

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

QUETEMAC ER 300 (Quetiapine Fumarate 300 mg Extended Release Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ER tablet contains 300mg quetiapine fumarate

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

Pale yellow, capsule shaped film coated tablets debossed with “C 24” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Quetiapine is indicated for:

- treatment of schizophrenia.
- treatment of bipolar disorder:
 - For the treatment of moderate to severe manic episodes in bipolar disorder.
 - For the treatment of major depressive episodes in bipolar disorder.
 - For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to Quetiapine treatment.
- add-on treatment of major depressive episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to antidepressant monotherapy. Prior to initiating treatment, clinicians should consider the safety profile of quetiapine.

4.2 Posology and method of administration

Posology

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 and moderate to severe manic episodes in bipolar disorder

Quetiapine Fumarate 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 major depressive episodes in bipolar disorder

Quetiapine Fumarate should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. 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.

For preventing recurrence in bipolar disorder

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Quetiapine Fumarate for acute treatment of bipolar disorder should continue on Quetiapine Fumarate at the same dose administered at bedtime. Quetiapine Fumarate 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.

For add-on treatment of major depressive episodes in MDD:

Quetiapine Fumarate should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram,

fluoxetine, paroxetine, sertraline and venlafaxine) and at 50 mg/day in short-term monotherapy trials.

There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

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 Quetiapine Fumarate at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Special populations

Elderly:

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

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

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

Paediatric population:

Quetiapine Fumarate is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group.

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolized by the liver. Therefore, Quetiapine Fumarate 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.

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy.

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. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults, certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

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

Suicide/suicidal thoughts or clinical worsening

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

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

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

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful

monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

Metabolic risk

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose and lipids, which was seen in 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.

Extrapyramidal symptoms

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.

Somnolence and dizziness

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of

somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension

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

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

Sleep apnoea syndrome

Sleep apnoea syndrome 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

No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Neuroleptic malignant syndrome

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

Severe neutropenia and agranulocytosis

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

Interactions

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

Weight

Weight gain 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.

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases. 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 observed in clinical trials with quetiapine. Lipid changes should be managed as clinically appropriate.

QT prolongation

Quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses and in 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 in the elderly, in 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 generalised exanthematous pustulosis (AGEP), erythema multiforme (EM) 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 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. Most of these reactions occurred within 4 weeks after initiation of quetiapine therapy, some DRESS reactions occurred 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.

Elderly patients with dementia-related psychosis

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

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

Elderly with Parkinson's disease (PD)/parkinsonism

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

Dysphagia

Dysphagia has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction

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

Venous thromboembolism (VTE)

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

Pancreatitis

Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded

by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides, gallstones, and alcohol consumption.

Additional information

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

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.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects.

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

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during

administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

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

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

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

A retrospective study of children and adolescents who received valproate, Quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

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

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

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

4.5 Pregnancy , Lactation and fertility

Pregnancy

First trimester

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

Third trimester

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation

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

Fertility

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

4.7 Effects on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness.

Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 Undesirable effects

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

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

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).

Table 1 ADRs associated with quetiapine therapy

Very common	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders					
Decreased Haemoglobin ²²	Leucopenia ^{1, 28} , decreased neutrophil count, eosinophils increased ²⁷	Neutropenia ¹ , Thrombocytopenia, Anaemia, platelet count decreased ¹³	Agranulocytosis ²⁶		
Immune system disorders					
		Hypersensitivity (including allergic skin		Anaphylactic reaction ⁵	

		reactions)			
Endocrine disorders					
	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	
Metabolism and nutritional disorders					
Elevations in serum triglyceride levels ^{10,30} Elevations in total cholesterol (predominantly LDL cholesterol) ^{1,30} Decreases in HDL cholesterol ^{17,30} Weight Gain ^{8,30}	Increased appetite, blood glucose increased to hyperglycaemic levels ^{6,30}	Hyponatraemia ¹⁹ , Diabetes Mellitus ^{1,5} Exacerbation of pre-existing diabetes	Metabolic Syndrome ²⁹		
Psychiatric disorders					

	Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour ²⁰		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
Nervous system disorders					
Dizziness ^{4,16} Somnolence ^{2,16} headache, Extrapyramidal Symptoms ¹ , 21	Dysarthria	Seizure ¹ , Restless legs syndrome, Tardive dyskinesia ^{1,5} , Syncope ^{4,16} Confusional state			
Cardiac disorders					
	Tachycardia ⁴ , Palpitations ²³	QT prolongation ¹ , 12,18 Bradycardia ³²			Cardiomyopathy and myocarditis
Eye disorders					
	Vision blurred				
Vascular disorders					
	Orthostatic Hypotension ⁴ , 16		Venous Thromboembolism ¹		Stroke ³³
Respiratory, thoracic and mediastinal disorder					
	Dyspnoea ²³	Rhinitis			

Gastrointestinal disorders					
	Dry mouth	Constipation, dyspepsia, vomiting ²⁵	Dysphagia ⁷	Pancreatitis ¹ , Intestinal obstruction/ Ileus	
Hepato-biliary disorders					
	Elevations in serum alanine aminotransferase (ALT) ³ , Elevations in gamma-GT levels ³	Elevations in serum aspartate aminotransferase (AST) ³	Jaundice ⁵ , Hepatitis		
Skin and subcutaneous tissue disorders					
				Angioedema ⁵ , Stevens-Johnson Syndrome ⁵	Toxic Epidermal Necrolysis, Erythema Multiforme Drug reaction with eosinophilia and systemic symptoms (DRESS), Cutaneous vasculitis
Musculoskeletal and connective tissue disorders					
				Rhabdomyolysis	

Renal and urinary disorders					
		Urinary retention			
Pregnancy, puerperium and perinatal conditions					
					Drug withdrawal syndrome neonatal ³¹
Reproductive system and breast disorders					
		Sexual dysfunction	Priapism, galactorrhea, breast swelling, menstrual disorder		
General disorders and administration site conditions					
Withdrawal (discontinuation) Symptoms ^{1,9}	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome ¹ , hypothermia		
Investigations					
			Elevations in blood creatine phosphokinase ¹⁴ .		

1. See Section 4.4.

2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

3. Asymptomatic elevations (shift from normal to > 3x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
4. As with other antipsychotics with alpha1 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.
5. Calculation of frequency for these ADR's have only been taken from post-marketing data with the immediate release formulation of quetiapine.
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 clinical trials 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 acute placebo-controlled, monotherapy clinical trials, 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 observed.
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 clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
15. Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/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 placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
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.
21. See section 5.1.
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 trials 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 trials. 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 quetiapine clinical trials.
27. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as >1x 10⁹ cells/L at, any time.

28. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as $\leq 3 \times 10^9$ cells/L at any time.

29. Based on adverse event reports of metabolic syndrome from all clinical trials 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 clinical studies.

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 clinical trials with quetiapine.

33. Based on one 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 adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

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

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

SOC	Very Common	Common
Endocrine disorders	Elevations in prolactin ¹	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms ^{3,4}	Syncope
Vascular disorders	Increases in blood pressure ²	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability ³

1. Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1,130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.

2. Based on shifts above clinically significant thresholds (adapted from the National

Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

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

4. See section 5.1

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.

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.

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.

In case of overdose with extended-release quetiapine there is a delayed peak sedation and peak pulse and prolonged recovery compared with IR quetiapine overdose.

In case of a quetiapine extended-release overdose gastric bezoar formation has been reported and 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 some cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics; diazepines, oxazepines, thiazepines and oxepines. ATC code: N05AH04

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'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.

5.2 Pharmacokinetic properties

Absorption

Quetiapine is well absorbed following oral administration. Prolonged-release quetiapine 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 prolonged-release quetiapine 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 prolonged-release quetiapine is compared to immediate release quetiapine, the norquetiapine metabolite AUC is 18% lower.

Distribution

Quetiapine is approximately 83% bound to plasma proteins.

Biotransformation

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

Norquetiapine is primarily formed and eliminated via CYP3A4. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

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 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.

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.

5.3 Preclinical safety data

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

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

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

In a fertility study in rats, marginal reduction in male fertility and pseudo pregnancy, 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

Lactose monohydrate

Microcrystalline cellulose (RQ 101)

Sodium citrate dihydrate

Ethylcellulose

Povidone

Isopropyl alcohol

Purified water

Magnesium stearate

Instacoat yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container

Alu/White opaque PVC/PVDC Blister pack of 10 Tablets. Such as 10 Blisters in one carton along with pack insert.

6.6 Special Precaution for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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References:

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