

Seroquel XR

quetiapine fumarate

Extended-release tablets

P022480



Qualitative and Quantitative Composition

50 mg XR, prolonged-release tablet: Each tablet contains quetiapine fumarate delivering a dose of 50 mg of quetiapine free base.

200 mg XR, prolonged-release tablet: Each tablet contains quetiapine fumarate delivering a dose of 200 mg of quetiapine free base.

300 mg XR, prolonged-release tablet: Each tablet contains quetiapine fumarate delivering a dose of 300 mg of quetiapine free base.

400 mg XR, prolonged-release tablet: Each tablet contains quetiapine fumarate delivering a dose of 400 mg of quetiapine free base.

For Excipients, see 'Pharmaceutical Particulars'.

Pharmaceutical form

50 mg capsule-shaped, film-coated, 16.24 mm x 6.52 mm, prolonged-release tablet, peach coloured

200 mg capsule-shaped, film-coated, 17.22 mm x 6.65 mm, prolonged-release, tablet, yellow coloured

300 mg capsule-shaped, film-coated, 19 mm x 7.62 mm, prolonged-release tablet, pale yellow coloured

400 mg capsule-shaped, film-coated, 19 mm x 7.62 mm prolonged-release tablet, white coloured

Therapeutic indications

Seroquel XR is indicated for the treatment of schizophrenia

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

Posology and method of administration

Seroquel XR should be administered once daily, without food (at least one hour before a meal). The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia

The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically justified the dose may be increased to 800 mg daily. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

Switching from Seroquel immediate-release tablets:

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

Elderly:

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

concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of Seroquel XR 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.

Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, Seroquel XR should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was 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.

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the 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 XR, depending on clinical response, should be considered. The safety of doses above 800 mg/day has not been established in the clinical trials.

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 quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of Seroquel XR may be required to maintain control of psychotic symptoms in patients co-administered Seroquel XR and phenytoin, and other hepatic enzyme inducers (eg, barbiturates, rifampicin etc). The dose of Seroquel XR 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 were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. 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). 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. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of Seroquel XR should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors).

depending on the clinical response and tolerability of the individual patient.

Children and Adolescents:

The safety and efficacy of Seroquel XR have not been evaluated in children and adolescents.

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

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

Contraindications

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

Special warnings and special precautions for use

Neutropenia:
Severe neutropenia ($<0.5 \times 10^9/L$) 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 $<1.0 \times 10^9/L$. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed $1.5 \times 10^9/L$). (See section '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 section 'Undesirable Effects').

Concomitant Illness:

Seroquel XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period.

Seizures:

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

Tardive Dyskinesia:

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XR should be considered.

Neuroleptic Malignant Syndrome:

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 'Undesirable Effects'). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Seroquel XR should be discontinued and appropriate medical treatment given.

Withdrawal:

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

Elderly patients with dementia:

Pregnancy and lactation

The safety and efficacy of quetiapine during human pregnancy have not been established. Therefore, Seroquel XR 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 XR.

Effects on ability to drive and use machines

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

The incidences of ADRs associated with quetiapine therapy, are tabulated below (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

Table 1 Undesirable effects

Frequency	System Organ Class	Event	
Very Common ($\geq 10\%$)	Gastrointestinal disorders	Dry mouth	
	Nervous system disorders	Dizziness ^{1,5} Somnolence ²	
Common ($\geq 1\% - <10\%$)	Blood and lymphatic system disorders	Leukopenia	
	Cardiac disorders	Tachycardia ^{1,5}	
	Gastrointestinal disorders	Constipation Dyspepsia	
	General disorders and administration site conditions	Mild asthenia Peripheral edema Weight gain ³	
	Investigations	Elevations in serum transaminases (ALT, AST) ⁴ Neutrophil count decreased ⁷ Blood glucose increased to hyperglycaemic level ⁸	
	Nervous system disorders	Syncope ^{1,5}	
	Respiratory, thoracic, and mediastinal disorders	Rhinitis	
	Vascular disorders	Orthostatic hypotension ^{1,5}	
	Uncommon ($\geq 0.1\% - <1\%$)	Blood and lymphatic system disorders	Eosinophilia
		Immune system disorders	Hypersensitivity Elevations in gamma-GT levels ⁴ Elevations in non-fasting serum triglyceride levels Elevations in total cholesterol (predominantly LDL cholesterol)
Investigations		Seizure ¹ Restless legs syndrome	
Nervous system disorders		Neuroleptic malignant syndrome ¹ Priapism	
Rare ($0.01\% - <0.1\%$)	General disorders and administration site conditions	anaphylactic reaction ⁶	
Very rare ($<0.01\%$)	Reproductive system and breast disorders		
	Immune system disorders		

Elderly patients with dementia:

Seroquel XR 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 quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Interactions:

See also 'Interactions with other medicaments and other forms of interaction' section.

