Seroquel

quetiapine fumarate

Film-coated tablets

P025984

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

Treatment of schizophrenia.

Treatment of manic episodes associated with bipolar disorder.

Posology and Method of Administration

Adults

For the treatment of schizophrenia:

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

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 daily, with or without food.

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.

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, which is likely to be lower than that in younger patients.

Children and adolescents

Seroquel is not indicated for use in children and adolescents below 18 years of age. Data from placebo-controlled clinical trials are set forth in sections *'Special Warnings and Precautions for Use'*, *'Undesirable Effects'*, *'Pharmacodynamic Properties'* and *'Pharmacokinetic Properties'*.

Renal and hepatic impairment

The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment.

Patients with renal or hepatic impairment 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.

Contraindications

Seroquel is contraindicated in patients who are hypersensitive to any component of this product.

Use in children and adolescents (10 to 17 years of age)

Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials with Seroquel in children and adolescent patients, the same special warnings and special precautions for use that appear above for adults should be considered for paediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate (see *'Undesirable Effects'*).

Long-term safety data including growth, maturation, and behavioural development, beyond 26 weeks of treatment with Seroquel, is not available for children and adolescents (10 to 17 years of age).

Elderly Patients with Dementia

Seroquel is not approved for the treatment of patients with dementia-related psychosis. In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. 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.

Interactions with other medicaments 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 when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval (see *'Special Warnings and Precautions for Use'*).

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

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN) and Seroquel (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

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.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, 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, and hence, in each patient, consideration for a higher dose of Seroquel, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of Seroquel is 600 to 800 mg/day depending on indication (see *'Posology and Method of Administration'*). Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of Seroquel with another microsomal enzyme inducer, phenytoin, also caused increases in clearance of quetiapine. Increased doses of Seroquel may be required to maintain control of psychotic symptoms in patients co-administered Seroquel and phenytoin, or other hepatic enzyme inducers (eg, barbiturates, rifampicin). The dose of Seroquel may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (eg, sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The

Special Warnings and Precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression 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.

Other psychiatric conditions for which quetiapine 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. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4400 children and adolescents and 77000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine (see *'Pharmacodynamic Properties'*).

Neutropenia

Severe neutropenia (<0.5 X 10^9/L) has been uncommonly reported in Seroquel clinical trials. Most cases of severe neutropenia have occurred within the first two months of starting therapy with Seroquel. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L) (see *'Undesirable Effects'*).

Increases in blood glucose and hyperglycaemia

Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (see *'Undesirable Effects'*).

Lipids

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

Concomitant illness

Seroquel should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Seroquel may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients.

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

QT Prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with 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_c interval, and concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, 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'*).

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. However, caution is recommended when Seroquel is co-administered with potent CYP3A4 inhibitors (such as azole antifungals and macrolide antibiotics, and protease inhibitors) (see also *'Special Warnings* and *Precautions for Use'* and *'Pharmacokinetics'*).

Pregnancy and lactation

The safety and efficacy of Seroquel during human pregnancy have not been established (see *'Pre-clinical safety data:* Reproduction studies' for animal reproductive toxicology data). Therefore, Seroquel should only be used during pregnancy if the benefits justify the potential risks.

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.

Effect on ability to drive and use machines

Because Seroquel may cause somnolence, patients should be cautioned about operating hazardous machines, including motor vehicles.

Undesirable effects

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

As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Seroquel.

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

Table 1

Frequency	System Organ Class	Event
Very common (≥10%)	Gastrointestinal disorders	Dry mouth
	General disorders and Administration site conditions	Withdrawal (discontinuation) symptoms[1,10]
	Investigations	Elevations in serum triglyceride levels[11]
		Elevations in total Cholesterol (predominantly LDL cholesterol)[12]
		Weight gain[3]
	Nervous system disorders	Dizziness[1,5,17]
		Somnolence[2,17]
Common (≥1% - <10%)	Blood and lymphatic system disorders	Leukopenia
	Cardiac disorders	Tachycardia[1,5]
	Eye Disorders	Vision blurred
	Gastrointestinal disorders	Constipation
		Dyspepsia
	General disorders and administration site conditions	Mild asthenia
		Peripheral edema
		Irritability
	Investigations	Elevations in serum transaminases (ALT_1AST)[4]
		Neutrophil count decreased[7]
		Blood glucose increased to hyperglycaemic level[8]
		Elevations in serum prolactin[15]
	Nervous system disorders	Syncope[1,5,17]
		Extrapyramidal symptoms[1,16]
	Metabolism and nutrition disorders	Increased appetite
	Respiratory, thoracic, and mediastinal disorders	Rhinitis
	Vascular disorders	Orthostatic hypotension[1,5,17]
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥0.1% - < 1%)	Blood and lymphatic system disorders	Eosinophilia
	Gastrointestinal disorders	Dysphagia[9]
	Immune system disorders	Hypersensitivity
	Investigations	Elevations in gamma-GT levels[4]

