Quetiapine Sandoz 25 mg and 100 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT
Quetiapine Sandoz 25 mg Tablets.
Quetiapine Sandoz 100 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Quetiapine Sandoz 25 mg Tablets
Each film-coated tablet contains 25 mg quetiapine (as 28.78 mg quetiapine fumarate).
Quetiapine Sandoz 100 mg Tablets
Each film-coated tablet contains 100 mg quetiapine (as 115.13 mg quetiapine fumarate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.

Quetiapine Sandoz 25 mg Tablets
Salmon-pink coloured, round film-coated tablet.

Quetiapine Sandoz 100 mg Tablets
Yellow, round (8.8 mm diameter) film-coated tablet, with a breaking notch on one side.
The tablet can be divided into equal quarters.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
- Treatment of schizophrenia.
- Treatment of acute manic episodes associated with bipolar I disorder.
- Treatment of depressive episodes associated with bipolar disorder.
- Preventing recurrence in maintenance treatment of bipolar I disorder (manic, mixed or depressive episode) as monotherapy or in combination with lithium or valproate.

4.2 Posology and method of administration
Quetiapine should be administered with or without food.

Adults
For the treatment of schizophrenia:
Quetiapine should be administered twice daily, with or without food.

The total daily dose for the first 4 days of therapy is 50 mg Quetiapine (Day 1), 100 mg Quetiapine (Day 2), 200 mg Quetiapine (Day 3) and 300 mg Quetiapine (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg Quetiapine per day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range of 150 to 750 mg Quetiapine per day.

For the treatment of manic episodes associated with bipolar disorder:
Quetiapine should be administered twice daily, with or without food.

As monotherapy or as adjunct therapy to mood stabilizers, the total daily dose for the first four days of therapy is 100 mg Quetiapine (Day 1), 200 mg Quetiapine (Day 2), 300 mg Quetiapine (Day 3) and 400 mg Quetiapine (Day 4). Further dosage adjustments up to 800 mg Quetiapine per day by Day 6 should be in increments of no greater than 200 mg Quetiapine 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 Quetiapine per day. The usual effective dose is in the range of 400 to 800 mg Quetiapine per day.

The safety of doses above 800 mg/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 Quetiapine 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:
Quetiapine should be administered once daily at bedtime, with or without food.

Quetiapine should be titrated as follows: the daily dose for the first four days of therapy is 50 mg Quetiapine (Day 1), 100 mg Quetiapine (Day 2), 200 mg Quetiapine (Day 3) and 300 mg Quetiapine (Day 4). Quetiapine 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 with higher doses (600 mg Quetiapine) group. Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks (see sections 4.8 and 5.1).

For preventing recurrence in maintenance treatment of bipolar disorder:
Patients who have responded to quetiapine in combination therapy with lithium or valproate for acute treatment of bipolar disorder should continue on quetiapine therapy at the same dose. The quetiapine dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 400 mg to 800 mg/day. Patients who have responded to quetiapine for acute treatment of bipolar disorder should continue on quetiapine therapy at the same dosing regimen. The quetiapine dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day.

Elderly
As with other antipsychotics, quetiapine should be used with caution in elderly patients, especially during the initial phase of treatment. Elderly patients should be started on Quetiapine 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Children and adolescents under 18 years
Quetiapine is not indicated for use in children and adolescents below 18 years of age. Data from placebo-controlled clinical trials are set forth in sections 4.4, 4.8, 5.1 and 5.2.

Renal and hepatic impairment
The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment.

Quetiapine is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment.

Patients with renal or hepatic impairment should start with 25 mg quetiapine per day. Depending on clinical response and tolerability of the individual patient, the dose should be increased daily, in increments of 25 to 50 mg quetiapine, to an effective dose.

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

4.4 Special warnings and precautions for use
Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive 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).

Neutropenia and agranulocytosis
Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) without infection has been uncommonly reported in short-term placebo controlled monotherapy quetiapine clinical trials. 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. 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).

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.

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

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. 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.

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.

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 for aspiration pneumonia.

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

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).

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

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.

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 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, hypokalaemia or hypomagnesaemia (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 such as 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).

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.

Children and adolescents (10 to 17 years of age)

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).

Elderly patients with dementia

Quetiapine is not approved for the treatment of dementia-related psychosis.
In a meta-analysis of atypical antipsychotics, 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.

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.

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 anticholinergic 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 '*Interaction with other medicinal products and other forms of interaction', 'Undesirable effects', 'Pharmacodynamic properties', 'Mechanism of Action', and 'Overdose'*).

Interactions

See also 'section 4.5 Interaction with other medicinal products and other forms of interaction'.
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.

Lactose
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, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution should be exercised when quetiapine is used concomitantly with medicinal products 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 (see section 4.4).

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

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

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of quetiapine and thioridazine caused increases in clearance of quetiapine.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, 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 (see section 4.2).

Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also causes increases in clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g., barbiturates, rifampicin etc). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4

and CYP2D6 inhibitor). In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean T_{max} was unchanged. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors).

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

4.6 Pregnancy and lactation

The safety and efficacy of quetiapine during human pregnancy have not yet been established (see section 5.3). Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

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

Non-Teratogenic Effects

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Blood and lymphatic system disorders
Common: leucopenia[1,25]

Immune system disorders
Uncommon: hypersensitivity
Very rare: anaphylactic reaction[6]

Metabolism and nutritional disorders
Common: increased appetite

Psychiatric disorders
Common: abnormal dreams and nightmares
Rare: somnambulism and other related events such as sleep-related eating disorders

Nervous system disorders
Very common: dizziness[1,5,17], somnolence[2,17], extrapyramidal symptoms[1,16]
Common: dysarthria
Uncommon: seizure[1], restless legs syndrome, tardive dyskinesia[1], syncope[1,5,17], confusional state

Cardiac disorders
Common: tachycardia[1,5], palpitations[21]
Uncommon: QT prolongation[16,19], bradycardia[26]

Eye disorders
Common: vision blurred

Vascular disorders
Common: orthostatic hypotension[1,5,17]

Respiratory, thoracic and mediastinal disorders
Common: dyspnea[21]
Uncommon: rhinitis

Gastrointestinal disorders
Very common: dry mouth
Common: constipation, dyspepsia, vomiting[23]
Uncommon: dysphagia[1,9]
Rare: intestinal obstruction/ileus

Renal and urinary disorders
Uncommon: Urinary retention

Hepato-biliary disorders
Rare: hepatitis (with or without jaundice)[29]

Musculoskeletal and connective tissue disorders
Very rare: Rhabdomyolysis

Skin and subcutaneous tissue disorders
Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema Multiforme (EM), cutaneous vasculitis

Reproductive system and breast disorders
Rare: priapism, galactorrhoea

General disorders and administration site conditions
Very common: withdrawal (discontinuation) symptoms[1,10]
Common: mild asthenia, peripheral edema, irritability, pyrexia
Rare: neuroleptic malignant syndrome[1], hypothermia
Not known: Neonatal withdrawal[28]

Investigations
Very common: elevations in serum triglyceride levels[11], elevations in total cholesterol (predominantly LDL cholesterol)[12], decreases in HDL cholesterol[1,18], decreased haemoglobin[20], weight gain[3]
Common: elevations in serum alanine aminotransferase (ALT)[4], elevations in gamma-GT levels[4], neutrophil

count decreased[1,7], eosinophils increased[24], blood glucose increased to hyperglycaemic levels[1,8], elevations in serum prolactin[15], decreases in Total T_4[22], decreases in Free T_4[22], decrease in Total T_3[22], increases in TSH[22]

Uncommon: elevations in serum aspartate aminotransferase (AST)[4], platelet count decreased[14], decreases in Free T_3[22]

Rare: elevations in blood creatine phosphokinase[13], agranulocytosis[27]

1) See section 4.4 'Special warnings and precautions for use'.
2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
3) Based on ≥ 7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
4) Asymptomatic elevations (shift from normal to ≥ 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
5) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.
6) The inclusion of anaphylactic reaction is based on post-marketing reports.
7) In all short-term placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥ 1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count < 1.5 X 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count <1.0 x 10^9/L, among patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <0.5 X 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo treated patients and the incidence ≥ 0.5 - <1.0 X 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients.
8) Fasting blood glucose ≥126 mg/dL or a non-fasting blood glucose ≥200 mg/dL on at least one occasion.
9) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
10) In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (e.g. insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolve after 1 week post-discontinuation.
11) Triglycerides ≥200 mg/dL (patients ≥18 years of age) or ≥150 mg/dl (patients <18 years of age) on at least one occasion.
12) Cholesterol ≥240 mg/dL (patients ≥18 years of age) or ≥200 mg/dL (patients <18 years of age) on at least one occasion.
13) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
14) Platelets ≤ 100 x 10^9/L on at least one occasion.
15) Prolactin levels (patients ≥18 years of age): >20 µgram/L males; >30 µgram/L females at any time.
16) See text below.
17) May lead to falls.
18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
19) Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
20) Decreased haemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. In short term placebo-controlled trials, decreased haemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 8.3% of quetiapine patients compared to 6.2% of placebo patients. In the long-term randomised withdrawal trials, the time to onset of decreased haemoglobin is variable and the trend in the incidence of decreased haemoglobin declines with longer exposure.
21) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying

cardiac/respiratory disease.

22) Based on shifts from normal baseline to potentially clinically important value at any time post- baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 X LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
23) Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
24) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as ≥ 1 x 10^9 cells/L at any time.
25) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 10^9cells/L at any time.
26) May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.
27) Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (<0.5 x 10^9/L) and infection.
28) See *'Pregnancy and lactation'*.
29) SERM Clinical Overview, 2014-March. Hepatic Events. GEL locator: [CNS.000-377-593].

