Seroquel
quetiapine fumarate
Film-coated tablets

Qualitative and Quantitative Composition
25 mg tablet: round, 6 mm, peach coloured, biconvex, film-coated tablet containing quetiapine fumarate delivering a dose of 25 mg of quetiapine free base.

100 mg tablet: round, 8.5 mm, yellow coloured, biconvex, film-coated tablet containing quetiapine fumarate delivering a dose of 100 mg of quetiapine free base.

200 mg tablet: round, 11 mm, white, biconvex, film-coated tablet containing quetiapine fumarate delivering a dose of 200 mg of quetiapine free base.

300 mg tablet: capsule-shaped, 19 mm x 7.62 mm, white, film-coated tablet containing quetiapine fumarate delivering a dose of 300 mg of quetiapine free base.

For excipients see *'Pharmaceutical Particulars'*.

Therapeutic indications
Seroquel is indicated for the treatment of:
- Schizophrenia

Bipolar Disorder including:
- Manic episodes associated with bipolar disorder
- Major depressive episodes in bipolar disorder
- Preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment

Posology and Method of Administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

Seroquel can be administered with or without food.

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

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

For the treatment of manic episodes associated with bipolar disorder: Seroquel should be administered twice a day. As monotherapy or as adjunct therapy to mood stabilizers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes associated with bipolar disorder: Seroquel should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder: For prevention of recurrence of manic, depressive or mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue on therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

Elderly

As with other antipsychotics, Seroquel should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Seroquel 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose. The rate of dose titration of Seroquel 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% to 50% in elderly patients when compared to younger patients.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and adolescents

Seroquel is not indicated for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in '*Special Warnings and Precautions for Use', 'Undesirable Effects', 'Pharmacodynamic Properties' and 'Pharmacokinetic Properties'*.

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.

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 '*Interaction with other medicinal products and other forms of interaction'*).

Special Warnings and Precautions for use

As Seroquel has several indications, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Children and adolescents (10 to 17 years of age)

Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults (see '*Undesirable effects'*), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients treated with quetiapine, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see '*Undesirable effects'*).

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 addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which Seroquel is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. Meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). A population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other antidepressants.

Extrapyramidal symptoms
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see '*Undesirable effects'* and '*Pharmacodynamic Properties'*).

The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive dyskinesia
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see '*Undesirable effects'*).

Somnolence and dizziness
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see '*Undesirable effects'*). 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.

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see '*Undesirable effects'*) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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; this is more common in elderly patients than in younger patients. 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.

Sleep apnoea syndrome
Sleep apnoea syndrome has been reported in patients using quetiapine. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, quetiapine should be used with caution.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Seroquel or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see *'Undesirable Effects'*).

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see *'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 and agranulocytosis
Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) has been 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, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. 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 1.5×10^9/L) (see '*Pharmacodynamic properties'*).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Anti-cholinergic (muscarinic) effects
Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anticholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma. (See Sections Interaction with other medicinal products and other forms of interaction, Undesirable effects, Overdose, Pharmacodynamic Properties.)

Interactions

See also '*Interactions with other medicinal products and other forms of interaction'.*

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).

Weight

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see '*Undesirable effects'* and '*Pharmacodynamic properties'*).

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see '*Undesirable effects'*). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness), and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids

Increases in triglycerides, LDL and total cholesterol have been observed in clinical trials with quetiapine (see *'Undesirable Effects'*). Lipid changes should be managed as clinically appropriate.

Metabolic Risk

Given the observed changes in weight, blood glucose (see '*Hyperglycaemia*') and lipids seen in clinical studies, patients (including those with normal baseline values) may experience worsening of their metabolic risk profile, which should be managed as clinically appropriate (see also '*Undesirable effects'*).

QT Prolongation

In clinical trials and use in accordance with the prescribing information quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see '*Undesirable effects'*) and in overdose (see '*Overdose*'). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (see *'Interaction with other medicinal products and other forms of interaction'*).

Cardiomyopathy and Myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal have been reported very rarely with quetiapine treatment. SCARs commonly present as a combination of the following symptoms: extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. If signs and symptoms suggestive of these severe skin reactions appear, quetiapine should be withdrawn immediately and alternative treatment should be considered.

Withdrawal

Acute withdrawal symptoms including insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see '*Undesirable effects'*).

Misuse and abuse

Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

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 have been seen in randomised placebo controlled clinical 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 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 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.

Elderly patients with Parkinson's disease (PD)/parkinsonism
A population-based retrospective study of quetiapine for the treatment of patients with MDD, showed an increased risk of death during use of quetiapine in patients aged >65 years. This association was not present when patients with PD were removed from the analysis. Caution should be exercised if quetiapine is prescribed to elderly patients with PD.

Hepatic effects
If jaundice develops, Seroquel should be discontinued.

Dysphagia
Dysphagia (see *'Undesirable effects'*) and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see *'Undesirable effects'*). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous Thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see '*Lipids'*), gallstones, and alcohol consumption.

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

Additional information
Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see '*Undesirable effects'* and '*Pharmacodynamic properties'*). The data showed an additive effect at week 3.

