

## **Annex III**

### **Summary of product characteristics, labelling and package leaflet**

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

**SUMMARY OF PRODUCT CHARACTERISTICS,  
LABELLING AND PACKAGE LEAFLET**

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg film-coated tablets  
Seroquel 100 mg film-coated tablets  
Seroquel 150 mg film-coated tablets  
Seroquel 200 mg film-coated tablets  
Seroquel 300 mg film-coated tablets  
Seroquel 3-Day Starterpack (Combined pack)  
Seroquel 4-Day Starterpack

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Seroquel 25 mg contains 25 mg quetiapine (as quetiapine fumarate)  
Excipient : 18 mg lactose (anhydrous) per tablet

Seroquel 100 mg contains 100 mg quetiapine (as quetiapine fumarate)  
Excipient : 20 mg lactose (anhydrous) per tablet

Seroquel 150 mg contains 150 mg quetiapine (as quetiapine fumarate)  
Excipient : 29 mg lactose (anhydrous) per tablet

Seroquel 200 mg contains 200 mg quetiapine (as quetiapine fumarate)  
Excipient : 39 mg lactose (anhydrous) per tablet

Seroquel 300 mg contains 300 mg quetiapine (as quetiapine fumarate)  
Excipient : 59 mg lactose (anhydrous) per tablet

Seroquel 3-Day Starterpack (Combined pack) contains 6 tablets Seroquel 25 mg and 2 tablets Seroquel 100 mg

Seroquel 4-Day Starterpack contains 6 tablets Seroquel 25 mg, 3 tablets Seroquel 100 mg and 1 tablet Seroquel 200 mg

For a full list of excipients see section 6.1

## **3. 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 150 mg tablets are pale yellow, round biconvex and engraved with SEROQUEL 150 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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Seroquel is indicated for:

- treatment of Schizophrenia.
  
- treatment of bipolar disorder:
  - For the treatment of moderate to severe manic episodes in bipolar disorder
  - For the treatment of major depressive episodes in bipolar disorder
  - For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

### 4.2 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**

For the treatment of schizophrenia, Seroquel should be administered twice a day. The total daily dose for the first four 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 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 moderate to severe manic episodes in bipolar disorder**

For the treatment of manic episodes associated with bipolar disorder, Seroquel should be administered twice a day. 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/day by Day 6 should be in increments of no greater than 200 mg/day.

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

##### **For the treatment of major depressive episodes in bipolar disorder**

Seroquel should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

##### **For preventing recurrence in bipolar disorder**

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within

the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

#### **Elderly:**

As with other antipsychotics, Seroquel should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration 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.

#### **Paediatric Population**

Seroquel 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 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.

### **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 also section 4.5)

### **4.4 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.

#### **Paediatric population**

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 with 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, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) 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 with 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, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania, and bipolar depression (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 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).

**Metabolic Risk**

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patients' metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also 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 sections 4.8 and 5.1).

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:**

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).

**Somnolence and dizziness:**

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. 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.

**Orthostatic hypotension:**

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see Section 4.8) 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.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially 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 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 creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

**Severe Neutropenia and agranulocytosis:**

Severe neutropenia (neutrophil count  $<0.5 \times 10^9/L$ ) has been 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, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count  $<1.0 \times 10^9/L$ . Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed  $1.5 \times 10^9/L$ ) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors



## **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 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 Sections 4.8 and 5.1).

## **Hyperglycaemia**

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.

## **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).

## **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.

## **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 ) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

### **Constipation and intestinal obstruction**

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8 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. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

### **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.

### **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 section 4.4), gallstones, and alcohol consumption.

#### **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.

### **Lactose**

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

## **4.5 Interaction 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 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.

In a 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).

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.

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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

#### *First trimester*

The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

#### *Third trimester*

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.

### Breastfeeding

Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

### Fertility

The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (see section 5.3 preclinical data).

