

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Seroquel 300mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300mg quetiapine (as quetiapine fumarate).

Excipients include lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

Product imported from Italy and Spain:

White biconvex, film-coated tablets with 'Seroquel' imprinted on one side and '300' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of schizophrenia.

Treatment of moderate to severe manic episode.

Treatment of major depressive episodes in bipolar disorder.

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

4.2 Posology and method of administration

Seroquel should be administered twice daily, with or without food.

Adults:

For the treatment of schizophrenia, Seroquel 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 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, Seroquel 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, Seroquel should be administered once daily at bedtime as this may reduce the likelihood of daytime 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 patient's response Seroquel may be titrated up to 600 mg daily. Antidepressant efficacy was demonstrated at 300 mg and 600 mg/day, however no additional benefit was seen in the 600 mg group above 300 mg daily during short-term treatment

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

Elderly: As with other antipsychotics, Seroquel 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 Seroquel have not been evaluated in children and adolescents.

Renal Impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic Impairment:

Quetiapine is extensively metabolised by the liver. Therefore, Seroquel 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 'Interactions with other medicaments and other types of interaction').

4.4 Special warnings and precautions for use

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:

Seroquel 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 Seroquel or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Extrapyramidal 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.

Tardive Dyskinesia:

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel should be considered (see section 4.8).

Neuroleptic Malignant Syndrome:

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Seroquel (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, Seroquel 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 Seroquel clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Seroquel. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with Seroquel. 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 $1.5 \times 10^9/L$). (See section 5.1).

Interactions:

See also (4.5) Interactions with other medicinal products and other forms of interactions.

Concomitant use of Seroquel with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of Seroquel therapy. In patients receiving a hepatic enzyme inducer, initiation of Seroquel treatment should only occur if the physician considers that the benefits of Seroquel 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 Undesirable effects).

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.

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 with concomitant neuroleptics especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Withdrawal

Acute withdrawal symptoms such as nausea, vomiting, and insomnia have been described after abrupt cessation of antipsychotic drugs including Seroquel. Gradual withdrawal is advisable.

Elderly patients with dementia-related psychosis

Seroquel is not approved for the treatment of patients with 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. Seroquel 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 Seroquel studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in Seroquel-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 Seroquel treatment and death in elderly patients with dementia.

Lactose

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

Additional information

Seroquel 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.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, Seroquel 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 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 Seroquel therapy. Co-administration of Seroquel 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 Seroquel treatment should only occur if the physician considers that the benefits of Seroquel 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 'Special Warnings and Special Precautions for Use').

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

The pharmacokinetics of quetiapine were not altered following coadministration with cimetidine.

The pharmacokinetics of lithium were not altered when coadministered with Seroquel.

The pharmacokinetics of sodium valproate and Seroquel were not altered to a clinically relevant extent when coadministered.

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 QTc interval.

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, Seroquel should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which Seroquel 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 Seroquel

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 Seroquel 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 Seroquel.

The incidences of ADRs associated with Seroquel 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

Unknown: Neutropenia ¹

Immune system disorders

Uncommon: Hypersensitivity

Very rare: Anaphylactic reaction ⁶

Metabolism and nutritional disorders

Very rare: Diabetes Mellitus ^{1, 5, 6}

Nervous system disorders

Very Common: Dizziness ⁴, somnolence ², headache

Common: Syncope⁴, Extrapyramidal symptoms ^{1,13}

Uncommon: Seizure ¹, restless leg syndrome

Very rare Tardive dyskinesia ⁶

Cardiac disorders

Common: Tachycardia ⁴

Eye Disorders:

Common: Vision blurred

Vascular disorders

Common: Orthostatic hypotension ⁵

Respiratory, thoracic and mediastinal disorder

Common: Rhinitis

Gastrointestinal disorders

Very Common: Dry mouth,

Common: Constipation, dyspepsia

Uncommon: Dysphagia

Hepato-biliary disorders

Rare: Jaundice ⁶

Very rare: Hepatitis ⁶

Skin and subcutaneous tissue disorders

Very rare: Angioedema ⁶, Stevens-Johnson syndrome ⁶

Reproductive system and breast disorders

Rare: Priapism

General disorders and administration site conditions

Very Common: Withdrawal (discontinuation) symptoms ^{1,10}

Common: Mild asthenia, peripheral oedema

Rare: Neuroleptic malignant syndrome ¹

Investigations

Very Common: Elevations in the serum triglyceride levels ¹¹

Common: Elevations in the total cholesterol (predominantly LDL cholesterol) ¹²
Weight gain, elevations in serum transaminases (ALT, AST) ⁴, decreased neutrophil count, blood glucose increased to hyperglycaemic levels ⁷

Uncommon: Elevations in gamma-GT levels ³

- 1 See Section 4.4 Special Warnings and Special Precautions for Use.
- 2 Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of Seroquel.
- 3 Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered Seroquel. These elevations were usually reversible on continued Seroquel treatment.
- 4 As with other antipsychotics with alpha1 adrenergic blocking activity, Seroquel 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 $\geq 126\text{mg/dL}$ ($\geq 7.0\text{ mmol/L}$) or a non fasting blood glucose $\geq 200\text{mg/dL}$ ($\geq 11.1\text{ mmol/L}$) on at least one occasion.
- 8 An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.
- 9 Occurs predominantly during the early weeks of treatment.
- 10 The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
- 11 Triglycerides $\geq 200\text{mg/dL}$ ($\geq 2.258\text{ mmol/L}$) on at least one occasion.
- 12 Cholesterol $\geq 240\text{mg/dL}$ ($\geq 6.2064\text{ mmol/L}$) on at least one occasion.
- 13 See text below

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. In long-term studies of schizophrenia and bipolar disorder the aggregated incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

Seroquel 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 Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel 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 Seroquel 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 seroquel 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 Seroquel alone resulting in death or coma or QT-prolongation.

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.

Patients with pre-existing severe cardiovascular disease may be at increased risk of the effects of overdose. (See section 4.4 Special warnings and precautions for use: Cardiovascular).

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
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 exhibits 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 effects (EPS) liability of Seroquel. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl 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.

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.

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. 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-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that Seroquel 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.

The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of Seroquel 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 Seroquel 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 Seroquel 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 Seroquel 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.

Unlike many other antipsychotics, Seroquel does not produce sustained elevations in prolactin, which is considered a feature of atypical antipsychotics. In a multiple fixed-dose clinical trial, in patients with schizophrenia, there were no differences in prolactin levels at study completion, for Seroquel across the recommended dose range, and placebo. In the treatment of moderate to severe manic episodes, Seroquel 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 Seroquel's effectiveness in preventing subsequent manic or depressive episodes. Seroquel 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.

The mean last week median dose of Seroquel 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, Seroquel 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 Seroquel 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 Seroquel 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 Seroquel in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Seroquel was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Seroquel was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

Clinical trials have demonstrated that Seroquel is effective 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 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 Seroquel 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 Seroquel and 0% in placebo treated patients and the incidence $\geq 0.5 - < 1.0 \times 10^9/L$ was 0.75% in patients treated with Seroquel 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/1.73m²), 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 with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see 4.2 Posology and Method of Administration). 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, but 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

Calcium hydrogen phosphate dihydrate
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose (E460)
Macrogol 400
Povidone
Sodium starch glycollate Type A
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Carton with tablets in blisters.
Carton (pack) contents: 60 tablets (6 blisters of 10 tablets).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA0465/153/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st December 2006.

Date of first renewal: 1st of December 2011.

10 DATE OF REVISION OF THE TEXT

November 2013