Interactions 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.

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see special warnings and use).

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

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of Seroquel therapy. Co-administration of Seroquel and phenytoin (another microsomal enzyme inducer) caused a greatly increasesd clearance of quetiapine by approximately 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 '*Special warnings and special precautions for use'*).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of Seroquel and thioridazine caused increases in clearance of quetiapine by approximately 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. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy group.

Formal interaction studies with commonly used cardiovascular medicinal products 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.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

Fertility, pregnancy and lactation

The safety and efficacy of quetiapine during human pregnancy have not been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined though. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed.

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully.

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast feeding should therefore be advised to avoid breast feeding while taking quetiapine.

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

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

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with quetiapine.
The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).	
Blood and lymphatic system disorders	
Very common:	Decreased haemoglobin[23]
Common:	Leucopenia[1, 29], decreased neutrophil count, eosinophils increased[28]
Uncommon:	Thrombocytopenia, Anaemia, Platelet count decreased[14]
Rare:	Agranulocyctosis[27]
Unknown:	Neutropenia[1]
Immune system disorders	
Uncommon:	Hypersensitivity (including allergic skin reactions)
Very rare:	Anaphylactic reaction [6]
Endocrine disorders	
Common:	Hyperprolactinaemia[16], decreases in Total T_4[25], decreases in Free T_4[25], decreases in Total T_3[25], increases in TSH[25]
Uncommon:	Decreases in free T_3[25], Hypothroidism[22]
Very rare:	Inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders	
Very common:	Elevations in serum triglyceride levels[11, 31], Elevations in total cholesterol (predominantly LDL cholesterol) [12, 31], Decreases in HDL cholesterol[18, 31], Weight gain[9, 31]
Common:	Increased appetite, blood glucose levels increased to hyperglycaemic levels[7,31]
Uncommon:	Hyponatraemia[20], Diabetes Mellitus[1,5,6]
Rare:	Metabolic syndrome[30]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[21]

Rare:	Somnambulism and other related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders	
Very common:	Dizziness[4, 17], somnolence[2, 17], headache, Extrapyramidal symptoms[1, 13]
Common:	Dysarthria
Uncommon:	Seizure [1], Restless leg syndrome, Tardive dyskinesia[1,6]syncope[4, 17]
Cardiac disorders	
Common:	Tachycardia[4], Palpitations[24]
Uncommon:	QT prolongation[1, 13, 19], bradycardia[33]
Eye disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension[4, 17]
Rare:	Venous thromboembolism [1]
Unknown:	Stroke[34]
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnea [22]
Uncommon:	Rhinitis
Gastrointestinal disorders	
Very common:	Dry mouth
Common:	Constipation, dyspepsia, vomiting[26]
Uncommon:	Dysphagia [8]
Rare:	Pancreatitis[1], Intestinal obstruction/Ileus
Hepato-biliary disorders	
Common:	Elevations in serum transaminases (ALT, AST)[3], Elevations in gamma-GT levels[3]
Rare:	Jaundice[6], Hepatitis
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema[6], Stevens-Johnson syndrome[6]
Unknown:	Toxic Epidermal Necrolysis, Erythema Multiforme
	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Very rare:	Rhabdomyolysis
Renal and urinary disorders	
Uncommon:	Urinary retention
Pregnancy, puerperium and perinatal conditions	
Unknown:	Drug withdrawal syndrome neonatal [32]
Reproductive system and breast disorders	

Uncommon:	Sexual dysfunction
Rare:	Priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	
Very common:	Withdrawal (discontinuation) symptoms[1, 10]
Common:	Mild asthenia, peripheral oedema, irritability, pyrexia
Rare:	Neuroleptic malignant syndrome[1], hypothermia
Investigations	
Rare:	Elevations in blood creatine phosphokinase[15]

(1) See section '*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 quetiapine.
(3) Asymptomatic elevations (shift from normal to ≥3 x ULN at any time) 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 $alpha_1$ 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 '*Special warnings and special precautions for use'*).
(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.
(6) Calculation of frequency for these ADRs have been taken from post-marketing data only.
(7) Fasting blood glucose ≥126mg/dL (≥7.0 mmol/L) or a non fasting blood glucose ≥200mg/dL (≥11.1 mmol/L) on at least one occasion.
(8) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
(9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
(10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
(11) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.
(12) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
(13) See text below.
(14) Platelets ≤100 x 10^9/L on at least one occasion.
(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
(16) Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time.
(17) May lead to falls.
(18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
(19) Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
(20) Shift from >132 mmol/L to <132 mmol/L on at least one occasion.
(21) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (See '*Special warnings and precautions for use'* and '*Pharmacodynamic properties').*
(22) See ('*Pharmacodynamic properties'*).
(23) Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was –1.50 g/dL.

