Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Setinin XL 400 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Setinin XL 400 mg prolonged-release tablet contains 400 mg quetiapine (as quetiapine fumarate).

Excipients with known effect:
Setinin XL 400 mg prolonged-release tablet contains 59.7 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Setinin XL 400 mg tablets are white to off-white, capsule shaped with dimensions of 22.1 mm x 8.9 mm, biconvex, film coated, printed with '245' on one side with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Setinin XL is indicated for: Treatment of schizophrenia
- Setinin XL is indicated for treatment of bipolar disorder:
- For the treatment of moderate to severe manic episodes in bipolar disorder
- For the treatment of major depressive episodes in bipolar disorder
- For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment
- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of Setinin XL (see section 4.4).

4.2 Posology and method of administration

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

Adults:
For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder
Setinin XL 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 major depressive episodes in bipolar disorder
Setinin XL should be administered one daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

For preventing recurrence in bipolar disorder

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

For add-on treatment of major depressive episodes in MDD
Setinin XL should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine - see section 5.1) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

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

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

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

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

Paediatric population
Setinin XL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

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

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

Method of administration
The tablets should be administered once daily without food (at least one hour before a meal). The tablets should be swallowed whole and not split, chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see section 5.1).

Paediatric population

Quetiapine prolonged-release is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine prolonged-release have shown that in addition to the known safety profile identified in adults (see section 4.8),
certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope) or may have different implications for children and adolescents (extrapyramidal symptomsand irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

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

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

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine prolonged-release treatment, due to the known risk factors for the disease being treated.

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

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

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

In shorter-term placebo controlled clinical studies of patients with major depressive episodes' in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine prolonged-release as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine prolonged-release and 1.3% (1/75) for placebo.

Metabolic risk

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

Extrapyramidal symptoms

In placebo controlled clinical trials of adult patient's quetiapine prolonged-release was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see sections 4.8 and 5.1).

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

Tardive dyskinesia

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

Somnolence and dizziness

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

Orthostatic hypotension

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

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

Sleep apnoea syndrome

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

Seizures

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

Neuroleptic malignant syndrome

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

Severe neutropenia and agranulocytosis

Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) has been reported in quetiapine prolonged-release clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine prolonged-release. There was no apparent dose relationship. During post-marketing experience some cases were fatal. Possible risk factors for neutropenia includes pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine prolonged-release 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 5.1).

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

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

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma. (See sections 4.5, 4.8, 5.1 and 4.9.).

Interactions

See section 4.5.

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

Weight

Weight gain has been reported in patients who have been treated with quetiapine prolonged-release, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see sections 4.8 and 5.1).

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine prolonged-release, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids

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

QT-prolongation

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

Cardiomyopathy and myocarditis:

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

Withdrawal

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

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

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 prolonged-release studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine prolonged-release 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.

Dysphagia
Dysphagia (see section 4.8) has been reported with quetiapine prolonged-release Quetiapine prolonged-release 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 prolonged-release (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

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

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see section 4.4), gallstones, and alcohol consumption.

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

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.

Additional Information
Quetiapine prolonged-release data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3.

4.5 Interaction with other medicinal products and other forms of interactions

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

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see section 4.4).

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

Carbamazepine and phenytoin
In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine prolonged-release given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine prolonged-release. This increase in clearance reduced systemic quetiapine prolonged-release exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine prolonged-release alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine prolonged-release therapy. Co-administration of quetiapine prolonged-release and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine prolonged-release by approx. 450%.
In patients receiving a hepatic enzyme inducer, initiation of quetiapine prolonged-release treatment should only occur if the physician considers that the benefits of quetiapine prolonged-release outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4).

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

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

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

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

In a 6-week, randomised, study of lithium and Setinin XL versus placebo and Setinin XL in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).

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

Cardiovascular medicinal products
Formal interaction studies with commonly used cardiovascular medicinal products have not been performed. Caution should be exercised when quetiapine prolonged-release is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT-interval.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

First trimester

The moderate amount of published data from exposed pregnancies (i.e. between 400 mg-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine prolonged-release should only be used during pregnancy if the benefits justify the potential risks.

Third trimester

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

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely.
When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It may be an offence to drive while under the influence of this medicine

4.8 Undesirable effects

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

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

Table 1 ADRs associated with quetiapine prolonged-releasetherapy

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) and not known (cannot be estimated from the available data).

