

Seroquel

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg film-coated tablets
Seroquel 100 mg film-coated tablets
Seroquel 150 mg film-coated tablets
Seroquel 200 mg film-coated tablets
Seroquel 300 mg film-coated tablets
Seroquel 3-Day Starterpack (Combined pack)
Seroquel 4-Day Starterpack

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Seroquel 25 mg contains 25 mg quetiapine (as quetiapine fumarate)
Seroquel 100 mg contains 100 mg quetiapine (as quetiapine fumarate)
Seroquel 150 mg contains 150 mg quetiapine (as quetiapine fumarate)
Seroquel 200 mg contains 200 mg quetiapine (as quetiapine fumarate)
Seroquel 300 mg contains 300 mg quetiapine (as quetiapine fumarate)
Seroquel 3-Day Starterpack (Combined pack) contains 6 tablets Seroquel 25 mg and 2 tablets Seroquel 100 mg
Seroquel 4-Day Starterpack contains 6 tablets Seroquel 25 mg, 3 tablets Seroquel 100 mg and 1 tablet Seroquel 200 mg

For Excipients, see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet
Seroquel 25 mg tablets are peach coloured
Seroquel 100 mg tablets are yellow
Seroquel 150 mg tablets are pale yellow
Seroquel 200 mg tablets are white.
Seroquel 300 mg tablets are white

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of schizophrenia.
Treatment of moderate to severe manic episode. 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, 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, 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.

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.

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 Contra-indications

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 (4.5) Interactions with other medicinal products and other forms of interaction.

4.4 Special Warnings and Special Precautions for Use

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 (See Section 4.8).

Extrapyramidal symptoms

In controlled clinical trials, the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range.

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). 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 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).

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 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 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 of 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.

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. A second study did not demonstrate an additive effect at week 6. There are no combination data available beyond week 6.

4.5 Interactions with other medicinal products and other forms of interactions

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).

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 Seroquel 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 Seroquel.

The pharmacokinetics of sodium valproate and Seroquel 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 QTc interval.

4.6 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 Effect 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 reaction⁶

Metabolism and nutritional disorders

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

Nervous system disorders

Very Common: Dizziness ⁴, somnolence ², headache

Common: Syncope ⁴

Uncommon: Seizure ¹, Restless legs syndrome

Very rare: Tardive dyskinesia⁶

Cardiac disorders

Common: Tachycardia ⁴

Vascular disorders

Common: Orthostatic hypotension ⁴

Respiratory, thoracic and mediastinal disorder

Common: Rhinitis

Gastrointestinal disorders

Common: Dry mouth, constipation, dyspepsia

Hepato-biliary disorders

Rare: Jaundice ⁶

Very rare: Hepatitis ⁶

Skin and subcutaneous tissue disorders

Very rare: Angioedema ⁶, Stevens-Johnson syndrome⁶

Reproductive system and breast disorders

Rare: Priapism

General disorders and administration site conditions

Common: Mild asthenia, peripheral oedema

Rare: Neuroleptic malignant syndrome ¹

Investigations

<i>Common:</i>	Weight gain, elevations in serum transaminases (ALT, AST) ³ , decreased neutrophil count, blood glucose increased to hyperglycaemic levels ⁷
<i>Uncommon:</i>	Elevations in gamma-GT levels ³ , elevations in non-fasting serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol)

- (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 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 ≥ 126 mg/dL or a non fasting blood glucose ≥ 200 mg/dL on at least one occasion

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.

Seroquel treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ 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 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 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.

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

ATC code: N05A H04

Mechanism of action:

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁- and D₂- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel. 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 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 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-naive 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. (See Section 4.8)

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.

Lack of induction of EPS is considered a feature of atypical antipsychotics.

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. There are no combination data available beyond 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.

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 $30 \text{ ml/min/1.73m}^2$), 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 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 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 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 *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 Pre-clinical 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

<i>Core:</i>	<i>Coating:</i>
Povidone	Hypromellose
Calcium Hydrogen Phosphate Dihydrate	Macrogol 400
Microcrystalline Cellulose	Titanium Dioxide (E171)
Sodium Starch Glycolate Type A	Ferric Oxide, Yellow (E172) 25 mg, 100 mg and 150 mg tablets)
	Ferric Oxide, Red (E172) (25 mg tablets)
Lactose Monohydrate	
Magnesium Stearate	

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

Do not store above 30°C.

6.5 Nature and Contents of Container

HDPE bottle and PVC/aluminium blisters

Pack sizes

Bottles: Seroquel 150 mg:	100 tablets
Seroquel 300 mg:	60 tablets

Blisters:

<i>Tablet Strength</i>	<i>Carton (pack) contents</i>	<i>Blisters</i>	
25 mg tablets	6 tablets	1 blister of 6 tablets	
	20 tablets	2 blisters of 10 tablets	
	30 tablets	3 blisters of 10 tablets	
	50 tablets	10 blisters of 5 tablets	
	50 tablets	5 blisters of 10 tablets	
	60 tablets	6 blisters of 10 tablets	
	100 tablets	10 blisters of 10 tablets	
	100 mg, 150 mg, 200 mg and 300 mg tablets	10 tablets	1 blister of 10 tablets
		20 tablets	2 blisters of 10 tablets
		30 tablets	3 blisters of 10 tablets
50 tablets		10 blisters of 5 tablets	
50 tablets		5 blisters of 10 tablets	
60 tablets		6 blisters of 10 tablets	
90 tablets		9 blisters of 10 tablets	
100 tablets		10 blisters of 10 tablets	
120 tablets		12 blisters of 10 tablets (150 mg and 300 mg tablets only)	
180 tablets		18 blisters of 10 tablets (150 mg and 300 mg tablets only)	
	240 tablets	24 blisters of 10 tablets (150 mg and 300 mg tablets only)	
3-Day Starterpack (Combined pack)	8 tablets	1 blister containing 6 x 25 mg and 2 x 100 mg tablets	
4-Day Starterpack	10 tablets	1 blister containing 6 x 25mg, 3 x 100mg and 1 x 200mg tablets	

Not all pack sizes may be marketed.

6.6 Instructions for Use and Handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca BV
Postbus 599
2700 AN Zoetermeer
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

Seroquel 25 mg film-coated tablets	RVG 20826
Seroquel 100 mg film-coated tablets	RVG 20827
Seroquel 150 mg film-coated tablets	RVG 25602
Seroquel 200 mg film-coated tablets	RVG 20828
Seroquel 300 mg film-coated tablets	RVG 25603
Seroquel 4-Day Starterpack	RVG 25128

9. DATE OF FIRST AUTHORISATION:

27 April 1998

DATE OF LAST RENEWAL:

08 September 2004

10. DATE OF REVISION OF THE TEXT

5 March 2008

Based on Summary of Product Characteristics for The Netherlands. Please note that registration conditions differ internationally, so for prescribing information please check the Summary of Product Characteristics of your home country.