## 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 ( $\geq 10\%$ ) are somnolence, dizziness, headache, 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 (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

**Table 1** ADRs associated with quetiapine therapy

The frequencies of adverse events are ranked according to the following: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1000$ ), very rare ( $< 1/10,000$ ), and not known (cannot be estimated from the available data).

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
<i>Blood and lymphatic system disorders</i>	Decreased haemoglobin <sup>22</sup>	Leucopenia <sup>1, 28</sup> , decreased neutrophil count, eosinophils increased <sup>27</sup>	Thrombocytopenia, Anaemia, platelet count decreased <sup>13</sup>	Agranulocytosis <sup>26</sup>		Neutropenia <sup>1</sup>
<i>Immune system disorders</i>			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction <sup>5</sup>	
<i>Endocrine disorders</i>		Hyperprolactinaemia <sup>15</sup> , decreases in total T <sub>4</sub> <sup>24</sup> , decreases in free T <sub>4</sub> <sup>24</sup> , decreases in total T <sub>3</sub> <sup>24</sup> , increases in TSH <sup>24</sup>	Decreases in free T <sub>3</sub> <sup>24</sup> , Hypothyroidism <sup>21</sup>		Inappropriate antidiuretic hormone secretion	
<i>Metabolism and nutritional disorders</i>	Elevations in serum triglyceride levels <sup>10,30</sup> Elevations in total cholesterol (predominantly LDL cholesterol) <sup>11,30</sup> Decreases in HDL cholesterol <sup>17,30</sup> Weight gain <sup>8,30</sup>	Increased appetite, blood glucose increased to hyperglycaemic levels <sup>6,30</sup>	Hyponatraemia <sup>19</sup> , Diabetes Mellitus <sup>1,5</sup>	Metabolic syndrome <sup>29</sup>	Exacerbation of pre-existing diabetes	
<i>Psychiatric disorders</i>		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour <sup>20</sup>		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
<i>Nervous system disorders</i>	Dizziness <sup>4, 16</sup> , somnolence <sup>2,16</sup> , headache, Extrapyramidal symptoms <sup>1,21</sup>	Dysarthria	Seizure <sup>1</sup> , Restless legs syndrome, Tardive dyskinesia <sup>1, 5</sup> , Syncope <sup>4,16</sup>			
<i>Cardiac disorders</i>		Tachycardia <sup>4</sup> , Palpitations <sup>23</sup>	QT prolongation <sup>1,12, 18</sup> Bradycardia <sup>32</sup>			
<i>Eye Disorders</i>		Vision blurred				

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
<i>Vascular disorders</i>		Orthostatic hypotension <sup>4,16</sup>		Venous thromboembolism <sup>1</sup>		
<i>Respiratory, thoracic and mediastinal disorder</i>		Dyspnoea <sup>23</sup>	Rhinitis			
<i>Gastrointestinal disorders</i>	Dry mouth	Constipation, dyspepsia, vomiting <sup>25</sup>	Dysphagia <sup>7</sup>	Pancreatitis <sup>1</sup> , Intestinal obstruction/Ileus		
<i>Hepato-biliary disorders</i>		Elevations in serum alanine aminotransferase (ALT) <sup>3</sup> Elevations in gamma-GT levels <sup>3</sup>	Elevations in serum aspartate aminotransferase (AST) <sup>3</sup>	Jaundice <sup>5</sup> , Hepatitis		
<i>Skin and subcutaneous tissue disorders</i>					Angioedema <sup>5</sup> , Stevens-Johnson syndrome <sup>5</sup>	Toxic Epidermal Necrolysis, Erythema Multiforme
<i>Musculoskeletal and connective tissue disorders</i>					Rhabdomyolysis	
<i>Renal and urinary disorders</i>			Urinary retention			
<i>Pregnancy, puerperium and perinatal conditions</i>						Drug withdrawal syndrome neonatal <sup>31</sup>
<i>Reproductive system and breast disorders</i>			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
<i>General disorders and administration site conditions</i>	Withdrawal (discontinuation) symptoms <sup>1,9</sup>	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome <sup>1</sup> , hypothermia		
<i>Investigations</i>				Elevations in blood creatine phosphokinase <sup>14</sup>		

