NAME OF THE MEDICINAL PRODUCT

Kventiax 50 mg prolonged-release tablets
Kventiax 200 mg prolonged-release tablets
Kventiax 300 mg prolonged-release tablets
Kventiax 400 mg prolonged-release tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

50 mg prolonged-release tablets:
Each prolonged-release tablet contains 50 mg quetiapine (as quetiapine hemifumarate).
200 mg prolonged-release tablets:
Each prolonged-release tablet contains 200 mg quetiapine (as quetiapine hemifumarate).
300 mg prolonged-release tablets:
Each prolonged-release tablet contains 300 mg quetiapine (as quetiapine hemifumarate).
400 mg prolonged-release tablets:
Each prolonged-release tablet contains 400 mg quetiapine (as quetiapine hemifumarate).

Excipients with known effect
50 mg prolonged-release tablets:
Each prolonged-release tablet contains 119.44 mg lactose and 8.44 mg sodium.
200 mg prolonged-release tablets:
Each prolonged-release tablet contains 50.09 mg lactose and 19.38 mg sodium.
300 mg prolonged-release tablets:
Each prolonged-release tablet contains 75.15 mg lactose and 29.06 mg sodium.
400 mg prolonged-release tablets:
Each prolonged-release tablet contains 14.73 mg lactose and 23.46 mg sodium.

For the full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Prolonged-release tablet

50 mg prolonged-release tablets:
White to almost white, capsule shaped, slightly biconvex, film-coated tablets with bevelled edges, engraved with 50 on one side.
200 mg prolonged-release tablets:
Yellow brown, oval, biconvex, film-coated tablets.
300 mg prolonged-release tablets:
Pale brownish yellow, capsule shaped, biconvex, film-coated tablets.
400 mg prolonged-release tablets:
White to almost white, capsule shaped, biconvex, film-coated tablets, engraved with 400 on one side.

CLINICAL PARTICULARS

Therapeutic indications
Kventiax is indicated for the treatment of schizophrenia.

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

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

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

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

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

The efficacy of quetiapine prolonged-release tablets in bipolar disorder was established, in part, on the basis of extrapolation from the established effectiveness of quetiapine immediate-release tablets (see 'Clinical Efficacy')

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

Posology and method of administration

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

Adults:

For the treatment of schizophrenia and moderate to severe manic episodes associated with bipolar disorder
Kventiax should be administrated at least one hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically justified the dose may be increased to 800 mg daily. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

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

Maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex
While there is no body of evidence available to specifically address how long the patient treated with Kventiax should remain on it, maintenance of efficacy in Bipolar I Disorder was demonstrated with quetiapine (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase (see '*Clinical Efficacy'*).
Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment (see *'Clinical Efficacy'*).

For preventing recurrence in bipolar disorder
For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Kventiax for acute treatment of bipolar disorder should continue on Kventiax at the same dose administered at bedtime. Kventiax dose can be adjusted depending on clinical response and

tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy.

Recurrent major depressive disorder
When treating recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.

Kventiax should be administered once daily in the evening.

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

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

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

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

Switching from quetiapine immediate-release tablets
For more convenient dosing, patients who are currently being treated with divided doses of immediate release quetiapine tablets may be switched to Kventiax at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

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

In elderly patients with MDD, initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8 and then up to 300 mg depending on clinical response and tolerability.
Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

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

Renal impairment
Dosage adjustment is not necessary in patients with renal impairment.

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

Contraindications

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

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (see '*Interactions with other medicinal products and other forms of interaction'*).

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 7700 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine (see 'Pharmacodynamic properties'.)

Neutropenia and agranulocytosis
Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) without infection has been uncommonly reported in short-term placebo controlled monotherapy clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include preexisting 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 *'Undesirable effects'*).

Hyperglycaemia and Diabetes mellitus
Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.
Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti diabetic treatment despite discontinuation of the suspect drug.

