bipolar disorder.

Saquin SR is indicated for the prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

Saquin SR is indicated for the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex.

The efficacy of Saquin SR in bipolar disorder was established, in part, on the basis of extrapolation from the established effectiveness of Quetiapine.

Major depressive disorder

Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies.

4.2 Posology and method of administration

Saquin SR should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder

Saquin SR should be administered at least one hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically justified the dose may be increased to 800 mg daily. 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.

For the treatment of depressive episodes associated with bipolar disorder

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

Maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex

While there is no body of evidence available to specifically address how long the patient treated with Saquin SR should remain on it, maintenance of efficacy in Bipolar I Disorder was demonstrated with Quetiapine (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. 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.

For preventing recurrence in bipolar disorder

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

Recurrent major depressive disorder

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.

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

Patients who have not responded to Saquin SR after 6 weeks treatment for MDD should have treatment re-evaluated.

For maintenance therapy in MDD in patients who have responded to acute treatment, the effective dose during initial treatment should be continued.

It is generally recommended that responding patients be continued beyond the acute response, but the lowest possible dose needed to maintain remission. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

Long-term safety of Saquin SR in MDD has not been systematically evaluated (>52 weeks). Thus, the physician who elects to use Saquin SR in the treatment of MDD should use Saquin SR for the shortest time that is clinically indicated. When lengthier treatment is indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks.

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, 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 MDD, initial dosing should begin with 50 mg on Days 1- 3, the dose can be increased to 100 mg on Day 4 and 150 mg on Day 8, and then up to 300mg depending on clinical response.

Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and Adolescents:

The safety and efficacy of Saquin SR have not been evaluated in children and adolescents.

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

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

4.3 Contraindications

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

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

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. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4400 children and adolescents and 7700 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.

Neutropenia and agranulocytosis:

Severe neutropenia (neutrophil count $<0.5 \times 10^9/L$) 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 a couple of months of starting therapy with quetiapine. There was no apparent dose relationship.

Possible risk factors for neutropenia include pre-existing low white blood 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, should be managed as clinically appropriate.

Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9/L$. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed $1.5 \times 10^9/L$).

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship 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. Given this confounder, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increase risk of treatment-emergent hyperglycaemia-related adverse events in the patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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.

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.

Pancreatitis:

Pancreatitis has been reported in clinical trials and during post marketing experience, however a casual relationship has not been established. Among post marketing reports, 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 and therefore dose reduction or more gradual titration should be considered if this occurs.

In patients who have a history of or are at risk for sleep apnoea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

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.

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.

Tardive Dyskinesia and Extrapyrimal 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.

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.

QT Prolongation:

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post-marketing experience there were cases reported of QT prolongation with overdose. As with other antipsychotics, caution should be exercised when 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 for patients with increased risk of QT prolongation, ie. the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

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, headache, diarrhoea, vomiting, dizziness, and irritability 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.

Use in children and adolescents (10 to 17 years of age):

Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials with quetiapine 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 behavioural development, beyond 26 weeks of treatment with quetiapine, is not available for children and adolescents (10 to 17 years of age).

Elderly patients with dementia:

Saquin SR is not approved for the treatment of 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. However 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.

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 decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of quetiapine may need to be considered if 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 it 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.

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.

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.

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. A second study did not demonstrate an additive effect at week 6. There are no combination data available beyond week 6.

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 anticholinergic (muscarinic) effects.

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

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 antipsychotic 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.

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

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

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.

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 ($\geq 10\%$) 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

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

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
<i>Blood and lymphatic system disorders</i>		Leucopenia,	Thrombocytopenia,			Neutropenia
<i>Immune system disorders</i>			Hypersensitivity		Anaphylactic reaction	
<i>Endocrine disorders</i>		Hyperprolactinemia,			Inappropriate antidiuretic hormone secretion	
<i>Metabolism and nutritional disorders</i>		Increased appetite,	Hyponatraemia		Diabetes Mellitus	
<i>Psychiatric disorders</i>		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour		Somnambulism and other related events		
<i>Nervous system disorders</i>	Dizziness, somnolence, headache, Extrapyramidal symptoms	Dysarthria	Seizure, Restless legs syndrome, Tardive dyskinesia, Syncope			
<i>Cardiac disorders</i>		Tachycardia, Palpitations	Bradycardia			
<i>Eye disorders</i>		Vision blurred				
<i>Vascular disorders</i>		Orthostatic hypotension		Venous thromboembolism		