(24) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.
(25) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 X LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
(26) Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
(27) Shift in neutrophils from ≥1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment.
(28) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as ≥1 x 10^9 cells/L at any time.
(29) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤3 x 10^9 cells/L at any time.
(30) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
(31) In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (See '*Special warnings and precautions for use'*).
(32) See ('*Pregnancy and lactation'*).
(33) May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse reports of bradycardia and related events in all clinical trials with quetiapine.
(34) Based on one retrospective non-randomised epidemiological study.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported very rarely with the use of neuroleptics and are considered class effects (see '*Special warnings and special precautions for use'*).

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment.

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

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

(1) Prolactin levels (patients < 18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L.

(2) Based on shifts above clinically significant thresholds (adapted from the National Institute of Health criteria) or increases >20mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

(3) See '*Pharmacodynamic properties'*.

(4) Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

Overdose

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

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 reports of overdose of quetiapine alone resulting in death or coma. Additionally, the following events have been reported in the setting of monotherapy overdose with quetiapine: QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium, and/ or agitation.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see '*Special Warnings and Precautions for Use*': Cardiovascular).

Management of overdose

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.

Based on public literature, patients with delerium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

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.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

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

Pharmacological Properties
Pharmacodynamic properties

Pharmacotherapeutic group : Antipsychotics -: Diazepines, oxazepines and thiazepines

Therapeutic classification : N05A H04

Mechanism of action:

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2 receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Seroquel's therapeutic efficacy as an antidepressant.

Pharmacodynamic effects:

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also reverses the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of dopamine D_2 receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 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 extent to which the norquetiapine metabolite contributes to the pharmacological activity of Seroquel in humans is not known.

Clinical efficacy

Schizophrenia
The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of Seroquel of 75 to 750 mg/day, identified no difference between Seroquel and placebo in the incidence of EPS or use of concomitant anticholinergics. The long-term efficacy of Seroquel in prevention of schizophrenic relapses has not been verified in blinded clinical trials. In open label trials, in patients with schizophrenia, quetiapine was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response, suggesting some long-term efficacy.

Bipolar Disorder
In four placebo-controlled trials, evaluating doses of Seroquel up to 800 mg/day for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium,

there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

In clinical trials, Seroquel has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, Seroquel showed similar short-term efficacy.

In clinical trials, Seroquel has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. 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 in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The anti-depressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Seroquel than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Seroquel (mean duration of treatment 30 weeks). Seroquel reduced the risk of a recurrent mood (manic and depressed) event by 49 %. Seroquel was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

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). The risk of a recurrent event was reduced by 70%. Seroquel was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

Clinical safety

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). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia,

restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short term, fixed dose (50mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

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 all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 X 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.3% in placebo-treated patients. The incidence of shifts to >0.5 - <1.0 X 10^9/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 X 10^9/L was 2.9% and to <0.5 X 10^9/L was 0.21% in patients treated with quetiapine.

In fixed dose short-term placebo-controlled clinical trials, quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short-term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4: 3.4% for quetiapine versus 0.6% for placebo; free T_4: 0.7% for quetiapine versus 0.1% for placebo; total T_3: 0.54% for quetiapine versus 0.0% for placebo and free T_3: 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. In short-term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. In eight patients, where TBG was measured, levels of TBG were unchanged.

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of Seroquel (200-800 mg/day) versus risperidone (2-8 mg) in patients with schizophrenia or schizoaffective disorder, the percentage of

patients with increased lens opacity grade was not higher in Seroquel (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Children and adolescents (10 to 17 years of age)
The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n=284 patients, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Seroquel 400 mg/day and –6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Seroquel 400 mg/day and –9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

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

A 26-week open-label extension to the acute trails (n=380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, weight gain, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see *'Special Warnings and Precautions for Use' and 'Undesirable Effects')*.

Extrapyramidal Symptoms
In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained ≥7% of their body weight. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

Suicide/Suicidal thoughts or Clinical worsening

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

Pharmacokinetic properties

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

Clinical trials have demonstrated that Seroquel is effective when given twice a day. This is further supported by the data from a positron emission tomography (PET) study which identified that for quetiapine, $5HT_2$ and dopamine D_2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine.

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

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

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

Quetiapine is extensively metabolised, 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 plasma clearance of quetiapine is reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis). Since quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients (see *'Dosage and method of administration'*).

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

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean t_{max} was unchanged.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration

of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C_{max} in children was at the higher end of the range observed in adults. The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

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 T_3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts. (For cataracts/lens opacities, see '*Pharmacodynamic properties'*). Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

Pharmaceutical Particulars

List of excipients

Core	***Coating***
Povidone (PhEur) Calcium Hydrogen Phosphate Dihydrate (PhEur) Microcrystalline Cellulose (PhEur) Sodium Starch Glycollate Type A (PhEur) Lactose Monohydrate (PhEur) Magnesium Stearate (PhEur)	Hypromellose (PhEur) Macrogol 400 (PhEur) Titanium Dioxide (PhEur, E171) Ferric Oxide, Yellow (PhFr, E172) Ferric Oxide, Red (Ph. Eur, E172)

Special precautions for storage
Do not store above 30°C.

Shelf life
Please refer to expiry date on the outer carton.

Pack size
Please refer to the outer carton for pack size.

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