SEROQUEL®

quetiapine fumarate

Film-coated tablets

Qualitative and quantitative composition

SEROQUEL 25 mg contains 25 mg quetiapine (as quetiapine fumarate).
SEROQUEL 100 mg contains 100 mg quetiapine (as quetiapine fumarate).
SEROQUEL 200 mg contains 200 mg quetiapine (as quetiapine fumarate).
SEROQUEL 300 mg contains 300 mg quetiapine (as quetiapine fumarate).

For excipients, see *List of expicients*.

Pharmaceutical form

Film-coated tablet.
SEROQUEL 25 mg tablets are peach coloured, round biconvex and engraved with SEROQUEL 25 on one side.
SEROQUEL 100 mg tablets are yellow, round biconvex and engraved with SEROQUEL 100 on one side.
SEROQUEL 200 mg tablets are white, round biconvex and engraved with SEROQUEL 200 on one side.
SEROQUEL 300 mg tablets are white, capsule-shaped and engraved with SEROQUEL on one side and 300 on the other side.

Therapeutic indications

Treatment of schizophrenia
Treatment of manic episodes associated with bipolar disorder
Treatment of depressive episodes associated with bipolar disorder

Posology and method of administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition. SEROQUEL can be administered with or without food.

Adults

For the treatment of schizophrenia

SEROQUEL should be administered twice daily. 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. 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

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mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by day 6 should be in increments of no greater than 200 mg per day.

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

For the treatment of depressive episodes associated with bipolar disorder
SEROQUEL should be administered once daily at bedtime. SEROQUEL should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). SEROQUEL can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with SEROQUEL at 300 mg and 600 mg; however no additional benefit was seen in the 600 mg group (see *Undesirable effects* and *Clinical efficacy*)

Elderly
As with other antipsychotics, SEROQUEL should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on SEROQUEL 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose. The rate of dose titration of SEROQUEL may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30-50% in elderly subjects when compared to younger patients.

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

Children and adolescents
The safety and efficacy of SEROQUEL 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 metabolised by the liver. Therefore, SEROQUEL should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25-50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

Contraindications
Hypersensitivity to the active substance or to any of the excipients of this product.
Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is

contraindicated (see also *Interactions with other medicinal products and other forms of interaction*).

Special warnings and precautions for use

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

Suicide/suicidal thoughts or clinical worsening

Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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

Other psychiatric conditions for which 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 episodes. The same precautions observed when treating patients with major depressive episodes 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. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

Extrapyramidal symptoms

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

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

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

Somnolence and dizziness
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see *Undesirable effects*). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

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

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

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

Cardiovascular

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

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

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

Neutropenia and agranulocytosis
Severe neutropenia (neutrophil count <0.5 x10^9/L) without infection has been uncommonly reported in short term placebo controlled monotherapy clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate.

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 *Pharmacodynamic properties*).

Interactions
(See also *Interactions with other medicinal products and other forms of interaction*).
Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

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

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

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

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

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

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are potentially life threatening adverse drug reactions that have been reported during quetiapine exposure. SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

Withdrawal

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

Misuse and abuse

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

Elderly patients with dementia

Quetiapine is not approved for the treatment of dementia-related psychosis.

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

Dysphagia

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

Venous thromboembolism (VTE)

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

Constipation and intestinal obstruction

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

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

Concomitant illness
Quetiapine 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.

In patients who have a history of or are at risk for sleep apnoea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited;

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

Interactions with other medicinal products and other forms of interaction
Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for the cytochrome P450 mediated metabolism of quetiapine.

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

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

Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see *Special warnings and precautions for use*).

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

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

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

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

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Caution should be exercised treating patients receiving other medications having anticholinergic (muscarinic) effects (see Section *Special warnings and special precautions for Use)*.