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 (shift from normal to > 3X 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 section 4.4).
5. Calculation of Frequency for these ADR's have been taken from postmarketing data only.
6. Fasting blood glucose  $\geq 126$  mg/dL ( $\geq 7.0$  mmol/L) or a non fasting blood glucose  $\geq 200$  mg/dL ( $\geq 11.1$  mmol/L) on at least one occasion.
7. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
8. Based on  $>7\%$  increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
9. 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.
10. Triglycerides  $\geq 200$  mg/dL ( $\geq 2.258$  mmol/L) (patients  $\geq 18$  years of age) or  $\geq 150$  mg/dL ( $\geq 1.694$  mmol/L) (patients  $< 18$  years of age) on at least one occasion.
11. Cholesterol  $\geq 240$  mg/dL ( $\geq 6.2064$  mmol/L) (patients  $\geq 18$  years of age) or  $\geq 200$  mg/dL ( $\geq 5.172$  mmol/L) (patients  $< 18$  years of age) on at least one occasion. An increase in LDL cholesterol of  $\geq 30$  mg/dL ( $\geq 0.769$  mmol/L) has been very commonly observed. Mean change among patients who had this increase was  $41.7$  mg/dL ( $\geq 1.07$  mmol/L).
12. See text below
13. Platelets  $\leq 100 \times 10^9/L$  on at least one occasion
14. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
15. Prolactin levels (patients  $> 18$  years of age):  $> 20$   $\mu\text{g/L}$  ( $> 869.56$  pmol/L) males;  $> 30$   $\mu\text{g/L}$  ( $> 1304.34$  pmol/L) females at any time
16. May lead to falls
17. HDL cholesterol:  $< 40$  mg/dL ( $1.025$  mmol/L) males;  $< 50$  mg/dL ( $1.282$  mmol/L) females at any time.
18. Incidence of patients who have a QTc shift from  $< 450$  msec to  $\geq 450$  msec with a  $\geq 30$  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.
19. Shift from  $> 132$  mmol/L to  $\leq 132$  mmol/L on at least one occasion.
20. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see Sections 4.4 and 5.1).
21. See Section 5.1
22. Decreased haemoglobin to  $\leq 13$  g/dL ( $8.07$  mmol/L) males,  $\leq 12$  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.
23. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
24. 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  $< 0.8 \times \text{LLN}$  (pmol/L) and shift in TSH is  $> 5$  mIU/L at any time.
25. Based upon the increased rate of vomiting in elderly patients ( $\geq 65$  years of age).
26. Based on shift in neutrophils from  $\geq 1.5 \times 10^9/L$  at baseline to  $< 0.5 \times 10^9/L$  at any time during treatment and based on patients with severe neutropenia ( $< 0.5 \times 10^9/L$ ) and infection during all quetiapine clinical trials (See Section 4.4).
27. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as  $> 1 \times 10^9$  cells/L at any time.
28. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as  $\leq 3 \times 10^9$  cells/L at any time.
29. Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.

30. 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 Section 4.4).
31. See Section 4.6.
32. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event 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.

### Paediatric population

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.

**Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not 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).

SOC	Very Common	Common
<i>Endocrine disorders</i>	Elevations in prolactin <sup>1</sup>	
<i>Metabolism and nutritional disorders</i>	Increased appetite	
<i>Nervous system disorders</i>	Extrapyramidal symptoms <sup>3, 4</sup>	Syncope
<i>Vascular disorders</i>	Increases in blood pressure <sup>2</sup>	
<i>Respiratory, thoracic and mediastinal disorders</i>		Rhinitis
<i>Gastrointestinal disorders</i>	Vomiting	
<i>General disorders and administration site conditions</i>		Irritability <sup>3</sup>

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 >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.
- 4 See section 5.1

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).



