Ketipinor Tablet 25 mg, 100 mg & 200 mg

1. NAME OF THE MEDICINAL PRODUCT

KETIPINOR TABLET 25 MG
KETIPINOR TABLET 100 MG
KETIPINOR TABLET 200 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

25 mg tablet: Each film-coated tablet contains 25 mg quetiapine (as fumarate).
100 mg tablet: Each film-coated tablet contains 100 mg quetiapine (as fumarate).
200 mg tablet: Each film-coated tablet contains 200 mg quetiapine (as fumarate).

Excipient with known effect:
100 mg tablet: Each tablet contains 19.7 mg lactose (as monohydrate).
200 mg tablet: Each tablet contains 39.3 mg lactose (as monohydrate).

3. PHARMACEUTICAL DOSAGE FORM

Tablet, film-coated.

Ketipinor 25 mg: Brown/dark pink, round, convex, film-coated tablet, diameter 6 mm, debossed 'OR41' on one side and plain on the other side.

Ketipinor 100 mg: Light yellow, round, convex, film-coated tablet, diameter 8 mm, debossed 'OR411' on one side and plain on the other side.

Ketipinor 200 mg: White, round, convex, film-coated tablet, diameter 11 mm, debossed 'OR412' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of schizophrenia
- Treatment of acute manic episodes associated with bipolar I disorder. Ketipinor has not been demonstrated to prevent recurrence of manic or depressive episodes.
- Depressive episodes associated with bipolar disorder.
- Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate.

4.2 Dosage and method of administration

Adults

For the treatment of schizophrenia:

KETIPINOR should be administered twice daily, with or without food.
For the treatment of schizophrenia: the total daily dose for the first 4 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 range 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 manic episodes associated with bipolar disorder:

KETIPINOR should be administered twice daily, with or without food.
As monotherapy or as adjunct to mood stabilizers, 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 per day by Day 6 should be in increments of no greater than 200 mg per day.

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

The safety of doses above 800 mg per day has not been evaluated in clinical trials.

Effectiveness for more than 12 weeks has not been systematically evaluated in clinical trials for monotherapy. Therefore, the physician who elects to use KETIPINOR for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

For the treatment of depressive episodes associated with bipolar disorder:

KETIPINOR should be administered once daily at bedtime, with or without food.

KETIPINOR should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). KETIPINOR can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8. Antidepressant efficacy was demonstrated with quetiapine at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group. Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks (See section 4.8 “Undesirable effects’).

For the maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate:

Maintenance of efficacy in bipolar I disorder was demonstrated with quetiapine (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or valproate. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase.

Children and adolescents
The safety and efficacy of quetiapine have not been evaluated in children and adolescents.

Elderly
As with other antipsychotics, KETIPINOR should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on KETIPINOR 25 mg/day. The dose should be increased daily, in increments of 25 – 50 mg to an effective dose, which is likely to be lower than in younger patients. Note: the mean plasma clearance of quetiapine was reduced by 30-50% in elderly subjects when compared to younger patients.

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

4.3 Contra-indications

- Hypersensitivity to the active substance or to any of the excipients of the product
- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone (see also section 4.5).

4.4 Special warnings and special precautions for use

Children and adolescents (10 to 17 years)
Quetiapine is not indicated for use in children and adolescents below 18 years of age.

Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials with quetiapine in children and adolescent patients, the same special warnings and special precautions for use that appear above for adults should be considered for pediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate (See section 4.8).

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

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

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4400 children and adolescents and 77000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine (See section 5.1).

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

Tardive dyskinesia and extra pyramidal symptoms
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (See section 4.8).

In placebo-controlled clinical trials of adult patients with schizophrenia and bipolar mania the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients.

In short-term placebo-controlled clinical trials for bipolar depression, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (See section 4.8 for rates of EPS observed in all indications and ages).

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (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.

Neutropenia and agranulocytosis
Severe neutropenia ($<0.5 \times 10^9$/L) without infection has been uncommonly reported in short-term placebo controlled monotherapy clinical trials with Quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with Quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate.

Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5×10^9/L) (See section 4.8).

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 anticholineric effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anticholinergic 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 section 4.5, 4.8, 5.1, and 4.9).

Interactions
See also section 4.5.

Concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of quetiapine may need to be considered if quetiapine is used concomitantly with a hepatic enzyme inducer.

During concomitant administration of drugs, which are potent CYP3A4 inhibitors (such as azole antifungals and macrolide antibiotics, and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. (See also section 5.2). As a consequence of this, lower doses of quetiapine should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

Increases in blood glucose and hyperglycaemia

Increases in blood glucose and hyperglycemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (See section 4.8).

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

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

Lipids

Increases in triglycerides and cholesterol, and decreases in HDL have been observed in clinical trials with quetiapine (See section 4.8). Lipid changes should be managed as clinically appropriate.