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

Tardive Dyskinesia
As with other antipsychotics, there is a potential for Seroquel to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel should be considered.

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Seroquel (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.

Acute withdrawal reactions
Acute withdrawal symptoms including insomnia, nausea and vomiting have been described after abrupt cessation of antipsychotic drugs including quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal over a period of at least one to two weeks is advisable.

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

Concomitant use of Seroquel with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of Seroquel may need to be considered if Seroquel is used concomitantly with a hepatic enzyme inducer.

During concomitant administration of drugs which are potent CYP3A4 inhibitors (such as azole antifungals and macrolide antibiotics, and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials (see also *'Pharmacokinetics'*). As a consequence of this, lower doses of Seroquel should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

		Platelet count decreased[14]
	Nervous system disorders	Dysarthria
		Seizure[1]
		Restless legs syndrome
Rare (≥0.01% - < 0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome[1]
	Investigations	Elevations in blood creatine phosphokinase[13]
	Reproductive system and breast disorders	Priapism
		Galactorrhoea
Very rare (<0.01%)	Immune system disorders	Anaphylactic reaction[6]

[1] See section 'Special Warnings and Precautions for Use'.

[2] Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of Seroquel.

[3] Based on ≥7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

[4] Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered Seroquel. These elevations were usually reversible on continued Seroquel treatment.

[5] As with other antipsychotics with alpha1adrenergic blocking activity, Seroquel may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.

[6] The inclusion of anaphylactic reaction is based on post-marketing reports.

[7] In all placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count < 1.5 X 10^9/L, was 1.72% in patients treated with Seroquel compared to 0.73% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count <1.0 x 10^9/L, among patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <0.5 X 10^9/L was 0.21% in patients treated with Seroquel and 0% in placebo treated patients and the incidence ≥0.5 - <1.0 X 10^9/L was 0.75% in patients treated with Seroquel and 0.11% in placebo-treated patients.

[8] Fasting blood glucose ≥126mg/dL or a non fasting blood glucose ≥200mg/dL on at least one occasion.

[9] An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

[10] In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (eg insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolved after 1 week post-discontinuation.

[11] Triglycerides ≥200 mg/dL (patients ≥18 years of age) or ≥150 mg/dL (patients <18 years of age) on at least one occasion.
[12] Cholesterol ≥240 mg/dL (patients ≥18 years of age) or ≥200 mg/dL (patients <18 years of age) on at least one occasion.
[13] Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
[14] Platelets ≤100 x 10^9/L on at least one occasion.
[15] Prolactin levels (patients ≥18 years of age): >20 µg/L males; >30 µg/L females at any time.
[16] See text below
[17] May lead to falls

Extrapyramidal Symptoms
The following clinical trials (monotherapy and combination therapy) included treatment with Seroquel.

In short-term, placebo-controlled clinical trials of adult patients with schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for Seroquel and 8.0% for placebo; bipolar mania: 11.2% for Seroquel and 11.4% for placebo). In long-term studies of schizophrenia and bipolar disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between Seroquel and placebo.

Thyroid Levels
Seroquel treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first two to four weeks of Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that Seroquel causes clinically relevant hypothyroidism.

As with other antipsychotics, Seroquel may cause prolongation of the QTc interval, but in clinical trials, this was not associated with a persistent increase (see *'Special Warnings and Precautions for Use'*).

Acute withdrawal reactions have been reported (see *'Special Warnings and Precautions for Use'*).

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.

