

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

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

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

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.

Special Warnings and 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 '*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*').

Cardiovascular disease

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.

In clinical trials, quetiapine was not associated with a persistent increase in QT_c intervals. However, as with other antipsychotics, caution should be exercised when quetiapine is prescribed with drugs known to prolong the QT_c interval, especially in the elderly.

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 nausea, vomiting and insomnia have very rarely been described after abrupt cessation of antipsychotic drugs. 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 is advisable.

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

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.

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.

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 750 mg/day for the treatment of schizophrenia and 800 mg/day for the treatment of manic episodes associated with bipolar disorder. 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 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 section on *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).

| Frequency | System Organ Class | Event |
|-----------------------------------|--|---|
| Very common (≥10%) | Nervous system disorders | Dizziness ^{1,5} |
| | | Somnolence ² |
| Common (≥1% - <10%) | Blood and lymphatic system disorders | Leucopenia |
| | Cardiac disorders | Tachycardia ^{1,5} |
| | Gastrointestinal disorders | Dry Mouth |
| | | Constipation |
| | | Dyspepsia |
| | General disorders and administration site conditions | Mild asthenia Peripheral edema |
| | Investigations | Weight gain ³ |
| | | Elevations in serum transaminases (ALT ₁ 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 (≥0.1% - < 1%) | Blood and lymphatic system disorders | Eosinophilia |
| | Immune system disorders | Hypersensitivity |
| | Investigations | Elevations in gamma-GT levels ⁴ |
| | | Elevations in non-fasting serum triglyceride levels |
| | | Elevations in total cholesterol (predominantly LDL cholesterol) |
| | Nervous system disorders | Seizure ¹ |
| Restless legs syndrome | | |

| | | |
|---------------------------------|--|---|
| Rare (0.01% - < 0.1%) | General disorders and administration site conditions | Neuroleptic malignant syndrome ¹ |
| | Reproductive system and breast disorders | Priapism |
| 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 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 Seroquel. These elevations were usually reversible on continued Seroquel treatment.

⁵ As with other antipsychotics with alpha1 adrenergic 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 $\geq 1.5 \times 10^9/L$, 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.

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.

Hyperglycaemia or exacerbation of pre-existing diabetes have been reported in very rare cases during quetiapine treatment.

As with other antipsychotics, Seroquel may be associated with weight gain, predominantly during the early weeks of treatment.

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*').

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 postmarketing 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 '*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, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to dopamine D₂ receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic alpha₁ receptors, with a lower affinity at adrenergic alpha₂ 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.

The results of animal studies predictive of EPS liability revealed that quetiapine causes only weak catalepsy at effective dopamine D₂ 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 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-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.

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

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.

Seroquel does not produce sustained elevations in prolactin. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion between Seroquel, across the recommended dose range, and placebo.

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.

Pharmacokinetic properties

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

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, 5HT₂ and dopamine D₂ receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

The 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.

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 N-desalkyl quetiapine 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 '*Dosage 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.

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

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 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

| <i>Core</i> | <i>Coating</i> |
|--|-----------------------------------|
| 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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