

This is the Summary of Product Characteristics for Ireland. As regulatory conditions differ from country to country, please refer to the Summary of Product Characteristics for your home country.

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg, 150 mg, 200 mg, 300 mg and 400 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Seroquel XR 50 mg contains 50 mg quetiapine (as quetiapine fumarate)

Excipient : 119 mg lactose (anhydrous) per tablet

Seroquel XR 150 mg contains 150 mg quetiapine (as quetiapine fumarate)

Excipient : 71 mg lactose (anhydrous) per tablet

Seroquel XR 200 mg contains 200 mg quetiapine (as quetiapine fumarate)

Excipient : 50 mg lactose (anhydrous) per tablet

Seroquel XR 300 mg contains 300 mg quetiapine (as quetiapine fumarate)

Excipient : 47 mg lactose (anhydrous) per tablet

Seroquel XR 400 mg contains 400 mg quetiapine (as quetiapine fumarate)

Excipient : 15 mg lactose (anhydrous) per tablet

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Seroquel XR 50 mg tablets are peach-coloured and engraved with “XR 50” on one side

Seroquel XR 150 mg tablets are white and engraved with “XR 150” on one side

Seroquel XR 200 mg tablets are yellow and engraved with “XR 200” on one side

Seroquel XR 300 mg tablets are pale yellow and engraved with “XR 300” on one side

Seroquel XR 400 mg tablets are white and engraved with “XR 400” on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Seroquel XR is indicated for the treatment of schizophrenia.

Seroquel XR is effective in preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XR.

Seroquel XR is indicated for the treatment of moderate to severe manic episodes in the framework of bipolar disorder.

Seroquel XR is indicated for the treatment of major depressive episodes in bipolar disorder.

Seroquel XR is not indicated for the prevention of recurrence of manic or depressive episodes.

4.2 Posology and method of administration

Seroquel XR should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia and moderate to severe manic episodes associated with bipolar disorder

Seroquel XR should be administered at least one hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically

justified the dose may be increased to 800 mg daily. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of depressive episodes associated with bipolar disorder

Seroquel XR should be administered at bedtime. The 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 XR 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 (see section 5.1)

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

Switching from Seroquel immediate-release tablets:

For more convenient dosing, patients who are currently being treated with divided doses of immediate release Seroquel tablets may be switched to Seroquel XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly:

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

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 XR 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 metabolized by the liver. Therefore, Seroquel XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

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 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:

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

Seizures:

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

Extrapyramidal symptoms

In placebo controlled clinical trials quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder. (see section 4.8).

Tardive Dyskinesia:

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XR 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 creatinine phosphokinase. In such an event, Seroquel XR 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 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 $<1.0 \times 10^9/L$. 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 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 Seroquel XR treatment should only occur if the physician considers that the benefits of Seroquel XR 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 section 4.8).

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 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:

Seroquel XR 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 XR should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Lactose:

Seroquel XR 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

Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, Seroquel XR should be used with caution in combination with other centrally acting medicinal products 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 XR 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 Seroquel XR treatment should only occur if the physician considers that the benefits of Seroquel XR outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4).

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

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

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

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

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

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

Caution should be exercised when quetiapine is used concomitantly with medicinal products 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 XR should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

The frequencies of adverse events are ranked according to the following: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) and very rare ($< 1/10,000$).

Blood and lymphatic system disorders

Common: Leucopenia¹

Uncommon: Eosinophilia, Thrombocytopenia

Unknown: Neutropenia¹

Immune system disorders

Uncommon: Hypersensitivity

Very rare: Anaphylactic reaction⁶

Metabolism and nutritional disorders

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

Psychiatric disorders

Common: Abnormal dreams and nightmares

Nervous system disorders

Very common: Dizziness⁴, somnolence², headache

Common: Syncope⁴
Extrapyramidal symptoms^{1,13}

Uncommon: Seizure¹, Restless legs syndrome, Dysarthria

Very rare: Tardive dyskinesia⁶

Cardiac disorders

Common: Tachycardia⁴

Eye Disorders

Common: Vision blurred

Vascular disorders

Common: Orthostatic hypotension⁴

Respiratory, thoracic and mediastinal disorder

Common: Rhinitis

Gastrointestinal disorders

Very common: Dry mouth

Common: Constipation, dyspepsia

Uncommon: Dysphagia⁸

Hepato-biliary disorders

Rare: Jaundice⁶

Very rare: Hepatitis ⁶

Skin and subcutaneous tissue disorders

Very rare: Angioedema⁶, Stevens-Johnson syndrome⁶

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 serum triglyceride levels ¹¹
Elevations in total cholesterol (predominantly LDL cholesterol) ¹²