Table 2 Undesirable effects in children and adolescents

Frequency	System Organ Class	Event
Very common (≥10%)	Metabolism and nutrition disorders	Increased appetite
	Investigations	Elevations in serum prolactin[1]
		Increases in blood pressure[2]
	Nervous system disorders	Extrapyramidal symptoms[3]

[1] Prolactin levels (patients <18 years of age): >20 µg/L males; >26 µg/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 Institutes of Health criteria) or increases >20 mmHg 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 text below

Weight Gain in Children and Adolescents
In short-term clinical trials in paediatric patients (10-17 years of age), mean weight increase for patients treated with Seroquel was 2 kg and 17% gained ≥7 % of their body weight. After 26 weeks of treatment the mean weight increase for patients treated with Seroquel was 4.4 kg and 45% of the patients gained ≥7 % of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change: 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

Extrapyramidal Symptoms in Children and Adolescent Population:
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 (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) was generally low and 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.

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. 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'*).

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 in schizophrenia and mania 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. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

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/1.73m²) 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, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients (see *'Posology 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

Overdose

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone.

In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma.

In post marketing experience there were cases reported of QT prolongation with overdose.

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'*: Concomitant Illness).

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

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patient airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

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

Pharmacological Properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics
Therapeutic classification: NO5A 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 dopamine D_2 receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic $alpha_1$ receptors, with a lower affinity at adrenergic $alpha_2$ and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effects:

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also 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.

The results of animal studies predictive of EPS liability revealed that quetiapine causes only weak catalepsy at effective dopamine D_2 receptor blocking doses, that quetiapine causes selective reduction in the firing of mesolimbic A10 dopaminergic neurones versus the A9 nigrostriatal neurones involved in motor function, and that quetiapine exhibits minimal dystonic liability in neuroleptic-sensitised monkeys. In pre-clinical tests predictive of EPS, quetiapine is unlike standard 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 results of these tests predict that Seroquel should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia.

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.

Children and adolescents (10 to 17 years of age)

At steady-state the pharmacokinetics of the parent compound in children and adolescents (10-17 years of age) were similar to adults, while AUC and C_{max} of the active metabolite, norquetiapine, were higher in children and adolescents than in adults, 45% and 31%, respectively. However, when adjusted for weight AUC and C_{max} of the parent compound in children and adolescents were lower than in adults, 41% and 39% respectively, while the pharmacokinetics of the metabolite, norquetiapine, was similar.

Pre-clinical safety data

Acute toxicity studies

Quetiapine has low acute toxicity. Findings in mice and rats after oral (500 mg/kg) or intraperitoneal (100 mg/kg) dosing were typical of an effective neuroleptic agent and included decreased motor activity, ptosis, loss of righting reflex, fluid around the mouth and convulsions.

Repeat-dose toxicity studies

In multiple-dose studies in rats, dogs and monkeys, anticipated central nervous system effects of an antipsychotic drug were observed with quetiapine (eg, sedation at lower doses and tremor, convulsions or prostration at higher exposures).

Hyperprolactinaemia, induced through the dopamine D_2 receptor antagonist activity of quetiapine or its metabolites, varied between species but was most marked in the rat, and a range of effects consequent to this were seen in the 12-month study, including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females.

Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey.

Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.

Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects.

Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/kg/day, nor in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man.

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies.

Carcinogenicity studies

In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia.

In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Reproduction studies

Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.

Quetiapine had no teratogenic effects.

Mutagenicity studies

Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen.

Clinical efficacy:
The results of three placebo-controlled clinical trials, 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 concomitant use of anticholinergics.

In four controlled trials, evaluating doses of Seroquel up to 800 mg 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.

Suicide/suicidal thoughts or clinical worsening:
In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events was 0.9% for both quetiapine (61/6270) and for placebo (27/3047).

In these trials of patients with schizophrenia the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥25 years of age, and 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age.

In these trials of patients with bipolar mania the incidence of suicide related events was 0% for both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo (6/503) in patients ≥25 years of age, and 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

In these trials of patients with bipolar depression the incidence of suicide related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24 and 1.8% for both quetiapine (19/1616) and placebo (11/622) in patients ≥25 years of age. There have been no trials conducted in patients <18 years of age with bipolar depression (see *'Special Warnings and Precautions for Use'*).

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) and a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17). Treatment with Seroquel was initiated at 50 mg/day and on day

Pharmaceutical Particulars

List of excipients

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

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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