Lipids
Increases in triglycerides and cholesterol, and decreases in HDL have been observed in clinical trials with quetiapine (see *'Undesirable Effects'*). 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 the post marketing experience, however a causal relationship has not been established. Among the post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see '*Special warnings and precautions for use – Lipids'*), gallstones, and alcohol consumption.

Concomitant Illness
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs.
In patients who have a history of or are at risk for sleep apnea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

Dysphagia
Dysphagia (see *'Undesirable effects'*) and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see '*Undesirable effects*'). 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 *'Undesirable Effects'*).

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 *'Undesirable Effects'*).
In placebo-controlled clinical trials for schizophrenia and bipolar mania the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients. In short-term, placebo-controlled clinical trials for bipolar depression and major depressive disorder, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients. (See '*Undesirable Effects*' for rates of EPS observed in all indications.)

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

Serotonin syndrome
Concomitant administration of quetiapine and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see 'Interactions with other medicaments and other forms of interaction').
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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 '*Overdose*'). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, ie. the elderly, patents with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see *'Interactions with other medicinal products and other forms of interactions*').

Cardiomyopathy and Myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, (see '*Undesirable effects*'). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema

Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are potentially life-threateningadverse drug reactions 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 *'Undesirable Effects'*).

Misuse and abuse
Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

Use in children and adolescents (10 to 17 years of age)
Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials with quetiapine in children and adolescent patients, the same special warnings and special precautions for use that appear above for adults should be considered for pediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate (See *'Undesirable effects'*).
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
Kventiax is not approved for the treatment of dementia-related psychosis.
In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

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

Interactions
See also *'Interactions with other medicinal products and other forms of interactions'.*
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 used concomitantly with a hepatic enzyme inducer.
During concomitant administration of drugs, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors), plasma concentrations of it can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses

of quetiapine should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

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

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.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see *'Undesirable Effects'* and *'Pharmacodynamic Properties'*). The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6. There are no combination data available beyond week 6.

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

Sodium
50 mg prolonged-release tablets:
This medicinal product contains 8.44 mg sodium per tablet, equivalent to 0.42% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

200 mg prolonged-release tablets:
This medicinal product contains 19.38 mg sodium per tablet, equivalent to 0.97% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

300 mg prolonged-release tablets:
This medicinal product contains 29.06 mg sodium per tablet, equivalent to 1.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

400 mg prolonged-release tablets:
This medicinal product contains 23.46 mg sodium per tablet, equivalent to 1.17% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions with other medicinal products and other forms of interaction

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

Quetiapine should be used with caution in combination with serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see '*Special warnings and Precautions for use*').

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval (see *'Special warnings and precautions for use'*).

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see '*Special warnings and precautions for use'*).

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.

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

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

The pharmacokinetics of quetiapine were not significantly altered following co-administration with antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the 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. The safety of doses above 800 mg/day has not been established in the clinical trials.

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 caused increases in the 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).

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.

Pregnancy and lactation

The safety and efficacy of quetiapine during human pregnancy have not been established.
Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported. Therefore Kventiax should be used during pregnancy only if the potential benefit justifies the potential risk.
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.

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.

Undesirable effects

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

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

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

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).	
Blood and lymphatic system disorders	
Common:	Leucopenia [1, 27]
Uncommon:	Thrombocytopenia
Unknown:	Neutropenia [1]
Immune system disorders	
Uncommon:	Hypersensitivity
Very rare:	Anaphylactic reaction [6]
Endocrine disorders	
Common:	Hyperprolactinemia [16]
Very rare:	Inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders	
Common:	Increased appetite
Uncommon:	Hyponatraemia [24]
Very rare:	Diabetes Mellitus [1, 5, 6]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares Suicidal ideation and suicidal behaviour [25]
Rare:	Somnambulism and other related events
Nervous system disorders	
Very Common:	Dizziness [1, 4, 17], somnolence [2, 17], headache, extrapyramidal symptoms[1, 13]
Common:	Dysarthria
Uncommon:	Seizure [1], restless legs syndrome, Tardive dyskinesia [1], syncope [1, 4, 17] confusional state
Cardiac disorders	
Common:	Tachycardia [1, 4], palpitations [21]
Uncommon:	Bradycardia [28]
Not known	Cardiomyopathy, Myocarditis
Eye Disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension [1, 4, 17]
Rare:	Venous thromboembolism [1]
Respiratory, thoracic and mediastinal disorder	
Common:	Dyspnea [21]
Uncommon:	Rhinitis, Sleep apnoea[31]