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

During concomitant administration of drugs, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors), plasma

- 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 Occurs predominantly during the early weeks of treatment.
- 4 Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
- 5 As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine 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 $\geq 1.5 \times 10^9/L$, the incidence of at least one occurrence of neutrophil count $< 1.5 \times 10^9/L$, was 1.72% in patients treated with Seroquel compared to 0.73% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count $< 1.0 \times 10^9/L$, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9/L$, the incidence of at least one occurrence of neutrophil count $< 0.5 \times 10^9/L$ was 0.21% in patients treated with Seroquel and 0% in placebo treated patients and the incidence $\geq 0.5 - < 1.0 \times 10^9/L$ was 0.75% in patients treated with Seroquel and 0.11% in placebo-treated patients.
- 8 Fasting blood glucose $\geq 126\text{mg/dL}$ or a non fasting blood glucose $\geq 200\text{mg/dL}$ on at least one occasion.

In three-arm, short-term placebo-controlled clinical trials of Seroquel XR for schizophrenia, the aggregate incidence of EPS adverse events was 7.5% for Seroquel XR, 7.7% for Seroquel IR and 4.7% for placebo and without evidence of dose response. The incidence rates of the individual EPS adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness and muscle rigidity) were generally low and did not exceed 3% in any treatment group.

In short-term, placebo-controlled clinical trials of Seroquel IR for bipolar mania the aggregate incidence of EPS events was no different than placebo (Seroquel IR 15.7%, placebo 15.2%). In two short-term studies in bipolar depression the aggregate incidence of EPS from the combined data was 11.8% for Seroquel IR compared to 5.5% for placebo. In these bipolar depression studies, the incidence rates of the individual EPS adverse events were generally low and did not exceed 4% in any treatment group.

Quetiapine 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 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. 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 quetiapine causes clinically relevant hypothyroidism.

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.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 'Special warnings and special 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 patent 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

ATC code: N05A H04

Mechanism of action:

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin ($5HT_2$) 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, N-desalkyl quetiapine

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

There are no clinically relevant differences in the observed apparent oral clearance (CL/F) and exposure of quetiapine between subjects with schizophrenia and bipolar disorder.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²) but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite N-desalkyl quetiapine is <5% excreted in the urine.

Metabolism:

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

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of Seroquel XR with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the Seroquel XR C_{max} and AUC of 44% to 52% and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. This increase in exposure is not clinically significant.

Preclinical 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

liability of Seroquel. In pre-clinical studies, quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 and serotonin 5HT_{1A} receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effects:

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also reverses the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of dopamine D₂ receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike standard antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D₂ receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D₂ receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that quetiapine should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia.

The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of Seroquel in humans is not known.

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

Clinical efficacy:

Schizophrenia

The efficacy of Seroquel XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Seroquel IR-to-Seroquel XR switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Seroquel XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

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

In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XR for 16 weeks, Seroquel XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XR treatment group compared to 68.2% for placebo. The mean dose was 669 mg.

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 D₂ 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.

Pharmaceutical particulars

List of excipients

Core

Microcrystalline cellulose (Ph.Eur)
Sodium citrate (Ph.Eur)
Lactose monohydrate (Ph.Eur)
Magnesium stearate (Ph.Eur)
Hydroxypropyl methylcellulose (hypromellose) (Ph.Eur)

Coating

Hydroxypropyl methylcellulose (hypromellose) (Ph.Eur)
Polyethylene glycol 400 (Macrogol) (Ph.Eur)
Titanium dioxide (E171)
Red iron oxide (E172) (50 mg tablets)
Yellow iron oxide (E172) (50, 200 and 300 mg tablets)

Incompatibilities

mean dose was 669 mg.

Bipolar Mania

In clinical trials, quetiapine (Seroquel IR) 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 quetiapine in responders, was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

Pharmacokinetic properties

General:

Quetiapine is well absorbed and extensively metabolised following oral administration. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite N-desalkyl quetiapine are 35% of that observed for quetiapine.

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

Seroquel XR achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}). Seroquel XR displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for Seroquel XR administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate (Seroquel IR) administered twice daily. The elimination half lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours, respectively.

Incompatibilities

None known.

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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