QT prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (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 QTc interval, and concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (See section 4.5).

Cardiomyopathy and myocarditis

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

Severe Cutaneous Adverse Reactions

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

Withdrawal

Acute withdrawal symptoms including insomnia, nausea and vomiting, have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (See section 4.8).

Elderly patients with dementia

Quetiapine is not approved for the treatment of patients with dementia-related psychosis. In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The

patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Dysphagia
Dysphagia (See section 4.8) and aspiration pneumonia have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, quetiapine should be used with caution in patients at risk of 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.

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 (See section 4.4), gallstones, and alcohol consumption.

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.

Concomitant illness
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients.

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

Additional information
Ketipinor 100 mg and 200 mg tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval (See section 4.4).

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, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 600 to 800 mg/day depending on indication. 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. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (eg, barbiturates, rifampicin etc). 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 CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 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 when co-administered with cimetidine.

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

In a 6-week, randomised, study of lithium and quetiapine prolonged-release tablets versus placebo and quetiapine prolonged-release tablets 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 (see section 5.1).

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

Caution should be exercised when quetiapine is prescribed with drugs causing electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy of quetiapine during human pregnancy have not been established. 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 Ketipinor therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Table 1 ADRs associated with quetiapine therapy

The frequencies of adverse events are ranked according to the following: Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 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, 28], 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]	
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 nutrition disorders	Elevations in serum triglyceride levels[10, 30], elevations in total cholesterol (predominantly LDL cholesterol)[11, 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		

SOC	Very common	Common	Uncommon	Rare	Very rare	Not Known
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 disorder		Tachycardia[4], Palpitations[23]	QT prolongation[1,12,] [18] Bradycardia[32]			Cardio-myopathy and myocarditis
Eye disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension[4,16]		Venous thromboem-bolism[1]		Stroke[33]
Respiratory, thoracic and mediastinal disorders		Dyspnoea[23]	Rhinitis			
Gastro-intestinal 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 aminotransfera se (AST)[3]	Jaundice[5], hepatitis		
Skin and subcutaneous tissue disorders					Angioedema[5], Stevens-Johnson syndrome[5]	Toxic epidermal necrolysis, Erythema Multiforme,Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with

SOC	Very common	Common	Uncommon	Rare	Very rare	Not Known
						Eosinophilia and Systemic Symptoms (DRESS), cutaneous vasculitis
Musculo-skeletal and connective tissue disorders					Rhabdo-myolysis	
Renal and urinary disorder			Urinary retention			
Pregnancy, puerperium and perinatal conditions						Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
General disorders and administrati-on 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 (see section 4.4).
(5) Calculation of Frequency for these ADR's have been taken from postmarketing 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 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 ≤ 100 x 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 mcg/L (>869.56 pmol/L) males; >30 mcg/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 (see sections 4.4 and 5.1).
(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 hemoglobin 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 T_4, free T_4, total T_3 and free T_3 are defined as < 0.8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.
(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 10^9/L at baseline to < 0.5 x 10^9/L at any time during treatment and based on patients with severe neutropenia (< 0.5 x 10^9/L) and infection during all quetiapine clinical trials (see section 4.4).
(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 > 1 x 10^9 cells/L at any time.
(28) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 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 (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 clinical trials with quetiapine.
(33) Based on one retrospective non-randomized 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.

Post-Market Adverse Reactions
Hepatic failure, including fatalities, has also been reported very rarely during the post-marketing period.

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 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 mcg/L (> 869.56 pmol/L) males; > 26 mcg/L (> 1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level > 100 mcg/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.

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2-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 alpha^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 5HT1A sites by norquetiapine may contribute to Ketipinor'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 D_2-receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration (see section 4.8).

Clinical efficacy

Clinical trials have demonstrated that Quetiapine is effective when given twice a day. This is further supported by data from a positron emission tomography (PET) study which identified that $5HT_2$ and D_2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine.

Schizophrenia
In clinical trials, quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, quetiapine showed similar short-term efficacy.

The results of three placebo-controlled clinical trials, including one that used a dose range of quetiapine of 75 to 750 mg/day, identified no difference between quetiapine and placebo in the incidence of EPS or use of concomitant anticholinergics.

Bipolar Mania
In clinical trials, quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg per day.

Bipolar Depression
In four clinical trials, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, quetiapine has been shown to be effective in patients with bipolar depression at doses of 300 and 600 mg/day, however, no additional benefit was seen with the 600 mg dose during short-term treatment.

In all four studies, quetiapine was superior to placebo in reduction of MADRS total score. The antidepressant effect of quetiapine was significant at Day 8 (Week 1) and was maintained through the end of the studies (Week 8).

Treatment with either quetiapine 300 or 600 mg at bedtime reduced depressive symptoms and anxiety symptoms in patients with bipolar depression. There were fewer episodes of treatment emergent mania with either dose of quetiapine than with placebo.

