Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Noletil XL 200mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 200 mg prolonged release tablet contains 200 mg Quetiapine (as Quetiapine Hemifumarate)
Excipients with known effect: 40.70 mg Lactose monohydrate and 3.5 mg sodium per tablet.

For a full list of Excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Yellow coloured, round shaped, biconvex film coated tablets, debossed with 'I2' on one side and plain on other
Note: Diameter of the tablet 9.60 ± 0.2 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Noletil XL is indicated for
Treatment of Schizophrenia, including:
- Preventing relapse in stable schizophrenic patients who have been maintained on Noletil XL (see section 5.1).

Treatment of bipolar disorder :
- For the treatment of moderate to severe manic episodes associated with bipolar disorder
- For the treatment of major depressive episodes associated with bipolar disorder
- For the preventing recurrence in bipolar disorder, in patients whose manic, or depressive episode has 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 Noletil 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

Noletil XL should be administered once daily, without food.

Method of administration
The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder
Noletil 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 depressive episodes associated with bipolar disorder
Noletil XL should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. 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 Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder
For prevention of recurrence of manic, depressive or mixed episodes in bipolar disorder, patients who have responded to Noletil XL for acute treatment of bipolar disorder should continue on Noletil XL at the same dose administered at bedtime. The dose may 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:
Noletil 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 tablet may be switched to Noletil XL at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

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

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

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

Children and Adolescents:
Quetiapin prolonged-release tablet 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 with Quetiapine tablet 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 is extensively metabolised by the liver. Therefore, Noletil XL should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 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.

Not all dosing regimes are practical/possible with the present strengths of Noletil XL and other authorized products containing Quetiapine are available.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product 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 Noletil XL is indicated for the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with MDD, 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).

Children and adolescents (10 to 17 years of age)
Noletil 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. Clinical trials with Quetiapine tablet 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 symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

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

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (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 treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which Noletil 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 antidepressants compared to placebo in patients less than 25 years old.

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

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 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 and 1.3% (1/75) for placebo.

Extrapyramidal symptoms:
In placebo controlled clinical trials of adult patients quetiapine 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 section 4.8 and 5.1).

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

Tardive Dyskinesia:
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Noletil XL 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 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.

Bipolar depression patients and patients with major depressive episodes in MDD 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.

Quetiapine 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.

Cardiovascular:
Noletil XL 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. A slower titration regimen could be considered in patients with underlying cardiovascular disease.

Seizures:
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine 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 (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 Tablets should be discontinued and appropriate medical treatment given.

Severe neutropenia:
Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) has been uncommonly reported in Noletil XL clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Noletil XL. There is no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine, Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5×10^9/L). (see Section 5.1)

Interactions:
See also Section 4.5.
Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of Quetiapine Prolonged-release Tablets treatment should only occur if the physician considers that the benefits of Quetiapine Prolonged-release Tablets outweigh the risks of removing the hepatic enzyme

inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Weight:
Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (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, 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 (see section 4.8). Lipid changes should be managed as clinically appropriate.

Metabolic Risk:
Given the observed changes in weight, blood glucose (see hyperglycaemia) and lipids seen in clinical studies, patients (including those with normal baseline values) may experience worsening of their metabolic risk profile, which should be managed as clinically appropriate (see also section 4.8).

QT Prolongation:
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. However, with overdose (see section 4.9) QT prolongation was observed. In post-marketing, QT prolongation was reported with quetiapine 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 is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patents 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 (see section 4.8). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

Withdrawal:
Acute withdrawal symptoms such as nausea, vomiting, insomnia, headache, diarrhoea, dizziness and irritability have been described after abrupt cessation of high doses of quetiapine. 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 Tablets 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 Tablets should be used with caution in patients with risk factors for stroke.

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.

Dysphagia

Dysphagia (See section 4.8) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

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'.

Venous thromboembolism:
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 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.

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.

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

Sodium:
Noletil XL tablets contains less than 1 mmol sodium (23 mg) per Noletil XL 200mg that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Given the primary central nervous system effects of quetiapine, Quetiapine Prolonged-release Tablets 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).

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, such as boceprevir or indinavir, is contraindicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of Quetiapine Prolonged-release Tablets therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of Quetiapine Prolonged-release Tablets treatment should only occur if the physician considers that the benefits of Quetiapine Prolonged-release Tablets 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).

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

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

The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine.