Gastrointestinal disorders	
Very Common:	Dry mouth
Common:	Constipation, dyspepsia, vomiting [23]
Uncommon:	Dysphagia [1, 8]
Rare:	Intestinal obstruction/Ileus
Not known	Bezoar[32]
Hepato-biliary disorders	
Rare:	Jaundice, hepatitis [6]
Renal and urinary disorders	
Uncommon:	Urinary retention
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema [6], Stevens-Johnson syndrome [6]
Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP) Erythema multiforme (EM), Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very rare:	Rhabdomyolysis
Reproductive system and breast disorders	
Uncommon:	Sexual dysfunction
Rare:	Priapism, Galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	
Very common:	Withdrawal (discontinuation) symptoms [1, 10]
Common:	Mild asthenia, peripheral oedema, irritability, pyrexia
Rare:	Neuroleptic malignant syndrome [1], hypothermia
Not known:	Neonatal withdrawal [30]
Investigations	
Very common:	Elevations in serum triglyceride levels [1, 11] Elevations in total cholesterol (predominantly LDL cholesterol) [12], Decreases in HDL cholesterol [18], Weight gain [9], decreased haemoglobin [19]
Common:	Elevations in serum alanine aminotransferase (ALT) [3], elevations in gamma-GT levels [3], decreased neutrophil count [1], eosinophils increased [26], blood glucose increased to hyperglycaemic levels [1, 7], QT prolongation [1, 13, 20], decreases in Total T_4 [22], decreases in Free T_4 [22], decreases in Total T_3 [22], increases in TSH [22]
Uncommon:	Elevations in serum aspartate aminotransferase (AST) [3], Platelet count decreased [14], decreases in free T_3 [22]
Rare	Elevations in blood creatine phosphokinase [15], agranulocytosis [29]

(1) See '*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) 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.
(4) As with other antipsychotics with $alpha_1$ adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See '*Special Warnings and precautions for Use'*).
(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.
(6) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of quetiapine.
(7) Fasting blood glucose ≥7.0 mmol/L or a non-fasting blood glucose ≥11.1 mmol/L) on at least one occasion.
(8) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
(9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment.

(10) 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.
(11) 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.
(12) 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).
(13) See text below.
(14) Platelets ≤100 X 10^9/L on at least one occasion.
(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
(16) Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time.
(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) 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.
(20) 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.
(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 anytime 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) Shift from >132 mmol/L to <132 mmol/L on at least one occasion.
(25) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine prolonged-release formulation therapy or early after treatment discontinuation (see '*Special warnings and precautions for use*' and '*Pharmacodynamic properties*').
(26) 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 109 cells/L at any time.
(27) 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 109cells/L at any time.
(28) 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.
(29) Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (<0.5 X 109/L) and infection.
(30) See *'Pregnancy and lactation'*.
(31) Atypical antipsychotic drugs, such as quetiapine, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Kventiax should be prescribed with caution.
(32) Observed only in overdose (see '*Overdose*') .

Extrapyramidal symptoms

The following clinical trials (monotherapy and combination therapy) in adult patients included treatment with quetiapine immediate-release and quetiapine prolonged-release tablets.

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo).
In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (eg. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group). In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for quetiapine prolonged-release 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 prolonged-release and 2.3% for placebo.
In long-term studies of schizophrenia, bipolar disorder, and major depressive disorder, the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

Thyroid Levels
Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total 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. In eight patients, where TBG was measured, levels of TBG were unchanged.