SOC	VeryCommon	Common	Uncommon	Rare	VeryRare	Notknown
Bloodandlymphaticsystemdisorders	Decreased haemoglobin[22]	Leucopenia[1,28] decreased neutrophil count, eosinophils increased[27]	Neutropenia[1] Thrombocytopenia, Anaemia, platelet count decreased[13]	Agranulocytosis[26]		
Immunesystemdisorders			Hypersensitivity (including allergic skin		Anaphylactic reaction[5]	

			reactions)			
Endocrinedisorders		Hyperprolactinaemia[15], decreases in total T4[24], decreases in free T4[24], decreases in total T3[24], increases in TSH[24]	Decreases in free T3[24], Hypothyroidism[21]		Inappropriate antidiuretic hormone secretion	
Metabolismandnutritionaldisorders	Elevations in serum triglyceride levels[10,30] Elevations in total cholesterol (predominantly LDL cholesterol)[11,30] Decreases in HDL cholesterol[17,30] Weight gain[8,30]	Increased appetite, blood glucose increased to hyperglycaemic levels[6,30]	Hyponatraemia[19], Diabetes Mellitus[1,5], Exacerbation of pre-existing diabetes	Metabolic syndrome[29]	Exacerbation of pre-existing diabetes	
Psychiatricdisorders		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[20]		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
Nervoussystemdisorders	Dizziness [4, 16], somnolence [2,16], headache, Extrapyramidal symptoms[1, 21]	Dysarthria	Seizure[1], Restless legs syndrome, Tardive dyskinesia[1,5], Syncope [4,16]			
EyeDisorders		Vision blurred				
Cardiacdisorders		Tachycardia[4], Palpitations[23]	QT prolongation [1,12,18] Bradycardia[32]			
Vascular disorders		Orthostatic hypotension[4,16]		Venous thromboembolism[1]		
Respiratory, thoracic and mediastinal disorder		Dyspnoea[23]	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting[25]	Dysphagia[7]	Pancreatitis[1], Intestinal obstruction/Ileus		
Hepato-biliary disorders		Elevations in serum alanine aminotransferase (ALT)[3], Elevatio	Elevations in serum aspartate aminotransfer as e (AST)[3]	Jaundice[5], Hepatitis		

		ns in gamma-GT levels[3]				
Skin and subcutaneous tissue disorders					Angioedema[5], Stevens-Johnson syndrome[5]	Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders					Rhabdomyolysis	
Renal and urinary disorders			Urinary retention			
Pregnancy, puerperium and perinatal conditions						Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
General disorders and administration site conditions	Withdrawal (discontinuation) symptoms[1,9]	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome[1], hypothermia		
Investigations				Elevations in blood creatine phosphokinase[14]		

1. See section 4.4.
2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine prolonged-release.
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 prolonged-release. These elevations were usually reversible on continued quetiapine prolonged-release treatment.
4. As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine prolonged-release may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (see section 4.4).
5. Calculation of frequency for these ADR's have only been taken from post-marketing data with the immediate-release formulation of quetiapine.
6. Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L) or a non-fasting blood glucose ≥200 mg/dL (≥11.1 mmol/L) on at least one occasion
7. An increase in the rate of dysphagia with quetiapine prolonged-release vs. placebo was only observed in the clinical trials in bipolar depression.
8. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

9. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
10. Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.
11. Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
12. See text below.
13. Platelets ≤100 x 10^9/L on at least one occasion.
14. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
15. Prolactin levels (patients>18 years of age): >20 microgram/L (>869.56 pmol/L) males;>30 microgram/L (>1304.34 pmol/L) females at any time.
16. May lead to falls.
17. HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
18. Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine prolonged-release the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine prolonged-release and placebo.
19. Shift from >132 mmol/L to <132 mmol/L on at least one occasion.
20. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see sections 4.4 and 5.1).
21. See section 5.1.
22. Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine prolonged-release patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was –1.50 g/dL.
23. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
24. Based on shifts from normal baseline to potentially clinically important value at 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.
25. Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
26. Based on shift in neutrophils from >=1.5x10^9/L at baseline to <0.5x10^9/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 10^9/L) and infection during all quetiapine prolonged-release clinical trials (see section 4.4).
27. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as >1x10^9 cells/L at any time.
28. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤3x10^9 cells/L at any time.
29. Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine prolonged-release.
30. In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see section 4.4).
31. See section 4.6.
32. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.