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

In a 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel 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).

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the fetal eye have not been examined, though. Therefore, Quetiapine Prolonged-release Tablets should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed.

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

Breast-feeding
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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with quetiapine.

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

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	
Very common:	Decreased haemoglobin[23]
Common:	Leucopenia[1, 29], decreased neutrophil count, eosinophils increased[28]
Uncommon:	Thrombocytopenia, Anaemia, platelet count decreased[14]
Rare:	Agranulocytosis[27]
Not Known:	Neutropenia[1]
Immune system disorders	
Uncommon:	Hypersensitivity (including allergic skin reactions)
Very rare:	Anaphylactic reaction[6]
Endocrine disorders	
Common:	Hyperprolactinaemia[16], decreases in total T_4 [25], decreases in free T_4 [25], decreases in total T_3 [25], increases in TSH [25]
Uncommon:	Decreases in free T_3[25], Hypothyroidism [22]
Very rare:	Inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders	
Very common:	Elevations in serum triglyceride levels[11, 31] Elevations in total cholesterol (predominantly LDL cholesterol)[12, 31] Decrease in HDL cholesterol[18, 31], Weight gain[9, 31]
Common:	Increased appetite, blood glucose increased to hyperglycaemic levels[7, 31]
Uncommon:	Hyponatraemia[20], Diabetes Mellitus[1, 5, 6]
Rare:	Metabolic syndrome[30]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[21]
Rare:	Somnambulism and related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders	
Very common:	Dizziness[4, 17], Somnolence[2, 17] , Headache
Common:	Syncope[4,17],Extrapyramidal symptoms[1, 22], Dysarthria
Uncommon:	Seizure[1] , Restless legs syndrome, Tardive dyskinesia[1, 6]
Cardiac disorders	
Common:	Tachycardia[4], Palpitations[24]
Uncommon:	QT prolongation[1, 13, 19,]
Not known:	Cardiomyopathy and myocarditis
Eye Disorders	
Common:	Vision blurred

Vascular disorders	
Common:	Orthostatic hypotension[4, 17]
Rare:	Venous thromboembolism[1]
Respiratory, thoracic and mediastinal disorder	
Common:	Rhinitis, Dyspnoea[24]
Gastrointestinal disorders	
Very common:	Dry mouth
Common:	Constipation, dyspepsia, vomiting[26]
Uncommon:	Dysphagia[8]
Rare:	Pancreatitis[1, ,]
Hepato-biliary disorders	
Common:	Elevationsin serum transaminases (ALT, AST)3, Elevations in gamma-GT levels3
Rare:	Jaundice[6], Hepatitis
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema [6], Stevens-Johnson syndrome [6]
not known:	Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms(DRESS), Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very rare:	Rhabdomyolysis
Pregnancy, puerperium and perinatal conditions	
not known:	Drug withdrawal syndrome neonatal[32]

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

Investigations

Rare:	Elevations in blood creatine phosphokinase [15]

(1) See section 4.4.
(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
(3) Asymptomatic elevations (shift from normal to >3 x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4).
(5) 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 ≥126mg/dL(≥ 7.0 mmol/L) or a non fasting blood glucose ≥200 mg/dL (≥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 in adults.
(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) Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
(20) Shift from >132 mmol/L to ≤ 132 mmol/L on at least one occasion.
(21) 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).
(22) See section 5.1.
(23) Decreased haemoglobin to ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was –1.50 g/dL.
(24) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
(25) 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.
(26) Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
(27) Shift in neutrophils from ≥1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment.
(28) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as >1 x 10^9 cells/L at any time.
(29) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 10^9 cells/L at any time.
(30) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
(31) 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)
(32) See Section 4.6.
(33) 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.

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

The frequencies of adverse events are ranked according to the following:Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data).	
Metabolism and nutritional disorders	
Very common:	Increased appetite
Endocrine disorders	
Very common:	Elevations in prolactin [1],
Nervous system disorders	
Very common :	*Extrapyramidal symptoms* [3, 4]
Common:	Syncope
Vascular disorders	
Very common :	Increases in blood pressure[2]
General disorders and administration site conditions	
Common:	Irritability [3]
Respiratory, thoracic and mediastinal disorders	
Common:	Rhinitis
Gastrointenstinal disorders	

Very Common: Vomiting

(1) Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.
(2) Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases > 20mmHg 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.
(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

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 and hypotension.