## 4.9 Overdose

### Symptoms

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. Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4, Orthostatic hypotension ).

### 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.

Based on public literature, patients with delirium and agitation and a clear anticholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics  
ATC code: N05A H04

#### Mechanism of action:

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5HT<sub>2</sub>) and dopamine D<sub>1</sub>- and D<sub>2</sub>- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT<sub>2</sub> relative to D<sub>2</sub>- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha<sub>1</sub> receptors, moderate affinity at adrenergic alpha<sub>2</sub> receptors and moderate to high affinity at several muscarinic receptors. Inhibition of NET and partial agonist action at 5HT<sub>1A</sub> sites by norquetiapine may contribute to Seroquel's therapeutic efficacy as an antidepressant.

### **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 D<sub>2</sub>-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<sub>2</sub>-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D<sub>2</sub>-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve Cebus monkeys after acute and chronic administration. (See Section 4.8)

### **Clinical efficacy:**

#### Schizophrenia

In three placebo-controlled clinical trials, in patients with schizophrenia, using variable doses of quetiapine, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics. A placebo-controlled trial evaluating fixed doses of quetiapine across the range of 75 to 750 mg/day showed no evidence of an increase in EPS or the use of concomitant anticholinergics. The long-term efficacy of Seroquel IR in prevention of schizophrenic relapses has not been verified in blinded clinical trials. In open label trials, in patients with schizophrenia, quetiapine was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response, suggesting some long-term efficacy.

#### Bipolar Disorder

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 the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. There are no data from long-term studies to demonstrate Seroquel's effectiveness in preventing subsequent manic or depressive episodes. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

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.

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 IR 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 IR 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 a 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

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<sub>2</sub>- and D<sub>2</sub>-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, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

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  $\geq 7\%$  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.

A 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania indicated that the combination of SEROQUEL XR with lithium leads to more adverse events (63% versus 48% in SEROQUEL XR in combination with placebo). The safety

results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the SEROQUEL XR with lithium add-on group (12.7%) compared to the SEROQUEL XR with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain ( $\geq 7\%$ ) at the end of treatment compared to patients in the placebo add-on group (4.7%).

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<sub>4</sub> 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 T<sub>4</sub>, 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/day) 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.

#### **Paediatric population**

##### **Clinical efficacy**

The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n=222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to

100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was -5.21 for Seroquel 400 mg/day and -6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement  $\geq 50\%$ ) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was -8.16 for Seroquel 400 mg/day and -9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as  $\geq 30\%$  reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XR in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

#### Clinical safety

In the short-term pediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain  $\geq 7\%$  of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 12.5% vs. 6% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended posttreatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

#### Long-term safety

A 26-week open-label extension to the acute trials (n=380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see sections 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

## **5.2 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.

### Biotransformation

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. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

### 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<sup>2</sup>), 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 section 4.2).

### **Paediatric population**

Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C<sub>max</sub> in children was at the higher end of the range observed in adults. The AUC and C<sub>max</sub> for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

### 5.3 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<sub>3</sub> 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 section 5.1).

In an embryofetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Core

Povidone  
Calcium Hydrogen Phosphate Dihydrate  
Microcrystalline Cellulose  
Sodium Starch Glycolate Type A  
Lactose Monohydrate  
Magnesium Stearate

#### Coating

Hypromellose 2910  
Macrogol 400  
Titanium Dioxide (E171)  
Ferric Oxide, Yellow (E172) 25 mg, 100 mg and 150 mg tablets)  
Ferric Oxide, Red (E172) (25 mg tablets)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

## 6.5 Nature and contents of container

PVC/aluminium blisters

Pack sizes

Blisters:

