Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Quetiapine Arrow 25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25mg of quetiapine (as quetiapine fumarate).

Excipients: lactose (anhydrous) 4.91mg, Sunset Yellow (E110) 0.045mg and Allura Red (E129) 0.014mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Peach, round coated biconvex tablet with 'QT' on one side and '  'on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of schizophrenia.
- Treatment of moderate to severe manic episodes.
- Treatment of major depressive episodes in bipolar disorder.

Quetiapine has not been demonstrated to prevent recurrence of manic or depressive episodes (see section 5.1).

4.2 Posology and method of administration

Quetiapine Tablets can be administered with or without food.

Adults
For the treatment of schizophrenia:
Quetiapine should be administered twice a day.
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).
From Day 4 onwards, the dose should be titrated to the usual effective dose range 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 manic episodes associated with bipolar disorder:
Quetiapine 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 per day by Day 6 should be in increments of no greater than 200 mg per day.
The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes in bipolar disorder:
Quetiapine should be administered once daily at bedtime as this may reduce the likelihood of day time sedation.

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. Depending on the patients' response quetiapine may be titrated up to 600mg daily. Antidepressant efficacy was demonstrated at 300mg and 600mg/day, however no additional benefit was seen in the 600mg/day group, above 300mg daily during short-term treatment (see section 5.1).

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. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

Elderly
As with other antipsychotics, quetiapine 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
The safety and efficacy of quetiapine have not been evaluated in children and adolescents.

Renal impairment
Dose adjustments are not necessary in patients with renal impairment

Hepatic impairment
Quetiapine is extensively metabolised by the liver, and therefore 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 on 25mg/day. The dose should be increased daily, in increments of 25 to 50mg, to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

- Hypersensitivity to quetiapine 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

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).

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 disease
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8).

Tardive dyskinesia
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered (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 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).

Lipids
Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid increases should be managed as clinically appropriate.

Extrapyramidale symptoms
In placebo controlled clinical trials 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).

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 treatment should only occur if the physician considers that the benefits of quetiapine 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).

Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8.).

Venous thromoembolism
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

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. 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 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 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 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.

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. A second study did not demonstrate an additive effect at week 6. There are no combination data available beyond week 6.
Other
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactas deficiency or glucose-galactose malabsorption should not take this medicine.

Quetiapine 25mg Tablets contain the colorants Sunset Yellow (E110) and Allura Red (E129) which may cause allergi reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally-acting agents 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 take quetiapine together with grapefruit juice.

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 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 treatment should only occur if the physician considers that the benefits of quetiapine 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 CYP2D6 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 agents have not been performed.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
The safety and efficacy of quetiapine during human pregnancy have not been established (see section 5.3). 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 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.

Lactation:
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.

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 edema, 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: Leuopenia [1]
Uncommon: Eosinophilia, Thrombocytopenia
Unknown: Neutropenia [1]

Immune system disorders
Uncommon: Hypersensitivity
Very rare: Anaphylactic reaction [6]

Endocrine disorders
Common: Hyperprolactinaemia [16]

Metabolism and nutritional disorders
Common: Increased appetite
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]
Uncommon: Seizure [1], Restless legs syndrome, Dysarthria
Very rare: Tardive dyskinesia [6]

Cardiac disorders
Common: Tachycardia [4]

Eye disorders
Common: Vision blurred

Vascular disorders
Common: Orthostatic hypotension [4, 17]
Unknown: Cases of venous thromboembolism, including cases pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs

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]

Pregnancy, puerperium and perinatal conditions
Not known: Drug withdrawal syndrome neonatal (see 4.6)

Reproductive system and breast disorders
Rare: Priapism, Galactorrhoea

General disorders and administration site conditions
Very common: Withdrawal (discontinuation) symptoms [1, 10]
Common: Mild asthenia, peripheral oedema, irritability
Rare: Neuroleptic malignant syndrome [1]

Investigations
Very common: Elevations in serum triglyceride levels [11]
Elevations in total cholesterol (predominantly LDL cholesterol) [12]
Weight gain [9]
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]
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 l 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) on at least one occasion.
[12]. Cholesterol ≥240mg/dL (≥6.2064 mmol/L) on at least one occasion.
[13]. See text below.
[14]. Platelets ≤100 x 109/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.

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 bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. In 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).

Quatiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T4 and free T4. 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 T4, irrespective of the duration of treatment. Smaller decreases in total T3 and reverse T3 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.

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 postmarketing 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).

In general, reported signs and symptoms were those resulting from an exaggeration of the substances known pharmacological effects, i.e., 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 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 5-HT2 and dopamine D1 and D2 receptors. It is this combination of receptor antagonism with a higher selectivity for serotonin 5-HT2 receptors relative to D2 receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal symptom (EPS) liability of quetiapine. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 and serotonin 5-HT1A 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 D2 receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike standard antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor supersensitivity after chronic administration. It 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-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that quetiapine should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia (see section 4.8).

The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of quetiapine in humans is not known.

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 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 valproic acid, 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's effectiveness in preventing subsequent manic or depressive episodes. Quetiapine data in combination with valproic acid 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. There are no combination data available beyond 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 per 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 immediate release 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 immediate release 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 immediate release 300 mg 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.

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, 5HT2 and D2 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 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 (placebocontrolled, 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.

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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours, respectively.

The pharmacokinetics of quetiapine and N-desalkyl quetiapine 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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite N-desalkyl quetiapine 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 by approx. 25% in persons with known hepatic impairment (stable alcoholic cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2).

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) 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.

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.

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

Tablet core:
Cellulose, microcrystalline
Calcium hydrogen phosphate dihydrate
Sodium starch glycolate (Type A)
Povidone
Lactose monohydrate
Magnesium stearate

Tablet coating:
Polyvinyl alcohol-part hydrolysed
Titanium dioxide (E171)
Macrogol
Talc

Sunset Yellow (E110)
Allura Red (E129)
Indigo Carmine (E132)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blisters in pack sizes of 6, 10, 14, 20, 28, 30, 50, 56, 60, 90, 100 and 100 (5 x 20) tablets per carton.

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

Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1130/23/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2010

10 DATE OF REVISION OF THE TEXT

July 2012