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. Additionally, the following events have been reported in the setting of monotherapy overdose with quetiapine: QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium, and/or agitation

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4).

Management of overdose:

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

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines

ATC code: N05A H04

Mechanism of action:
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT2) and dopamine D1- and D2- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Quetiapine Prolonged-release Tablets. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5HT1 receptors. Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2-receptors. Quetiapine has no appreciable affinity at muscarinic or benzodiazepine receptors.

Pharmacodynamic effects:

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration (See section 4.8).

Clinical efficacy and safety:

Schizophrenia
The efficacy of Noletil XL 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 tablet-to- Noletil XL 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. Noletil XL 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 Quetiapine immediate-release tablet 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of Noletil XL given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on Noletil XL for 16 weeks, Noletil XL was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Noletil XL treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with Noletil XL 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 Quetiapine prolonged-release tablet.

Bipolar Disorder
In the treatment of moderate to severe manic episodes, quetiapine demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. There are no data from long-term studies to demonstrate quetiapine's effectiveness in preventing subsequent
manic or depressive episodes. Quetiapine data in combination with divalproex or lithium in 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 Noletil XL showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine, with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Quetiapine tablet 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 Quetiapine tablet 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 Quetiapine tablet 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 in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine 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 group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine 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. Noletil XL150 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 Noletil XL as monotherapy treatment, however Noletil XL 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, Noletil XL 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 Noletil XL treatment for at least 12 weeks were randomised to either Noletil XL once daily or placebo for up to 52 weeks. The mean dose of Noletil XL during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for Noletil XL 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, Noletil XL 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 Noletil XL 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 Noletil XL was 160 mg/day. Other than the incidence of extrapyramidal symptoms (see section 4.8 Undesirable effects and 'Clinical Safety' below) the tolerability of Noletil XL 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 and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Noletil XL 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 Noletil XL and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events was generally low and did not exceed 4% in any treatment group.

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

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomised withdrawal period during which patients were randomised to quetiapine or placebo. For patients who were randomised to quetiapine, 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-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 109/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 X 109/L, was 1.9% in patients treated with quetiapine compared to 1.3% in placebo-treated patients. The incidence of shifts to >0.5 - <1.0 X 109/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count 1.5 X 109/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 X 109/L was 2.9% and to <0.5 X 109/L was 0.21% in patients treated with quetiapine.

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels..The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both 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 treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment

Cataracts/lens opacities

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

Children and adolescents (10 to 17 years of age)

Clinical efficacy

The efficacy and safety of Quetiapine 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 were excluded. Treatment with Quetiapine 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 tablet 400 mg/day and –6.56 for Quetiapine tablet 600 mg/day. Responder rates (YMRS improvement 50%) were 64% for Quetiapine tablet 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 tablet 400 mg/day and –9.29 for Quetiapine 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine 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 trail with Quetiapine Lambda 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 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 12.5% vs. 6% 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 at the time of the event.

Long-term safety

A 26-week open-label extension to the acute trials (n= 380 patients), with Quetiapine 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 section 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 for at least 26 weeks met this criterion.

5.2 Pharmacokinetic properties

Absorption:
Quetiapine is well absorbed following oral administration. Noletil XL 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.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When Noletil XL administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (Quetiapine immediate release tablet) 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 Noletil XL is compared to Quetiapine immediate release, the norquetiapine metabolite AUC is 18% lower.

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 Noletil XL 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. It is recommended that Noletil XL is taken once daily without food.

Distribution:
Quetiapine is approximately 83% bound to plasma proteins.

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.

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. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination:
The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. 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 and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations:

Gender:
The pharmacokinetics of quetiapine does not differ between men and women.

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

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

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

Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, 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, nor quetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for Quetiapine prolonged release tablets in children and adolescents.

5.3 Preclinical safety data

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

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

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Hypromellose
Sodium chloride
Povidone K-30
Talc
Magnesium stearate (E470b)

Coating:
Opadry 03B52117 yellow:
Hypromellose 6 cP (E464)
Titanium dioxide (E171)
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Noletil XL 200 mg Prolonged-release Tablets are packed in PVC/PVDC-Alu blister pack. Pack size of 10, 30, 50, 60 and 100 tablets per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1436/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 23rd November 2012
Date of Last Renewal: 15th July 2017

10 DATE OF REVISION OF THE TEXT