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

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

Paediatric population

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

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

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

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

1. Prolactin levels (patients < 18 years of age): >20 microgram/L (>869.56 pmol/L) males; >26 microgram/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level>100 microgram/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases>20 mmHg for systolic or>10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.
4. See section 5.1

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms

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

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

Management of overdose

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

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

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

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

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

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

In case of a quetiapine extended-release overdose gastric bezoar formation has been reported and appropriate diagnostic imaging is recommended to further guide patient management.
Endoscopic pharmacobezoar removal has been performed successfully in some cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines, ATC code: N05A H04

Mechanism of action
Quetiapine prolonged-release is an atypical antipsychotic agent. Quetiapine prolonged-release and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter
receptors. Quetiapine prolonged-release and norquetiapine exhibit affinity for brain serotonin (5HT2) and dopamine D1- and D2- receptors. It is thiscombination of receptor antagonism with a higher selectivity for 5HT2 relative to D2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidalside side effect (EPS) liability of quetiapine prolonged-release compared to typical antipsychotics. Quetiapine prolonged-release and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors, moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic effects). Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant.

Pharmacodynamic effects
Quetiapine prolonged-release is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or
electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade. In pre-clinical tests predictive of EPS, quetiapine prolonged-release is unlike typical antipsychotics and has an atypical profile. Quetiapine prolonged-release does not produce dopamine D2-receptor supersensitivity after chronic administration. Quetiapine prolonged-release
produces only weak catalepsy at effective dopamine D2-receptor blocking doses. Quetiapine prolonged-release demonstrates selectivity for the limbic system by producing depolarisation
blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine prolonged-release exhibits minimal dystonic liability in
haloperidol-sensitised or drug- naive Cebus monkeys after acute and chronic administration (see section 4.8).

Clinical efficacy
Schizophrenia
The efficacy of prolonged-release quetiapine 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 immediate-release -to-prolonged-release quetiapine 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. Prolonged-release quetiapine 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 randomisation to any visit. In patients stabilised on immediate-release quetiapine 400 mg to 800 mg, efficacy was maintained when
patients were switched to an equivalent daily dose of prolonged-release quetiapine given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on prolonged-release quetiapine for 16 weeks, prolonged-release quetiapine was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the prolonged-release quetiapine treatment group compared to 68.2% for placebo. The average dose was
669 mg. There were no additional safety findings associated with treatment with prolonged-release quetiapine for up to 9 months (median 7 months). In particular, reports of adverse events related
to EPS and weight gain did not increase with longer-term treatment with prolonged-release quetiapine.

Bipolar Disorder
In the treatment of moderate to severe manic episodes, quetiapine prolonged-release demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of prolonged- release quetiapine was further demonstrated with significance versus placebo in an additional 3 week study. Prolonged- release quetiapine was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. Quetiapine prolonged-release data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day prolonged-release quetiapine showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine prolonged-release, with a duration of 8 weeks' in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder,
immediate-release quetiapine 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg immediate-release quetiapine and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on immediate-release quetiapine 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating quetiapine prolonged-release in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with
quetiapine prolonged-release was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine prolonged-release was
administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and prolonged-release quetiapine versus placebo and prolonged-release quetiapine in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes' quetiapine prolonged-release was superior to placebo in
increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine prolonged-release group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine prolonged-release, when comparing continued treatment with quetiapine prolonged-release to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

Major depressive episodes in MDD
Two short-term (6 week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Prolonged-release quetiapine 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy(amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).

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

below).

The following studies were conducted with prolonged-release quetiapine as monotherapy treatment, however prolonged-release quetiapine is only indicated for use as add-on therapy:

In three out of four short term (up to 8 weeks) monotherapy studies, in patients with major depressive disorder, prolonged-release quetiapine 50 mg, 150 mg and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (LS mean change vs. placebo of 2-4 points).

In a monotherapy relapse prevention study, patients with depressive episodes stabilised on open-label prolonged- release quetiapine treatment for at least 12 weeks were randomised to either prolonged-release quetiapine once daily or placebo for up to 52 weeks. The mean dose of prolonged-release quetiapine during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for prolonged-release quetiapine treated patients and 34.4% for placebo- treated patients.

In a short-term (9 week) study non-demented elderly patients (aged 66 to 89 years) with major depressive disorder, prolonged-release quetiapine dosed flexibly in the range of 50 mg to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study patients randomised to prolonged-release quetiapine 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 mean dose of prolonged-release quetiapine was 160 mg/day. Other than the incidence of extrapyramidal symptoms (see section 4.8 and 'Clinical safety' below) the tolerability of prolonged-release quetiapine 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 19%.