<i>Respiratory, thoracic and mediastinal disorder</i>		Dyspnoea	Rhinitis, sleep apnoea			
<i>Gastrointestinal disorders</i>	Dry mouth	Constipation, dyspepsia, vomiting	Dysphagia	Intestinal obstruction/Ileus		Bezoar
<i>Hepato-biliary disorders</i>				Jaundice, Hepatitis		
<i>Renal and urinary disorders</i>			Urinary retention			
<i>Skin and subcutaneous tissue disorders</i>					Angioedema, Stevens-Johnson syndrome	Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP) Erythema multiforme (EM)
<i>Musculoskeletal and connective tissue disorders</i>					Rhabdomyolysis	
<i>Reproductive system and breast disorders</i>			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
<i>General disorders and administration site conditions</i>	Withdrawal (discontinuation) symptoms	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome, hypothermia		Neonatal withdrawal
<i>Investigations</i>	Elevations in serum triglyceride levels, Elevations in total cholesterol (predominantly LDL cholesterol), Decreases in HDL cholesterol, Weight gain, decreased haemoglobin	Elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels, decreased neutrophil count, eosinophils increased, blood glucose increased to hyperglycaemic levels, QT prolongation, decreases in	Elevations in serum aspartate aminotransferase (AST), Platelet count decreased, decreases in free T3	Elevations in blood creatine phosphokinase, agranulocytosis		

		Total T4, decreases in Free T4, decreases in Total T3, increases in TSH				
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Nervous System Disorders: Restless legs syndrome

Respiratory, Thoracic and Mediastinal Disorders: Sleep apnoea*

*Atypical antipsychotic drugs, such as, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Saquin SR should be prescribed with caution.

Renal and Urinary Disorder: Urinary retention

Extrapyramidal symptoms

The following clinical trials (monotherapy and combination therapy) in adult patients included treatment with Quetiapine and Quetiapine SR.

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 SR 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 SR and 2.3% for placebo.

In long-term studies of schizophrenia, bipolar disorder, and major depressive disorder, the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

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 T4: 3.4% for quetiapine versus 0.6% for placebo; free T4: 0.7% for quetiapine versus 0.1% for placebo; total T3: 0.54% for quetiapine versus 0.0% for placebo and free T3: 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 T3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T4 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 T4, 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 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) and very rare ($< 1/10,000$).

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

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 $\geq 7\%$ 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 $\geq 7\%$ 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 $\geq 7\%$ 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 SR group and 0.6 kg in the placebo group. 13.7 % of Quetiapine SR-treated patients and 6.8% of placebo-treated patients gained $\geq 7\%$ 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 SR and 0.0% for placebo.

4.9 Overdose

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of Quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams. In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

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, i.e., drowsiness and sedation, tachycardia, hypotension and anti-cholinergic 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 SR 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). Inhibition of NET and partial agonist action at 5HT_{1A} 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 D₂receptor 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-naïve Cebus monkeys after acute and chronic administration.

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

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 (T_{max}). 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) is equivalent, but the maximum plasma concentration (C_{max}) is 13% lower at steady state. When quetiapine prolonged release is compared to quetiapine immediate release, the norquetiapine metabolite AUC is 18% lower.

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 approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that quetiapine prolonged release is taken once daily without food.

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. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination

The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. 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.

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).

Paediatric population

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

active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for quetiapine prolonged release in children and adolescents.

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

Store below 30°C

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, 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 REGISTRATION HOLDER

GoodScience Sdn Bhd

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Kawasan Perindustrian Kundang,

Kundang Jaya, 48020 Rawang,

Selangor

9. DATE OF REVISION OF THE TEXT

09 December 2024

(font size min size: 7, as measure in Times New Roman)