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

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

Metabolism and nutritional disorders	
Very common:	Increased appetite
Investigations	
Very common:	Elevations in prolactin [1], increases in blood pressure [2]
Nervous system disorders	
Common:	Syncope [2]
General disorders and administration site conditions	
Common:	Irritability [3]
Respiratory, thoracic, and mediastinal disorders	
Common:	Rhinitis [2]
Gastrointestinal disorders	
Very common:	Vomiting [2]

(1) Prolactin levels (patients <18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L.

(2) Based on shifts above clinically significant thresholds (adapted from the National Institute 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 irritability might be associated with different clinical implications in children and adolescents as compared to adults.

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.

In one 8-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the mean increase in body weight was 1.4 kg in the quetiapine prolonged-release group and 0.6 kg in the placebo group. 13.7 % of Quetiapine prolonged-release-treated patients and 6.8% of placebo-treated patients gained ≥7 % of their body weight.

Extrapyramidal Symptoms in Children and Adolescent Population

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

In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar depression in which efficacy was not established, the aggregated incidence of extrapyramidal symptoms was 1.1% for quetiapine prolonged-release and 0.0% for placebo.

Overdose

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

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (See *'Special warnings and precautions for use – Concomitant Illness'*).

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

Management of overdose
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. In this context, published reports in the setting of anti-cholinergic symptoms describe a reversal of severe CNS effects, including coma and delirium, with administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade).
Close medical supervision and monitoring should be continued until the patient recovers.
Kventiax overdose may lead to gastric bezoar formation and an appropriate diagnostic imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass. Endoscopic pharmacobezoar removal has been performed successfully in many cases.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics;
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 dopamineD_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 quetiapines therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at 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 standars 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 A9 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.

Clinical efficacy
Schizophrenia
The efficacy of quetiapine prolonged-release tablets in the treatment of schizophrenia

was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled quetiapine immediate-release tablets-to-quetiapine prolonged-release tablets switching study in clinically stable outpatients with schizophrenia. The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Quetiapine prolonged-release tablets 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose. In the 6-week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, i.e., who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on quetiapine immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of quetiapine prolonged-release tablets given once daily. In a long-term study in stable schizophrenic patients who had been maintained on quetiapine prolonged-release tablets for 16 weeks, quetiapine prolonged-release tablets was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the quetiapine prolonged-release tablets treatment group compared to 68.2% for placebo. The average dose was 669 mg.

Bipolar Mania

In a clinical trial, quetiapine prolonged-release tablets has been shown to be effective as monotherapy in reducing manic symptoms in patients with bipolar mania at doses between 400 and 800 mg/day. The effect of quetiapine prolonged-release tablets was significant at Day 4 and was maintained through the end of the trial (Week 3). 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/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

Bipolar Depression

In a clinical trial, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, quetiapine prolonged-release tablets has been shown to be effective in patients with bipolar depression at doses of 300 mg/day. Quetiapine prolonged-release tablets was superior to placebo in reduction of MADRS total score. The antidepressant effect of quetiapine prolonged-release tablets was significant at Day 8 (Week 1) and was maintained through the end of the trial (Week 8).
In two clinical trials, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, quetiapine immediate-release tablets 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 both studies, quetiapine was superior to placebo in reduction of MADRS total score. The antidepressant effect of quetiapine immediate-release tablets was significant at Day 8 (Week 1) and was maintained through the end of the studies (Week 8). Treatment with either quetiapine immediate-release tablets 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 immediate-release tablets than with placebo. For the 300 mg dose group, statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10 and 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 immediate-release tablets 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 immediate-release tablets 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 immediate-release tablets 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 immediate-release tablets 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 immediate-release tablets for a minimum of 4 weeks in order to be randomized. In the randomization phase, patients either continued treatment with quetiapine immediate-release tablets (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 immediate-release tablets 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 immediate-release tablets 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 stabilised on quetiapine immediate-release tablets in combination with mood stabilizer (lithium or valproate) for a minimum of 12 weeks in order to be randomized. In the randomisation phase, patients either continued treatment with quetiapine immediate-release tablets (400 to 800 mg per day average dose 507 mg per day) in combination with mood stabiliser or received placebo in combination with mood stabiliser for up to 104 weeks. Quetiapine immediate-release tablets 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.