In 3 out of 4 studies, for the 300 mg and 600 mg dose group, statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10 and in 2 out of 3 studies, for the 300 mg dose group, overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF).

In two bipolar depression clinical trials with quetiapine in adult patients maintenance of antidepressant efficacy was established. These trials included an 8-week placebo-controlled acute phase, followed by a placebo-controlled continuation phase of at least 26 weeks but up to 52-weeks in duration. Patients were required to be stable at the end of the acute phase in order to be in the randomized into continuation phase. In both trials, quetiapine was superior to placebo in increasing the time to recurrence of any mood event (depressed, mixed or manic). The risk reduction from the pooled trials was 49%. The risk of a mood event for Quetiapine versus placebo was reduced by 41% for the 300-mg dose and by 55% for the 600-mg dose.

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

The efficacy of quetiapine in the combination treatment for recurrence prevention was established in 2 placebo-controlled trial in 1326 patients who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilized on quetiapine in combination with mood stabilizer (lithium or valproate) for a minimum of 12 weeks in order to be randomized.

In the randomization phase, patients either continued treatment with quetiapine (400 to 800 mg per day average dose 507 mg per day) in combination with mood stabilizer or received placebo in combination with mood stabilizer for up to 104 weeks. Quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressive), the primary endpoint. The risk reductions were 70%, 67%, and 74% for mood, manic and depressive events, respectively.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for quetiapine extended-release formulation and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for quetiapine extended-release formulation and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short term, fixed dose (50 mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥ 7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

A 6-week, randomised, study of lithium and quetiapine prolonged-release tablets versus placebo and quetiapine prolonged-release tablets in adult patients with acute mania indicated that the combination of quetiapine prolonged-release tablets with lithium leads to more adverse events (63% versus 48% in quetiapine prolonged-release tablets in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the quetiapine prolonged-release tablets with lithium add-on group (12.7%) compared to the quetiapine prolonged-release tablets with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain (≥ 7%) at the end of treatment compared to patients in the placebo add-on group (4.7%).

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count < 1.5 x 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. The incidence of shifts to > 0.5–<1.0 x 10^9/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count < 1.5 x 10^9/L was 2.9% and to < 0.5 x 10^9/L was 0.21% in patients treated with quetiapine.

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T_3 or T_4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism.

The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment.

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of quetiapine (200–800 mg/day) versus risperidone (2–8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in quetiapine (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 observed for quetiapine.
The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

Distribution
Quetiapine is approximately 83% bound to plasma proteins.

Biotransformation
Quetiapine is extensively 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.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination
The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. 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/1.73 m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively 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).

5.3 Preclinical safety data

Acute toxicity studies

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

Repeat-dose toxicity studies

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

Hyperprolactinaemia, induced through the dopamine D_2 receptor antagonist activity of quetiapine or its metabolites, varied between species but was most marked in the rat, and a range of effects consequent to this were seen in the 12-month study, including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females.

Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey.

Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.

Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects.

Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/kg/day, nor in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man (See section 5.1).

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

Carcinogenicity studies

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

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

Reproduction studies
Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.

Quetiapine had no teratogenic effects.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet strength	**Core**	**Film-coating**
25 mg	Croscarmellose sodium (Ph.Eur.) Magnesium stearate (Ph.Eur.) Microcrystalline cellulose (Ph.Eur.) Povidone (Ph.Eur.) Water, purified (Ph.Eur.)	Iron oxide red (NF) Iron oxide yellow (NF) Macrogol/PEG 3350 (Ph.Eur.) Polyvinyl alcohol (partly hydrolysed) (Ph.Eur.) Talcum (Ph.Eur.) Titanium dioxide (Ph.Eur.)
100 mg & 200 mg	Calcium hydrogen phosphate dihydrate (Ph.Eur.) Lactose monohydrate (Ph.Eur.) Magnesium stearate (Ph.Eur.) Microcrystalline cellulose (Ph.Eur.) Povidone (Ph.Eur.) Sodium starch glycolate (Ph.Eur.) Water, purified (Ph.Eur.)	Iron oxide yellow (NF) *(present only in 100 mg tablet)* Macrogol/PEG 3350 (Ph.Eur.) Polyvinyl alcohol (partly hydrolysed) (Ph.Eur.) Talcum (Ph.Eur.) Titanium dioxide (Ph.Eur.)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 30°C. Keep out of reach and sight of children.

6.5. **Packaging**

PVC/PVDC/Aluminium blister. The blisters are packed in cartons. **Tablet strength**	**Carton contents**	**Blisters**
25 mg Tablet	100 tablets	10 blisters of 10 tablets
100 mg Tablet	30 tablets	3 blisters of 10 tablets
200 mg Tablet	30 tablets	3 blisters of 10 tablets

Product registrant:
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