Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Quetiapine Pfizer 200mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of quetiapine (as quetiapine fumarate).
Excipient: 41.333 mg lactose monohydrate per tablet.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round, with diameter 11.2 mm, biconvex, film coated tablet imprinted with 'E 55' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Quetiapine Pfizer is indicated for the treatment of:

- Schizophrenia.

Quetiapine Pfizer is indicated for the 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 in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

4.2 Posology and method of administration

Quetiapine Pfizer can be administered with or without food.

Adults:

For the treatment of Schizophrenia

For the treatment of schizophrenia, Quetiapine Pfizer should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

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

For the treatment of moderate to severe manic episodes in bipolar disorder

For the treatment of manic episodes associated with bipolar disorder, Quetiapine Pfizer should be administered twice a day. The total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.
The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day.

For the treatment of depressive episodes in bipolar disorder
Quetiapine Pfizer should be administered once 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 for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

Elderly:
As with other antipsychotics, Quetiapine Pfizer should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30 - 50% in elderly subjects when compared to younger patients.
Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and Adolescents:
Quetiapine Pfizer 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 is extensively metabolised by the liver. Therefore, Quetiapine 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 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Children and adolescents (10 to 17 years of age)
Quetiapine Pfizer 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 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, and 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 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 in bipolar disorder 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 clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

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.

Somnolence:
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, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression 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.

Cardiovascular:
Quetiapine Pfizer 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. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (See Section 4.8).

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 (see section 4.8).

Tardive Dyskinesia:
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine Pfizer should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment. (See Section 4.8).

Neuroleptic Malignant Syndrome:
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine (see section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine Pfizer should be discontinued and appropriate medical treatment given.

Severe Neutropenia:

Severe neutropenia (neutrophil count <0.5 X 10^9/L) has been uncommonly reported in Quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Quetiapine. There was 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 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 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 Pfizer therapy. In patients receiving a hepatic enzyme inducer, initiation of Quetiapine Pfizer treatment should only occur if the physician considers that the benefits of Quetiapine Pfizer 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, there may be possible worsening of the metabolic risk profile in individual patients, 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. 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 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).

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation 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 Pfizer 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 Pfizer 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 of 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 Undesirable effects) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Lactose
Quetiapine Pfizer film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

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 Pfizer and preventive measures undertaken.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see 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 interaction

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

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

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of Quetiapine Pfizer 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 Pfizer treatment should only occur if the physician considers that the benefits of Quetiapine Pfizer 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 also section 4.4).

The pharmacokinetics of quetiapine 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).

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

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

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

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

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

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 foetal eye have not been examined, though. Therefore, Quetiapine Pfizer 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.

The degree to which quetiapine is excreted into human milk is unknown. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking Quetiapine Pfizer.

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, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000).

Blood and lymphatic system disorders

Common: Leucopenia [1]

Uncommon:	Eosinophilia, Thrombocytopenia
Unknown:	Neutropenia [1]
Immune system disorders	
Uncommon:	Hypersensitivity
Very rare:	Anaphylactic reaction[6]
Endocrine disorders	
Common:	Hyperprolactinaemia[16]
Very rare:	Inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders	
Common:	Increased appetite
Uncommon:	Hyponatraemia[20]
Very rare:	Diabetes Mellitus [1, 5,6]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares
Nervous system disorders	
Very Common:	Dizziness [4, 17] , somnolence [2, 17] , headache
Common:	Syncope [4, 17] Extrapyramidal symptoms[1, 13] , Dysarthria
Uncommon:	Seizure [1] , Restless legs syndrome, Tardive dyskinesia [1, 6]
Cardiac disorders	
Common:	Tachycardia [4]
Eye Disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension [4, 17]
Rare:	Venous thromboembolism[1]
Respiratory, thoracic and mediastinal disorder	
Common:	Rhinitis
Gastrointestinal disorders	
Very common:	Dry mouth
Common:	Constipation, dyspepsia
Uncommon:	Dysphagia[8]
Hepato-biliary disorders	
Rare:	Jaundice [6]
Very rare:	Hepatitis [6]
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema [6] , Stevens-Johnson syndrome[6]

