Quetiapine

Core Safety Profile

SEROQUEL (Quetiapine fumarate) film-coated tablets
SEROQUEL XR (quetiapine fumarate) prolonged-release tablets

4.2 Posology and method of administration (*Relevant safety information only)*
For quetiapine only – quetiapine can be administered with or without food

For quetiapine prolonged release only – quetiapine prolonged release should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

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

For quetiapine and quetiapine prolonged release
Elderly:
As with other antipsychotics, quetiapine should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of quetiapine may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients.
(For quetiapine prolonged release - Elderly patients 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.)
Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and Adolescents:
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment:
Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:
Quetiapine is extensively metabolized by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dosing period.
Patients with hepatic impairment should be started with 25 mg/day for quetiapine and 50 mg/day for quetiapine prolonged release. The dose can be

increased in increments of 25 - 50 mg/day for quetiapine and increments of 50 mg/day for quetiapine prolonged release to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 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 section 4.5).

4.4 Special warnings and precautions for use

Children and adolescents (10 to 17 years of age)
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials quetiapine have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.
Furthermore, the long-term safety implications of treatment quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.
In placebo-controlled clinical trials with children and adolescent patients treated with quetiapine (quetiapine), quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8).

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

Somnolence:
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8). 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.

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. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see Section 4.8).

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 section 4.8).

Tardive Dyskinesia:
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 Section 4.8).

Neuroleptic Malignant Syndrome:
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatinine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe Neutropenia:
Severe neutropenia (neutrophil count <0.5 X 109/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, 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. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 109/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 109/L). (See section 5.1).

Interactions:
See also section 4.5.
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 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 Sections 4.8 and 5.1).

Hyperglycaemia:
~~Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see section 4.8).~~

Hyperglycaemia and/ or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). 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 section 4.8). Lipid changes should be managed as clinically appropriate.

Metabolic Risk:
Given the observed changes in weight, blood glucose (see hyperglycemia) and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate (see also section 4.8).

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 Section 4.8) and in overdose (see Section 4.9). 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 section 4.5).

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 section 4.8)

Elderly patients with dementia-related psychosis:
Quetiapine is not approved for the treatment of dementia-related psychosis.
An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.
In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo controlled 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 section 4.8 Undesirable effects) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

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

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.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.
Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily 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 section 4.4).
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.
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.

4.6 Fertility, 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. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed.
The degree to which quetiapine is excreted into human milk is unknown. Women who are breastfeeding should therefore be advised to avoid breast-feeding while taking quetiapine.

4.7 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 to this is known.

4.8 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 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
Common: Leucopenia[1]
Uncommon: Eosinophilia, Thrombocytopenia
Unknown: Neutropenia[1]

Immune system disorders
Uncommon: Hypersensitivity
Very rare: Anaphylactic reaction 6

Endocrine disorders
Common: Hyperprolactinemia 16
Very rare: Inappropriate antidiuretic hormone secretion

Metabolism and nutritional disorders
Common: Increased appetite
Uncommon: Hyponatraemia *20*
Very rare: Diabetes Mellitus 1,5,6

Psychiatric disorders
Common: Abnormal dreams and nightmares

Nervous system disorders
Very common: Dizziness[4],[17], somnolence [2],[17], headache
Common: Syncope[4],[17], Extrapyramidal symptoms [1],[13], Dysarthria
Uncommon: Seizure[1], Restless legs syndrome, Tardive dyskinesia [1, 6]

Cardiac disorders
Common: Tachycardia[4]

Eye Disorders
Common: Vision blurred

Vascular disorders
Common: Orthostatic hypotension [4],[17]
Rare: Venous thromboembolism[1]

Respiratory, thoracic and mediastinal disorder
Common: Rhinitis

Gastrointestinal disorders
Very common: Dry mouth
Common: Constipation, dyspepsia
Uncommon: Dysphagia[8]

Hepato-biliary disorders
Rare: Jaundice [6]
Very rare: Hepatitis [6]

Skin and subcutaneous tissue disorders
Very rare: Angioedema [6], Stevens-Johnson syndrome [6]

Musculoskeletal and connective tissue disorders
Very rare: Rhabdomyolysis

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
Rare: Neuroleptic malignant syndrome[1]

Investigations
Very common Elevations in serum triglyceride levels[11]
Elevations in total cholesterol (predominantly LDL cholesterol) [12],
Decreases in HDL cholesterol[18], Weight gain [9]
Common: Elevations in serum transaminases (ALT, AST) [3], decreased neutrophil count, blood glucose increased to hyperglycaemic levels[7]
Uncommon: Elevations in gamma-GT levels [3], Platelet count decreased[14], QT prolongation [1,13,19]

Rare Elevations in blood creatine phosphokinase 15, ~~Venous thromboembolism1~~

1. See Section 4.4.
2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
3. 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.
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 section 4.4).
5. Exacerbation of pre-existing diabetes has been reported in very rare cases.
6. Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of Quetiapine
7. Fasting blood glucose ≥126mg/dL(≥7.0 mmol/L) or a non fasting blood glucose ≥200mg/dL (≥11.1 mmol/L) on at least one occasion
8. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression
9. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment
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 109/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 □g/L (>869.56 pmol/L) males; >30 □g/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

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.
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). In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) 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 T4 and free T4. The reduction in total

and free T4 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 T4, irrespective of the duration of treatment. Smaller decreases in total T3 and reverse T3 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.

Children and adolescents (10 to 17 years of age)
The same ADRs described above for adults should be considered for children and adolescents.
The following table summarises ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.
The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

Metabolism and nutritional disorders
Very common: Increased appetite

Investigations
Very common: Elevations in prolactin[1], increases in blood pressure[2]

Nervous system disorders
Very common: Extrapyramidal symptoms [3]

General disorders and administration site conditions
Common: Irritability[4]

1. Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. See 5.1.
4. Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

4.9 Overdose

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 post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QTprolongation.
Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4: Cardiovascular).

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension.
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. 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.
Close medical supervision and monitoring should be continued until the patient recovers.