Major Depressive Disorder

In clinical trials, quetiapine prolonged-release tablets has been shown to be effective as monotherapy and adjunct therapy for the treatment of patients who met DSM-IV criteria for major depressive disorder. Three short-term (6 or 8 week) monotherapy trials, randomized 1445 patients who had a mean Hamilton Rating Scale for Depression (HAM-D) total score of 26 at enrollment. Quetiapine prolonged-release tablets at doses of 50 mg, 150 mg, and 300 mg demonstrated superiority over placebo in reducing depressive symptoms as measured by improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Statistically significant improvement of symptoms of major depressive disorder as measured by change in MADRS total score was observed by day 4. Quetiapine prolonged-release tablets also demonstrated improvement in anxiety symptoms as measured by the Hamilton Rating Scale for Anxiety (HAM-A) total score. The majority of the patients were dosed once daily with either 150 mg or 300 mg per day (one trial included a fixed dose Quetiapine prolonged-release tablets once daily 50 mg/day arm).

Two short-term (6 week) trials, enrolled 919 patients who had previously shown an inadequate response to at least one antidepressant and had a mean HAM-D total score of 24 at enrolment. Quetiapine prolonged-release tablets at doses of 150 mg and 300 mg, given as adjunct treatment to ongoing antidepressant therapy demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in (MADRS) total score. Statistically significant improvement of symptoms of major depressive disorder as measured by the MADRS total score was observed by week 1. Quetiapine prolonged-release tablets also demonstrated improvement in anxiety symptoms as measured by the HAM-A total score.

In a relapse prevention study, patients (n=771 randomised patients) responding to at least 12 weeks of acute open- label treatment with quetiapine prolonged-release tablets were randomised to either quetiapine prolonged-release tablets once daily or placebo for up to 52 weeks. Quetiapine prolonged-release tablets was more effective than placebo in preventing relapse. The risk of relapse was 14.2% for quetiapine prolonged-release tablets -treated patients and 34.4% for placebo-treated patients. The mean dose was 177 mg/day.

In non-demented elderly patients (aged 66 to 89 years) quetiapine prolonged-release tablets dosed flexibly in the range of 50 mg to 300 mg per day demonstrated superiority over placebo in reducing depressive symptoms as measured by improvement in MADRS total score. In this study patients randomised to quetiapine prolonged-release tablets received 50mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. Other than the incidence of extrapyramidal symptoms (see 'Undesirable effects') the tolerability of quetiapine prolonged-release tablets once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomized patients over

75 years of age was 19%. The mean dose of quetiapine prolonged-release tablets was 160 mg/day.

Generalised Anxiety Disorder

In clinical trials, quetiapine prolonged-release tablets has been shown to be effective as monotherapy for the treatment of patients who met DSM-IV criteria for generalised anxiety disorder. Three short-term (8 week) monotherapy trials, randomised 2678 patients who had a mean Hamilton Rating Scale for Anxiety (HAM-A) total score of 26 at enrolment. Quetiapine prolonged-release tablets at doses of 50 mg, 150 mg, and 300 mg demonstrated superiority over placebo in reducing anxiety symptoms as measured by improvement in the HAM-A total score at week 8. Quetiapine prolonged-release tablets was superior to placebo in reducing psychic symptoms at all doses and somatic symptoms at the 150 mg dose. Statistically significant improvements of symptoms of generalised anxiety disorder as measured by change in HAM-A total score was observed by day 4. Quetiapine prolonged-release tablets also demonstrated improvement in depressive symptoms as measured by the MADRS total score (mean total score at enrolment was ≤16). Statistically significant improvements in the 150 mg dose group were also seen in quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF). Superior improvements at all doses were seen in sleep symptoms, as measured with the PSQI global score. The majority of the patients were dosed once daily with quetiapine prolonged-release tablets 150 mg.