Musculoskeletal and connective tissue disorders	
Very rare:	Rhabdomyolysis
Reproductive system and breast disorders	
Uncommon:	Sexual dysfunction
Rare:	Priapism, Galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	
Very common	Withdrawal (discontinuation) symptoms [1,10]
Common:	Mild asthenia, peripheral oedema, irritability
Rare:	Neuroleptic malignant syndrome [1]
Investigations	
Very common	Elevations in serum triglyceride levels [11] Elevations in total cholesterol (predominantly LDL cholesterol) [12] Decreases in HDL cholesterol [18] , Weight gain[9], Decreased haemoglobin[21]
Common:	Elevations in serum transaminases (ALT, AST) [3] , decreased neutrophil count, blood glucose increased to hyperglycaemic levels [7]
Uncommon:	Elevations in gamma-GT levels [3] , Platelet count decreased [14] , QT Prolongation [1, 13, 19]
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 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 been taken from postmarketing data only.
7. Fasting blood glucose ≥126mg/dL (≥7.0 mmol/L) or a non fasting blood glucose ≥200mg/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 ≥200mg/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 ≥240mg/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. 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.

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.

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

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first two to four weeks of Quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that Quetiapine causes clinically relevant hypothyroidism.

Children and adolescents (10 to 17 years of age)

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

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, >1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).	
Metabolism and nutritional disorders	
Very common:	Increased appetite
Investigations	
Very common:	Elevations in prolactin [1] , increases in blood pressure [2]
Nervous system disorders	
Very common:	Extrapyramidal symptoms [3]
General disorders and administration site conditions	
Common:	Irritability [4]

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. See section 5.1.
4. 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.

4.9 Overdose

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

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

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

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. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action:
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Quetiapine compared to typical antipsychotics.

Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic 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 D_2-receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2-receptor supersensitivity after chronic administration.

Quetiapine produces only weak catalepsy at effective dopamine D_2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. (See Section 4.8).

Clinical efficacy:

In three placebo-controlled clinical trials, in patients with schizophrenia, using variable doses of quetiapine, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics. A placebo-controlled trial evaluating fixed doses of quetiapine across the range of 75 to 750 mg/day showed no evidence of an increase in EPS or the use of concomitant anticholinergics.

In four placebo-controlled clinical trials, evaluating doses of Quetiapine up to 800 mg/day for the treatment of moderate to severe manic episodes, two each in monotherapy and as combination therapy to lithium or divalproex, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

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 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 effectiveness in preventing subsequent manic or depressive episodes. Quetiapine 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.

The mean last week median dose of Quetiapine in responders was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

In 4 clinical trials with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Quetiapine IR 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 IR 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 IR 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.

Clinical trials have demonstrated that Quetiapine is effective in schizophrenia and mania when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours.

This is further supported by the data from a positron emission tomography (PET) study, which identified that for quetiapine, $5HT_2$- and D_2-receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

The long-term efficacy of Quetiapine IR in prevention of schizophrenic relapses has not been verified in blinded clinical trials. In open label trials, in patients with schizophrenia, quetiapine was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response, suggesting some long-term efficacy.

In placebo-controlled monotherapy trials in patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $< 1.5 \times 10^9$/L, was 1.72% in patients treated with Quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L), the incidence of at least one occurrence of neutrophil count $< 0.5 \times 10^9$/L was 0.21% in patients treated with Quetiapine and 0% in placebo treated patients and the incidence ≥ 0.5 - $< 1.0 \times 10^9$/L was 0.75% in patients treated with Quetiapine and 0.11% in placebo-treated patients.

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

Children and adolescents (10 to 17 years of age)
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 400 mg/day and –6.56 for Quetiapine 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Quetiapine 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 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.

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

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 sections 4.4 and 4.8).

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

In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained ≥7% of their body weight. When adjusting for normal growth over 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.

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 Pharmacokinetic properties

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

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women.

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

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

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

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.

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, 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.

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 T_3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts. (For cataracts/lens opacities see 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:
Povidone (K30)
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycolate Type A
Lactose monohydrate
Magnesium stearate
Colloidal anhydrous silica
Talc

Coating:
Hypromellose 6 cps
Macrogol 400
Titanium dioxide (E171)

Black imprinting ink containing shellac, iron oxide black (E172) and propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles and PVC/aluminium foil blisters.

Presentations:
Bottles:100, 250, 500 or 1000 tablets

Blisters: 1, 10, 20, 30, 50, 60, 90, 100, 120, 180 or 240 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 822/53/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd September 2011

10 DATE OF REVISION OF THE TEXT