<b>Tablet Strength</b>	<b>Carton (pack) contents</b>	<b>Blisters</b>	
<b>25 mg tablets</b>	<i>6 tablets</i>	<i>1 blister of 6 tablets</i>	
	<i>20 tablets</i>	<i>2 blisters of 10 tablets</i>	
	<i>30 tablets</i>	<i>3 blisters of 10 tablets</i>	
	<i>50 tablets</i>	<i>10 blisters of 5 tablets</i>	
	<i>50 tablets</i>	<i>5 blisters of 10 tablets</i>	
	<i>60 tablets</i>	<i>6 blisters of 10 tablets</i>	
		<i>12 blisters of 5 tablets</i>	
	<i>100 tablets</i>	<i>10 blisters of 10 tablets</i>	
	<b>100 mg, 150 mg, 200 mg and 300 mg tablets</b>	<i>10 tablets</i>	<i>1 blister of 10 tablets</i>
		<i>20 tablets</i>	<i>2 blisters of 10 tablets</i>
<i>30 tablets</i>		<i>3 blisters of 10 tablets</i>	
<i>50 tablets</i>		<i>10 blisters of 5 tablets</i>	
<i>50 tablets</i>		<i>5 blisters of 10 tablets</i>	
<i>60 tablets</i>		<i>6 blisters of 10 tablets</i>	
<i>90 tablets</i>		<i>9 blisters of 10 tablets</i>	
<i>100 tablets</i>		<i>10 blisters of 10 tablets</i>	
<i>120 tablets</i>		<i>12 blisters of 10 tablets (150 mg and 300 mg tablets only)</i>	
<i>180 tablets</i>		<i>18 blisters of 10 tablets (150 mg and 300 mg tablets only)</i>	
<i>240 tablets</i>	<i>24 blisters of 10 tablets (150 mg and 300 mg tablets only)</i>		
<b>3-Day Starterpack (Combined pack)</b>	<i>8 tablets</i>	<i>1 blister containing 6 x 25 mg and 2 x 100 mg tablets</i>	
<b>4-Day Starterpack</b>	<i>10 tablets</i>	<i>1 blister containing 6 x 25mg, 3 x 100mg and 1 x 200mg tablets</i>	

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 April 1998



12-October-2009

**10. DATE OF REVISION OF THE TEXT**

## **LABELLING**

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

### **CARTON**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg film-coated tablets  
quetiapine

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 25 mg quetiapine (as fumarate)

#### **3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

#### **4. PHARMACEUTICAL FORM AND CONTENTS**

6 film-coated tablets  
20 film-coated tablets  
30 film-coated tablets  
50 film-coated tablets  
60 film-coated tablets  
100 film-coated tablets

#### **5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

#### **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

#### **7. OTHER SPECIAL WARNING(S), IF NECESSARY**

#### **8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<[To be completed nationally]>

{Name and Address }

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

<[To be completed nationally]>

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Seroquel 25 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

BLISTER FOIL

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg film-coated tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

Exp

**4. BATCH NUMBER**

Lot

**5. OTHER**

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

### **CARTON**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 100 mg (or 150 mg, or 200 mg or 300 mg) film-coated tablets  
quetiapine

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 100 mg (or 150 mg, or 200 mg or 300 mg) quetiapine (as fumarate)

#### **3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

#### **4. PHARMACEUTICAL FORM AND CONTENTS**

10 film-coated tablets  
20 film-coated tablets  
30 film-coated tablets  
50 film-coated tablets  
60 film-coated tablets  
90 film-coated tablets  
100 film-coated tablets  
120 film-coated tablets (150 mg and 300 mg tablets only)  
180 film-coated tablets (150 mg and 300 mg tablets only)  
240 film-coated tablets (150 mg and 300 mg tablets only)

#### **5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

#### **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

#### **7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<[To be completed nationally]>

{Name and Address }

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

<[To be completed nationally]>

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Seroquel 100 mg (or 150 mg, or 200 mg or 300 mg)

