

SUMMARY OF PRODUCT CHARACTERISTICS

Qutipin 50/100/200/300

(Quetiapine Fumarate Tablets USP 50/100/200/300 mg)

1. NAME OF THE MEDICINAL PRODUCT

Qutipin 50/100/200/300

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Quetiapine fumarate equivalent to quetiapine 50/100/200/300 mg

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Qutipin is indicated for:

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

4.2 Posology and method of administration

Qutipin is available in the strengths of 50, 100, 200 and 300 mg tablets and may not be suitable for all dosage recommendations given below. Therefore, other suitable available strengths and dosage forms of quetiapine should be used in such cases.

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

Adults

For the treatment of schizophrenia

For the treatment of schizophrenia, **Qutipin** should be administered twice a day. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards, the dose should be titrated to the usual effective dose of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

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

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

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

For the treatment of major depressive episodes in bipolar disorder

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

For preventing recurrence in bipolar disorder

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

Elderly

As with other antipsychotics, **Qutipin** should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was

reduced by 30 - 50% in elderly subjects when compared to younger patients.

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

Paediatric population

Qutipin is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebocontrolled clinical trials is presented in see sections **4.4**, **4.8** and **5.2**.

Renal impairment

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment

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

Method of Administration

Qutipin can be administered with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated (see **section 4.5**).

4.4 Special warnings and precautions for use

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

Paediatric population

Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Reported clinical studies with quetiapine have shown that in addition to the known safety profile identified in adults (see **section 4.8**), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and

one was identified that has not been previously seen in reported adult studies (increases in blood pressure). Changes in thyroid function tests have also been reported in children and adolescents.

Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been reported beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In reported placebo-controlled clinical studies with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania and bipolar depression (see **section 4.8**).

Suicide/suicidal thoughts or clinical worsening

Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, selfharm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A reported meta-analysis of placebo controlled clinical studies of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

In reported shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-

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

Metabolic risk

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycaemia) and lipids, which was seen in reported clinical studies, patients' metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also **section 4.8**).

Extrapyramidal symptoms

In reported placebo controlled clinical studies of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see **section 4.8**).

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

Tardive dyskinesia

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see **section 4.8**).

Somnolence and dizziness

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see **section 4.8**). In reported clinical studies for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see **section 4.8**) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

Sleep apnoea syndrome

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

Seizures

In reported controlled clinical studies there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see **section 4.8**).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see **section 4.8**). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis

Severe neutropenia (neutrophil count $<0.5 \times 10^9/L$) has been reported in quetiapine studies. Most cases of severe neutropenia have been reported within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. Some fatal cases have been reported during post marketing. Possible risk factors for neutropenia include preexisting low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases have been reported in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9/L$. Patients should be observed for signs and

symptoms of infection and neutrophil counts followed (until they exceed $1.5 \times 10^9/L$).

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

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

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see **sections 4.5, 4.8 and 4.9**).

Interactions

See **section 4.5**

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Weight

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see **section 4.8**).

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see **section 4.8**). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised

antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been reported with quetiapine (see **section 4.8**). Lipid changes should be managed as clinically appropriate.

QT prolongation

In reported clinical studies and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. QT prolongation has been reported with quetiapine at the therapeutic doses (see **section 4.8**) and in overdose (see **section 4.9**). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see **section 4.5**).

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical studies and during the postmarketing experience (see **section 4.8**). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal have been reported very rarely with quetiapine treatment.

SCARs commonly present as a combination of the following symptoms: extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. Most of these reactions reported within 4 weeks after initiation of quetiapine therapy, some DRESS reactions reported within 6 weeks after initiation of quetiapine therapy. If signs and symptoms suggestive of these severe skin reactions appear, quetiapine should be withdrawn immediately and alternative treatment should be considered.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see **section 4.8**).

Elderly patients with dementia-related psychosis

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

An approximately 3-fold increased risk of cerebrovascular adverse events has been reported in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

Elderly patients with dementia-related psychosis are reported to be at an increased risk of death compared to placebo. In two 10-week placebo-controlled quetiapine studies reported in the same patient population; (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 reported studies died from a variety of causes that were consistent with expectations for this population.

Elderly patients with Parkinson's disease (PD)/parkinsonism

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

Dysphagia

Dysphagia (see **section 4.8**) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see **section 4.8**). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)

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

Pancreatitis

Pancreatitis has been reported in clinical studies 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 (see **section 4.4**), gallstones, and alcohol consumption.

Additional information

Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see **section 4.8**). The reported data showed an additive effect at week 3.

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.

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 (see **section 4.4**).

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome

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

In a reported multiple dose study in patients to assess the pharmacokinetics of quetiapine given before and during treatment with

carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect has been reported in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Coadministration 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) (see **section 4.4**).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%.