In a relapse prevention study, patients (n=433 randomised patients) responding to at least 12 weeks of acute open-label treatment with quetiapine prolonged-release tablets were randomised to either quetiapine prolonged-release tablets once daily or placebo for up to 52 weeks. Quetiapine prolonged-release tablets was more effective than placebo in preventing relapse. The risk of relapse was 10.2% for quetiapine prolonged-release tablets-treated patients and 38.9% for placebo-treated patients. The mean dose was 163 mg/day.

In non-demented elderly patients (aged 66 to 86 years) quetiapine prolonged-release tablets dosed flexibly in the range of 50 mg to 300 mg per day demonstrated superiority over placebo in reducing anxiety symptoms as measured by improvement in HAM-A total score. In this study patients randomised to quetiapine prolonged-release tablets received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The tolerability of quetiapine prolonged-release tablets once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomised patients over 75 years of age was 13%. The mean dose of quetiapine prolonged-release tablets was 168 mg/day.

Children and adolescents (10 to 17 years of age)

A pharmacokinetic modelling study has indicated similar quetiapine exposure following administration of quetiapine prolonged-release tablets (once daily) or administration of quetiapine immediate-release tablets (twice daily) at the same total daily doses in the paediatric population (see 'Pharmacokinetic properties'). The efficacy data with quetiapine immediate-release tablets summarized below therefore informs the dosing instructions for quetiapine prolonged-release tablets (see 'Posology and method of administration').

Schizophrenia

The efficacy of quetiapine immediate-release tablets in the treatment of schizophrenia in adolescents (13–17 years of age) was demonstrated in a 6-week, double-blind, placebo-controlled trial. Patients who met DSM-IV diagnostic criteria for schizophrenia were randomized into one of three treatment groups: quetiapine immediate-release tablets 400 mg/day (n = 73), quetiapine immediate-release tablets 800 mg/day (n = 74), or placebo (n = 75). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/per day. Subsequently, the dose was titrated to the a target dose of 400 or 800 mg using increments of 100 mg/day, given two or three times daily. The primary efficacy variable was the mean change from baseline in total Positive and Negative Syndrome Scale. Results of the study demonstrated efficacy of quetiapine immediate-release tablets 400 mg/day and 800 mg/day compared to placebo. Greater efficacy of the 800 mg dose compared with the 400 mg dose has not been established.

Bipolar mania

The efficacy of quetiapine immediate-release tablets in the treatment of acute manic episodes associated with Bipolar I Disorder in children and adolescents (10 to 17 years of age) was demonstrated in a 3-week, double-blind, placebo-controlled, multicenter trial. Patients who met DSM-IV diagnostic criteria for a manic episode were randomized into one of three treatment groups:

quetiapine immediate-release tablets 400 mg/day (n = 95), quetiapine immediate-release tablets 600 mg/day (n = 98), or placebo (n = 91). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/day. Subsequently, the dose was titrated to a target dose of 400 or 600 mg using increments of 100 mg/day, given two or three times daily. The primary efficacy variable was the mean change from baseline in total YMRS score. Results of the study demonstrated superior efficacy of quetiapine immediate-release tablets 400 mg/day and 600 mg/day compared with placebo. Greater efficacy of the 600 mg dose compared with the 400 mg dose has not been established.

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 '*Special warnings and special precautions for use'*). In these trials of patients with major depressive disorder the incidence of suicide related events was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo in patients 18-24 and 0.6% (11/1798) for quetiapine and 0.7% for placebo (7/1054) in patients ≥ 25 years of age. There have been no trials conducted in patients <18 years of age with major depressive disorder.