Common: Weight gain⁹, elevations in serum transaminases (ALT, AST)³, decreased neutrophil count, blood glucose increased to hyperglycaemic levels ⁷

Uncommon: Elevations in gamma-GT levels³, 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 may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4).
- (5) Exacerbation of pre-existing diabetes has been reported in very rare cases.
- (6) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of Seroquel
- (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 quetiapine 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.
- (14) Platelets $\leq 100 \times 10^9/\text{L}$ on at least one occasion.
- (15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

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.

Quetiapine 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 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 Seroquel alone. However, survival has also been reported following acute overdoses of up to 30 grams. In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

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

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance'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 can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal 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 (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 undesirable 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 α₁ receptors, with a lower affinity at adrenergic α₂- 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-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that Seroquel XR 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:

The efficacy of Seroquel XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Seroquel immediate release-to-Seroquel XR switching study in clinically stable outpatients with schizophrenia. The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Seroquel XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

In the 6-week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, ie, who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on Seroquel immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of Seroquel XR given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XR for 16 weeks, Seroquel XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XR treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with Seroquel XR for up to 9 months (median 7 months). In particular, reports of adverse events related to EPS and weight gain did not increase with longer-term treatment with Seroquel XR.

Unlike many other antipsychotics, quetiapine does not produce sustained elevations in prolactin, which is considered a feature of atypical agents. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion, for quetiapine across the recommended dose range, and placebo.

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, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of Seroquel XR was further demonstrated with significance versus placebo in an additional 3 week study. Seroquel XR was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day Seroquel XR showed superior efficacy to placebo in reduction of MADRS total score.

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

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

5.2 Pharmacokinetic properties

Absorption:

Quetiapine is well absorbed following oral administration. Seroquel XR achieves peak quetiapine and N-desalkyl quetiapine plasma concentrations at approximately 6 hours after administration (T_{max}). Steady-state peak molar concentrations of the active metabolite N-desalkyl quetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and N-desalkyl quetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When Seroquel XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (Seroquel immediate release) administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13% lower at steady state. When Seroquel XR is compared to Seroquel immediate release, the N-desalkyl quetiapine metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the Seroquel XR C_{max} and AUC of approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that Seroquel XR is taken once daily without food.

Distribution:

Quetiapine is approximately 83% bound to plasma proteins.

Metabolism:

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. 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.

Elimination:

The elimination half lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabelled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite N-desalkyl quetiapine is <5% excreted in the urine.

Special populations

Gender:

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

Elderly:

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

Renal impairment:

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

Hepatic impairment:

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

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

Core

Cellulose, microcrystalline

Sodium citrate

Lactose monohydrate

Magnesium stearate

Hypromellose

Coating

Hypromellose

Macrogol

Titanium dioxide (E171)

Iron oxide, yellow (E172) (50, 200 and 300 mg tablets)

Iron oxide, red (E172) (50 mg tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polychlorotrifluoroethylene and polyvinylchloride with aluminium blister

<i>Tablet Strength</i>	<i>Carton (pack) contents</i>	<i>Blisters</i>
<i>50 mg, 150 mg, 200 mg, 300 mg and 400 mg tablets</i>	<i>10 tablets</i>	<i>1 blister of 10 tablets</i>
	<i>30 tablets</i>	<i>3 blisters of 10 tablets</i>
	<i>50 tablets</i>	<i>10 blisters of 5 tablets</i>
	<i>50 tablets</i>	<i>5 blisters of 10 tablets</i>
	<i>60 tablets</i>	<i>6 blisters of 10 tablets</i>
	<i>100 tablets</i>	<i>10 blisters of 10 tablets</i>
	<i>100 tablets</i>	<i>100 blisters of 1 tablet</i>

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd

600 Capability Green

Luton

LU1 3LU

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

50 mg tablets: PA 970/18/8

150 mg tablets: PA 970/18/12

200 mg tablets: PA 970/18/9

300 mg tablets: PA 970/18/10

400 mg tablets: PA 970/18/11

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

50 mg, 200 mg, 300 mg and 400 mg: 15th February 2008

150 mg: 30th January 2009

10. DATE OF REVISION OF THE TEXT

11th March 2009