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

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

In a reported 6-week, randomised, study of lithium and quetiapine extended release versus placebo and quetiapine extended release in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A reported retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Formal interaction studies with commonly used cardiovascular medicinal products have not been reported.

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

First trimester

An increased risk of malformations due to treatment has not been reported. However, based on all reported data, a definite conclusion cannot be drawn. Reported animal studies have shown reproductive toxicity (see **section 5.3**). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

Third trimester

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

Breast-feeding

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

Fertility

The effects of quetiapine on human fertility have not been reported. Effects related to elevated prolactin levels have been reported in rats, although these are not directly relevant to humans (see **section 5.3**).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Table 1: ADRs associated with quetiapine therapy

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

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders	Decreased haemoglobin ²²	Leucopenia ¹ , decreased neutrophil count, eosinophils increased ²⁷	Neutropenia ¹ , Thrombocytopenia, Anaemia, platelet count decreased ¹³	Agranulocytosis ²⁶		
Immune system disorders			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction ⁵	

<i>Endocrine disorders</i>		Hyperprolactinaemia ¹⁵ , decreases in total T ₄ ²⁴ , decreases in free T ₄ ²⁴ , decreases in total T ₃ ²⁴ , increases in TSH ²⁴	Decreases in free T ₃ ²⁴ , Hypothyroidism ²¹		Inappropriate antidiuretic hormone secretion	
<i>Metabolic and nutritional disorders</i>	Elevations in serum triglyceride levels ^{10, 30} Elevations in total cholesterol (predominantly LDL cholesterol) ¹ 1, 30	Increased appetite, blood glucose increased to hyperglycaemic levels ^{6, 30}	Hyponatraemia ¹⁹ , Diabetes Mellitus ^{1, 5} Exacerbation of pre-existing diabetes	Metabolic syndrome ²⁹		

	Decreases in HDL cholesterol ^{17,30} , Weight gain ^{8,30}					
<i>Psychiatric disorders</i>		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour ²⁰		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		

<i>Nervous system disorders</i>	Dizziness ⁴ , 16, somnolence 2, 16, headache, Extrapyramidal symptoms ¹ , 2 1	Dysarthria	Seizure ¹ , Restless legs syndrome, Tardive dyskinesia ¹ , ⁵ , Syncope ⁴ , ¹⁶ Confusional state			
<i>Cardiac disorders</i>		Tachycardia ⁴ , Palpitations ²³	QT prolongation ¹ , 12, 18, Bradycardia ³²			cardiomyopathy and myocarditis
<i>Eye disorders</i>		Vision blurred				
<i>Vascular disorders</i>		Orthostatic hypotension ⁴ , 16		Venous thromboembolism ¹		Stroke ³³
<i>Respiratory, thoracic and mediastinal disorder</i>		Dyspnoea ²³	Rhinitis			
<i>Gastrointestinal disorders</i>	Dry mouth	Constipation, dyspepsia, vomiting ²⁵	Dysphagia ⁷	Pancreatitis ¹ , Intestinal obstruction/Ileus		
<i>Hepatobiliary disorders</i>		Elevations in serum alanine aminotransferase (ALT) ³ , Elevations in gamma-GT	Elevations in serum aspartate aminotransferase (AST) ³	Jaundice ⁵ , Hepatitis		

		levels ³				
<i>Skin and subcutaneous tissue disorders</i>					Angioedema ⁵ , StevensJohnson syndrome ⁵	Toxic Epidermal Necrolysis, Erythema Multiforme, Acute Generalized Exanthemat

						ous Pustulosis (AGEP), Drug Rash with Eosinophili a and Systemic Symptoms (DRESS), Cutaneous vasculitis
<i>Musculoskeletal and connective tissue disorders</i>					Rhabdomyolysis	
<i>Renal and urinary disorders</i>			Urinary retention			
<i>Pregnancy, puerperium and perinatal conditions</i>						Drug withdrawal syndrome neonatal ³¹
<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 ^{1,9}	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome ¹ , hypothermia		
<i>Investigations</i>				Elevations in blood creatine phosphokinase ¹⁴		

1. See **section 4.4**

- Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
- Asymptomatic elevations (shift from normal to >3 x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT levels have been reported in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
- As with other antipsychotics with α_1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see **section 4.4**).