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of quetiapine immediate-release tablets (200-800 mg/day) versus risperidone (2-8 mg) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in quetiapine immediate-release tablets (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Pharmacokinetic properties

General

Quetiapine is well absorbed and extensively metabolised following oral administration. 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 pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine does not differ between men and women.

Quetiapine prolonged-release tablets achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}). Quetiapine prolonged-release tablets displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for quetiapine prolonged-release tablets administered once daily are comparable to those achieved for the same total daily dose of quetiapine immediate-release tablets administered twice daily. When quetiapine prolonged-release tablets administered once daily is compared to the same total daily dose of quetiapine immediate-release tablets administered twice daily, the area under the quetiapine plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13%

lower. When quetiapine prolonged-release tablets administered once daily is compared to the same total daily dose of the immediate release tablets of quetiapine administered once daily, the quetiapine prolonged-release tablets AUC is equivalent; and C_{max} is 59% lower. The AUC and C_{max} for the metabolite norquetiapine are 18% and 37% lower than the quetiapine, respectively. The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

The mean clearance of quetiapine in the elderly is approximately 30% to 50% lower than that seen in adults aged 18 to 65 years.

There are no clinically relevant differences in the observed apparent oral clearance (CL/F) and exposure of quetiapine between subjects with schizophrenia and bipolar disorder.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2), 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.

Metabolism
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. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approximately 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see '*Posology and method of administration*').
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.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the quetiapine prolonged-release formulation C_{max} and AUC of 44% to 52% and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. Quetiapine prolonged-rlease tablets should be taken at least one hour before a meal.

Children and adolescents (10 to 17 years of age)
The pharmacokinetics of quetiapine have been characterized in children and adolescents. At steady-state, the pharmacokinetics of the parent compound (quetiapine) in children and adolescents (10-17 years of age) were similar to adults, while AUC and C_{max} of the active metabolite, norquetiapine, were higher in children and adolescents than in adults, 45% and 31%, respectively. However, when adjusted for weight AUC and C_{max} of the parent compound in children and adolescents were lower than in adults, 41% and 39%, respectively, while the pharmacokinetics of the metabolite, norquetiapine, was similar.

A clinical pharmacokinetic study of quetiapine prolonged-release formulation has not been conducted in children and adolescents. However, modelling and simulations using physiologically based pharmacokinetic models (Simcyp paediatric models), indicated that children aged 10 – 12 years old

and adolescents 13 – 17 years old are likely to achieve similar quetiapine exposure (within 20% or less for AUC and within 30% or less for C_{max}) following administration of quetiapine prolonged-release formulation (once daily) or administration of quetiapine immediate-release formulation (twice daily) at the same total daily doses (See *'Dosing and Administration'*).

Preclinical safety data
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:
In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T_3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts. (For cataracts/lens opacities, see '*Pharmacodynamic properties'*).
In an embryofoetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.
In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core
Hypromellose
Lactose monohydrate
Cellulose, microcrystalline
Sodium citrate dihydrate - only in 50 mg and 400 mg prolonged-release tablets
Disodium phosphate dihydrate – only in 200 mg and 300 mg prolonged-release tablets
Magnesium stearate

Tablet coating of 50 mg and 400 mg prolonged-release tablets
Hypromellose
Titanium dioxide (E171)
Macrogol

Tablet coating of 200 mg and 300 mg prolonged-release tablets
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide, yellow (E172)

Incompatibilities

Not applicable.

Special precautions for storage

Store in the original package in order to protect from moisture.
Store below 30°C.

Nature and contents of container

Blister (OPA/Alu/PVC//Alu): 60 prolonged-release tablets.

Special precautions for disposal

No special requirements.

PRODUCT REGISTRATION HOLDER

PAHANG PHARMACY SDN. BHD.
Lot 5979, Jalan Teratai, 5 ½ Miles, Off Jalan Meru, 41050 Klang, Selangor, Malaysia

MANUFACTURER

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