Extrapyramidal Symptoms

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. In long-term studies of schizophrenia and bipolar disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

Thyroid Levels

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4: 3.4% for quetiapine versus 0.6% for placebo; free T_4: 0.7% for quetiapine versus 0.1% for placebo; total T_3: 0.54% for quetiapine versus 0.0% for placebo and free T_3: 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long- term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. About 0.7% (26/3489) of quetiapine patients experienced Thyroid Stimulating Hormone (TSH) increases in monotherapy studies. In eight patients, where TBG was measured levels of TBG were unchanged. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, 12% (24/196) of the quetiapine treated patients compared to 7% (15/203) placebo treated patients had elevated TSH levels.

As with other antipsychotics, quetiapine may cause prolongation of the QTc interval, but in clinical trials, this was not associated with a persistent increase (see section 4.4).

Acute withdrawal reactions have been reported (see section 4.4).

Children and adolescents (10 to 17 years of age)

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

Metabolism and nutritional disorders
Very common: increased appetite

Investigations
Very common: elevations in serum prolactin[1], increases in blood pressure[2]

Gastrointestinal disorders
Very common: vomiting

Nervous system disorders
Common: syncope

Respiratory, thoracic and mediastinal disorders
Common: rhinitis

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

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

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

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

4.9 Overdose
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone.
In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma.
In post marketing experience there were cases reported of QT prolongation with overdose.
Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see

section 4.4).
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 anticholinergic effects.

Management of overdose
There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. In this context, published reports in the setting of anti-cholinergic symptoms describe a reversal of severe CNS effects, including coma and delirium, with administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring. In cases of quetiapine overdose refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, diazepines, oxazepines, and thiazepines.
ATC code: N05A H04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interacts with a broad spectrum of neurotransmitter receptors. Quetiapine and norquetiapine exhibits affinity for 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 dopamine 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 has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity for histaminergic and adrenergic alpha-1 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 for several muscarinic receptor subtypes which may explain anti-cholinergic (muscarinic) effects.

Pharmacodynamic effects
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also reverses the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of dopamine 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 A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Clinical efficacy
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:

Suicide/suicidal thoughts or clinical worsening

In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events was 0.8% for both quetiapine (76/9327) and for placebo (37/4845).
In these trials of patients with schizophrenia, the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥ 25 years of age, and 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age.
In these trials of patients with bipolar mania the incidence of suicide related events was 0% for both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo (6/503) in patients ≥ 25 years of age, and 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.
In these trials of patients with bipolar depression the incidence of suicide related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24 and 1.8% for both quetiapine (19/1616) and placebo (11/622) in patients ≥ 25 years of age. There has been one trial conducted in patients 10-17 years of age in which efficacy was not established. The incidence of suicide related events was 1.0% (1/92) for quetiapine and 0% (0/100) for placebo. In this study there were two additional events in two patients that occurred during an extended post-treatment follow-up phase of the study; one of these patients was on quetiapine at the time of the event (see section 4.4).

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of Quetiapine (200 - 800 mg/day) versus risperidone (2 - 8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in Quetiapine compared with risperidone for patients with at least 21 months of exposure.

5.2 Pharmacokinetic properties

Quetiapine is well absorbed and extensively metabolised following oral administration.
The bioavailability of quetiapine is not significantly affected by administration with food.
Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine does not differ between men and women.
The mean clearance of quetiapine in elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine.
Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is observed only at concentrations approximately 5 to 50-fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug.

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 (e.g., 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 core:

Calcium hydrogen phosphate dihydrate
Cellulose, microcrystalline
Lactose monohydrate
Magnesium stearate
Povidone
Silica colloidal hydrated
Sodium starch glycolate, type A

Tablet coat:
Hypromellose
Macrogol 4000
Titanium dioxide
Lactose monohydrate
Iron oxide yellow

In addition for Quetiapine Sandoz 25 mg Tablets, Iron oxide red.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to outer carton.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Quetiapine Sandoz 25 mg Tablets
PVC/COC/PVDC/Aluminium blister containing 30, 60 or 100 film-coated tablets.
PVC/PE/PVDC/Aluminium blister containing 30, 60 or 100 film-coated tablets.

Quetiapine Sandoz 100 mg Tablets
PVC/COC/PVDC/Aluminium blister containing 30, 60 or 100 film-coated tablets.
PVC/PE/PVDC/Aluminium blister containing 30, 60 or 100 film-coated tablets.

Not all pack sizes will be available.

6.6 Special precautions for disposal
No special requirements.

7. MANUFACTURER
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İnönü Mahallesi, Gebze Plastikçiler Organize Sanayi Bölgesi,
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8. DATE OF REVISION OF THE TEXT
Mar 2023