5. Calculation of frequency for these ADR's have been taken from reported post-marketing data only.
6. Fasting blood glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) or a non-fasting blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) on at least one occasion.
7. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the reported clinical studies in bipolar depression.
8. Based on $>7\%$ increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
9. The following withdrawal symptoms have been observed most frequently in reported acute placebocontrolled, monotherapy clinical studies, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
10. Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients <18 years of age) on at least one occasion.
11. Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly reported. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).
12. See text below.
13. Platelets $\leq 100 \times 10^9/L$ on at least one occasion.
14. Based on reported clinical study adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
15. Prolactin levels (patients >18 years of age): >20 $\mu\text{g/L}$ (>869.56 pmol/L) males; >30 $\mu\text{g/L}$ (>1304.34 pmol/L) females at any time.
16. May lead to falls.
17. HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
18. Incidence of patients who have a QTc shift from <450 msec to ≥ 450 msec with a ≥ 30 msec increase. In reported placebo-controlled studies 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.
19. Shift from >132 mmol/L to ≤ 132 mmol/L on at least one occasion.
20. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see **section 4.4**).
21. Quetiapine treatment has been associated with dose related decreases in thyroid hormone levels
22. Decreased haemoglobin to ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all reported studies including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was -1.50 g/dL.
23. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.

24. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all reported studies. Shifts in total T₄, free T₄, total T₃ and free T₃ are defined as <0.8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.
25. Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
26. Based on shift in neutrophils from > =1.5 x 10⁹/L at baseline to <0.5 x 10⁹/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 10⁹/L) and infection during all reported quetiapine clinical studies (see **section 4.4**).
27. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all reported studies. Shifts in eosinophils are defined as >1 x 10⁹ cells/L at any time.
28. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all reported studies. Shifts in WBCs are defined as ≤3 x 10⁹ cells/L at any time.
29. Based on adverse event reports of metabolic syndrome from all reported clinical studies with quetiapine.
30. In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in reported clinical studies (see **section 4.4**).
31. See **section 4.6**.
32. 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 reported clinical studies with quetiapine.
33. Based on a reported retrospective non-randomised epidemiological study.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment.

Paediatric population

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

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

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

SOC	Very Common	Common
<i>Endocrine disorders</i>	Elevations in prolactin ¹	
<i>Metabolism and nutritional disorders</i>	Increased appetite	
<i>Nervous system disorders</i>	Extrapyramidal symptoms ³	Syncope
<i>Vascular disorders</i>	Increases in blood pressure ²	
<i>Respiratory, thoracic and mediastinal disorders</i>		Rhinitis
<i>Gastrointestinal disorders</i>	Vomiting	
<i>General disorders and administration site conditions</i>		Irritability ³

1. Prolactin levels (patients < 18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L)

females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/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 reported acute (3-6 weeks) placebo-controlled studies in children and adolescents.

3. Note: The frequency is consistent to that reported in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Regulatory Authority.

4.9 Overdose

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see **section 4.4**, Orthostatic hypotension).

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

Close medical supervision and monitoring should be continued until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 *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 alpha₁ receptors and moderate affinity at adrenergic alpha₂ receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anticholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT_{1A} sites by norquetiapine may contribute to quetiapine'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 reported 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-naïve Cebus monkeys after acute and chronic administration (see **section 4.8**).

Cataracts/lens opacities

The cataractogenic potential of quetiapine (200-800 mg/day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder has been reported. The percentage of patients with increased lens opacity grade was not higher in quetiapine (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

Quetiapine is approximately 83% bound to plasma proteins.

Biotransformation

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Reported *in vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is reported only at concentrations approximately 5 to 50-fold higher than those reported at a dose range of 300 to 800 mg/day in humans. Based on these reported *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 reported animal studies it

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

Elimination

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

Special populations

Gender

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

Elderly

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that 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/1.73m²), but the individual clearance values are within the range for normal subjects.

Hepatic impairment

The mean quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see **section 4.2**).

Paediatric population

Reported pharmacokinetic data were sampled in children aged 10-12 years old and adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C_{max} in children was at the higher end of the range reported in adults. The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of reported *in vitro* and *in vivo* genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in reported long-term clinical research:

In rats, pigment deposition in the thyroid gland has been reported; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T₃ levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been reported; and in dogs lens opacity and cataracts (for cataracts/lens opacities).

In a reported embryofetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a reported fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicified microcrystalline cellulose, crospovidone, colloidal anhydrous silica, anhydrous citric acid, polysorbate 80, silicon dioxide, magnesium stearate and opadry brown (Qutipin 50), Opadry Yellow (Qutipin 100), Opadry white (Qutipin 200 and 300).

6.2

Incompatibilities

s Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for Storage

Store up to 30°C, protected from light.

6.5 Nature and contents of container

QUITIPIN is available as 50, 100, 200 and 300mg in blisters of 10 tablets

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Sun Pharmaceutical Industries Limited

8. MARKETING AUTHORISATION NUMBER(S)

50mg: 15611,

100mg: 15612,

200mg: 17697,

300mg: H2013/CTD891/138

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10-05-2021

10. **DATE OF REVISION OF THE TEXT**
February 2026