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

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

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

Pregnancy and lactation

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

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

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

Effect 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, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

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

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100, rare (≥1/10,000, <1/1000) and very rare (<1/10,000).	
Blood and lymphatic system disorders	
Very common	Decreased haemoglobin[23]
Common:	Leucopenia [1, 29],decreased neutrophil count, eosinophils increased[28]
Uncommon:	Thrombocytopenia, anaemia, platelet count decreased[14]
Rare:	Agranulocytosis[27]
Unknown:	Neutropenia [1]
Immune system disorders	
Uncommon:	Hypersensitivity (including allergic skin reactions)
Very rare:	Anaphylactic reaction[6]
Endocrine disorders	
Common:	Hyperprolactinaemia[16], decreases in total T_4 [25], decreases in free T_4 [25], decreases in total T_3 [25], increases in TSH [25]
Uncommon:	Decreases in free T_3 [25], hypothyroidism[22]
Very rare:	Inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders	
Very common:	Elevations in serum triglyceride levels [11,31] Elevations in total cholesterol (predominantly LDL cholesterol) [12,31] Decreases in HDL cholesterol [18,31], weight gain [9,31]
Common:	Increased appetite, blood glucose increased to hyperglycaemic levels [7, 31]

Uncommon:	Hyponatraemia [20], diabetes mellitus [1,5,6]
Rare:	Metabolic syndrome[30]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares, suicidal ideation and suicidal behaviour[21]
Rare:	Somnambulism and related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders	
Very common:	Dizziness [4, 17], somnolence [2,17], headache, extrapyramidal symptoms[1, 22]
Common:	dysarthria
Uncommon:	Seizure [1], restless legs syndrome, tardive dyskinesia [1, 6] syncope [4,17],
Cardiac disorders	
Common:	Tachycardia [4], palpitations[24]
Uncommon:	QT prolongation [1,13, 19], bradycardia[33]
Eye Disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension [4,17]
Rare:	Venous thromboembolism[1]
Respiratory, thoracic and mediastinal disorder	
Common:	dyspnoea [24]
Uncommon:	Rhinitis
Gastrointestinal disorders	
Very common:	Dry mouth
Common:	Constipation, dyspepsia, vomiting[26]
Uncommon:	Dysphagia[8]
Rare:	Pancreatitis[1] Intestinal obstruction/Ileus
Hepato-biliary disorders	
Common:	Elevations in ALT Elevations in gamma-GT levels[3]
Uncommon:	Elevations in AST
Rare:	Jaundice[6], hepatitis (with or without jaundice)
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema[6], Stevens-Johnson syndrome[6]
Unknown:	Toxic Epidermal Necrolysis, erythema multiforme (EM) , Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Very rare:	Rhabdomyolysis
Pregnancy, puerperium and perinatal conditions	
Unknown:	Drug withdrawal syndrome neonatal[32]
Reproductive system and breast disorders	
Uncommon:	Sexual dysfunction
Rare:	Priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	
Very common:	Withdrawal (discontinuation) symptoms [1,10]
Common:	Mild asthenia, peripheral oedema, irritability, pyrexia
Rare:	Neuroleptic malignant syndrome [1], hypothermia
Renal and urinary disorders	
Uncommon:	Urinary retention
Investigations	

Rare: Elevations in blood creatine phosphokinase[15]

1. See *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 quetiapine.
3. Asymptomatic elevations (shift from normal to >3 X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
4. As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see *Special warnings and precautions for use*).
5. Exacerbation of pre-existing diabetes has been reported in very rare cases.
6. Calculation of frequency for these ADR's have been taken from postmarketing data only.
7. Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L) or non-fasting blood glucose ≥200 mg/dL (≥11.1 mmol/L) on at least one occasion.
8. An increase in the rate of dysphagia with quetiapine vs placebo was only observed in the clinical trials in bipolar depression.
9. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
10. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
11. Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.
12. Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
13. See text below
14. Platelets ≤100 x 10^9/L on at least one occasion
15. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
16. Prolactin levels (patients>18 years of age): >20 μg/L (>869.56 pmol/L) males; >30 μg/L (>1304.34 pmol/L) females at any time
17. May lead to falls
18. HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
19. Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
20. Shift from >132 mmol/L to ≤132 mmol/L on at least one occasion.

21. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see *Special warnings and precautions for use* and *Undesirable effects*).
22. *See Pharmacodynamic properties.*
23. Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in hemoglobin at any time was -1.50 g/dL.
24. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
25. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.
26. Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
27. Shift in neutrophils from ≥1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment.
28. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as >1 x 10^9 cells/L at any time.
29. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤3 x 10^9 cells/L at any time.
30. Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
31. In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see *Special warnings and precautions for use*).
32. See *Pregnancy and lactation.*
33. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse reports of bradycardia and related events in all clinical trials with quetiapine.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Overdose

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

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams. In postmarketing experience, there have been reports of overdose of quetiapine alone resulting in death or coma. Additionally, the following events have been reported in the setting of monotherapy overdose with quetiapine: QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium, and/or agitation.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see *Special warnings and precautions for use*, Cardiovascular).

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

In this context, published reports in the setting of anti-cholinergic symptoms describe a reversal of severe CNS effects, including coma and delirium, with administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

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

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

Pharmacological properties
Pharmacotherapeutic group: Antipsychotics.
ATC code: N05A H04

Pharmacodynamic properties
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 quetiapine compared to typical antispychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to SEROQUEL's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes, which may explain anti-cholinergic (muscarinic effects).

Pharmacodynamic effects

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

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Seroquel in humans is not known.

Clinical efficacy

Schizophrenia

The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of SEROQUEL of 75 to 750 mg/day, identified no difference between SEROQUEL and placebo in the incidence of EPS or use of concomitant anticholinergics.

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.

Bipolar mania

In four placebo-controlled clinical trials, evaluating doses of SEROQUEL up to 800 mg/day for the treatment of moderate to severe manic episodes, two each in monotherapy and as combination therapy to lithium or divalproex, 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 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.

Bipolar depression

In 4 clinical trials with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, SEROQUEL 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg SEROQUEL IR and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on SEROQUEL 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating SEROQUEL in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with SEROQUEL was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). SEROQUEL was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

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

Clinical trials have demonstrated that SEROQUEL is effective in schizophrenia and mania when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study, which identified that for quetiapine, $5HT_2$- and 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.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression.

In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo.

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

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

In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.

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

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of SEROQUEL (200-800 mg/day) versus risperidone (2-8 mg) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in SEROQUEL (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Pharmacokinetic properties
Absorption
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

Distribution
Quetiapine is approximately 83% bound to plasma proteins.

Metabolism
Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

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

Elimination
The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations
Gender
The kinetics of quetiapine do not differ between men and women.

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

Renal Impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2), but the individual clearance values are within the range for normal subjects.

Hepatic Impairment
The mean quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see *Posology and method of administration*).

Preclinical safety data
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research.

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy**,** a lowering in plasma T_3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts (for cataracts/lens opacities (see *Pharmacodynamic properties*).

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

Pharmaceutical particulars

List of excipients

Core	Coating
Povidone (Ph. Eur) Calcium hydrogen phosphate dihydrate (Ph. Eur) Microcrystalline cellulose (Ph. Eur) Sodium starch glycollate Type A (Ph. Eur) Lactose monohydrate (Ph. Eur) Magnesium stearate (Ph. Eur)	Hypromellose (Ph. Eur) Macrogol 400 (Ph. Eur) Titanium dioxide (Ph. Eur, E171) Ferric oxide, Yellow (Ph. Eur, E172) (25 mg and 100 mg tablets) Ferric oxide, red (Ph.Eur, E172) (25 mg tablets)

Special precautions for storage

Do not store above 30°C.

HARUS DENGAN RESEP DOKTER

Pack size

SEROQUEL 25 mg – Box, 6 blisters @ 10 film-coated tablets (Reg. No.: DKI1435300917A1)
SEROQUEL 100 mg – Box, 6 blisters @ 10 film-coated tablets (Reg. No.: DKI1435300917B1)
SEROQUEL 200 mg – Box, 6 blisters @ 10 film-coated tablets (Reg. No.: DKI1435300917C1)
SEROQUEL 300 mg – Box, 6 blisters @ 10 film-coated tablets (Reg. No.: DKI1435300917D1)

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Wuxi, Jiangsu - China

Imported by:

PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

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