Clinical safety

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

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

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

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

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

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x
10^9/L, was 1.9% in patients treated with quetiapine prolonged-release compared to 1.5% in placebo-treated patients. The incidence of shifts to >0.5-<1.0 x 10^9/L was the same (0.2%) in patients treated with quetiapine prolonged-release as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x 10^9/L was 2.9% and to <0.5 x10^9/L was 0.21% in patients treated with quetiapine prolonged-release.

Quetiapine prolonged-release treatment was associated with dose-related decreases in thyroid hormone levels..The incidences of shifts in TSH was 3.2 % for quetiapine prolonged-release versus
2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were
not associated with clinically symptomatic hypothyroidism. The reduction in total and free T4 was maximal within the first six weeks of quetiapine prolonged-release treatment, with no further
reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine prolonged-release treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of quetiapine prolonged-release (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 prolonged-release (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Paediatric population
Clinical efficacy
The efficacy and safety of quetiapine prolonged-release was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the
patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to quetiapine prolonged- release were excluded. Treatment with quetiapine prolonged-release was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for quetiapine prolonged-release 400 mg/day and –6.56 for quetiapine prolonged-release 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for quetiapine prolonged-release 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for quetiapine prolonged-release 400 mg/day and –9.29 for
quetiapine prolonged-release 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine prolonged-release was superior to placebo with respect to the percentage of patients achieving response, defined as ≥30% reduction from baseline in PANSS total score.

Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with quetiapine in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

Clinical safety
In the short-term pediatric trials with quetiapine prolonged-release described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain ≥7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 13.7% vs. 6.8% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended posttreatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine prolonged-release at the time of the event.

Long-term safety
A 26-week open-label extension to the acute trials (n= 380 patients), with quetiapine prolonged-release flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and
adolescents than in adult patients (see sections 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine prolonged-release for at least 26 weeks met this criterion.

5.2 Pharmacokinetic properties

Absorption
Quetiapine prolonged-release is well absorbed following oral administration. Prolonged-release quetiapine achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (Tmax). Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine prolonged-release.

The pharmacokinetics of quetiapine prolonged-release and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When prolonged-release quetiapine administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (Cmax) is 13% lower at steady state. When prolonged-release quetiapine is compared to immediate-release quetiapine, the norquetiapine
metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine prolonged-release, a high-fat meal was found to produce statistically significant increases in the prolonged-release quetiapine Cmax and AUC of approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the Cmax or AUC of quetiapine prolonged-release. It is recommended that prolonged-release quetiapine is taken once daily without food.

Distribution
Quetiapine prolonged-release is approximately 83% bound to plasma proteins.

Biotransformation
Quetiapine prolonged-release 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 prolonged-release.

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

Quetiapine prolonged-release 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 prolonged-release with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug.
From animal studies it appears that quetiapine prolonged-release can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine prolonged-release.

Elimination
The elimination half-lives of quetiapine prolonged-release and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabelled drug was excreted in the urine and
21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine prolonged-release and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender
The pharmacokinetics of quetiapine prolonged-release does not differ between men and women.

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

Renal impairment
The mean plasma clearance of quetiapine prolonged-release was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 m2), but the individual clearance values are within the range for normal subjects.

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

Paediatric population

Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine prolonged-release twice daily. At steady-state,
the dose-normalised plasma levels of the parent compound, quetiapine prolonged-release , in children and adolescents (10-17 years of age) were in general similar to adults, though Cmax in children was at the higher end of the range observed in adults. The AUC and Cmax for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for prolonged-release quetiapine in children and adolescents.

5.3 Preclinical safety data

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

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration
and a decrease of red and white blood cell count have been observed; and in dog's lens opacity and cataracts. (For cataracts/lens opacities see section 5.1).

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose, microcrystalline
Magnesium oxide, light
Carrageenan lambda
Povidone (K-30)
Magnesium stearate

Tablet coating
Carrageenan lambda
Titanium dioxide (E171)
Macrogol 400

Printing ink
Opacode S-1-17823 black ink: Shellac glaze, iron oxide black (E172), propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Alu/PVC/PVdC blisters and OPA/Alu/PVC-Alu blisters.

Pack sizes: 10, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjördur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/103/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd March 2012
Date of last renewal: 31st March 2016

10 DATE OF REVISION OF THE TEXT

October 2019