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

BLISTER FOIL

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 100 (or 150 mg, or 200 mg or 300 mg) mg film-coated tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

Exp

**4. BATCH NUMBER**

Lot

**5. OTHER**



## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

### **CARTON 3-Day starter pack**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg and 100 mg film-coated tablets  
quetiapine

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 25 mg quetiapine (as fumarate)  
Each tablet contains 100 mg quetiapine (as fumarate)

#### **3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

#### **4. PHARMACEUTICAL FORM AND CONTENTS**

8 film-coated tablets

Combined pack

This pack contains:

6 x 25 mg film-coated tablets

2 x 100 mg film-coated tablets

#### **5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

#### **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

#### **7. OTHER SPECIAL WARNING(S), IF NECESSARY**

#### **8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<[To be completed nationally]>

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

<[To be completed nationally]>

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Seroquel 25 mg and 100 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL 3-Day starter pack**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg and 100 mg tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

Exp

**4. BATCH NUMBER**

Lot

**5. OTHER**

Day 1  
Day 2  
Day 3  
morning  
evening  
25 mg  
2x25 mg  
100 mg

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

### **CARTON 4-Day starter pack**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg, 100 mg and 200 mg film-coated tablets  
quetiapine

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 25 mg quetiapine (as fumarate)  
Each tablet contains 100 mg quetiapine (as fumarate)  
Each tablet contains 200 mg quetiapine (as fumarate)

#### **3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

#### **4. PHARMACEUTICAL FORM AND CONTENTS**

10 film-coated tablets

Combined pack

This pack contains:

6 x 25 mg film-coated tablets  
3 x 100 mg film-coated tablets  
1 x 200 mg film-coated tablets

#### **5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

#### **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

#### **7. OTHER SPECIAL WARNING(S), IF NECESSARY**

#### **8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<[To be completed nationally]>

{Name and Address }

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

<[To be completed nationally]>

**13. BATCH NUMBER**

LOT

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Seroquel 25 mg, 100 mg and 200 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL 4-Day starter pack**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel 25 mg, 100 mg and 200 mg tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

Exp

**4. BATCH NUMBER**

Lot

**5. OTHER**

Day 1  
Day 2  
Day 3  
Day 4  
morning  
evening  
25 mg  
2x25 mg  
100 mg  
200 mg

**PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Seroquel 25 mg, 100 mg, 150 mg, 200 mg, 300 mg film-coated tablets Seroquel 3-Day Starterpack (Combined pack) Seroquel 4-Day Starterpack

quetiapine

#### **Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See Section 4.

#### **In this leaflet:**

1. What Seroquel is and what it is used for
2. What you need to know before you take Seroquel
3. How to take Seroquel
4. Possible side effects
5. How to store Seroquel
6. Contents of the pack and other information

#### **1. What Seroquel is and what it is used for**

Seroquel contains a substance called quetiapine. This belongs to a group of medicines called anti-psychotics. Seroquel can be used to treat several illnesses, such as:

- Bipolar depression: where you feel sad. You may find that you feel depressed, feel guilty, lack energy, lose your appetite or can't sleep.
- Mania: where you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Schizophrenia: where you may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed.

Your doctor may continue to prescribe Seroquel even when you are feeling better.

#### **2. What you need to know before you take Seroquel**

##### **Do not take Seroquel :**

- If you are allergic (hypersensitive) to quetiapine or any of the other ingredients of Seroquel (see section 6: Further information)
- If you are taking any of the following medicines:
  - some medicines for HIV
  - azole medicines (for fungal infections)
  - erythromycin or clarithromycin (for infections)
  - nefazodone (for depression).



Do not take Seroquel if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Seroquel.

### **Warnings and Precautions**

Talk to your doctor or pharmacist before taking Seroquel if:

- You, or someone in your family, have or have had any heart problems, for example heart rhythm problems, weakening of the heart muscle or inflammation of the heart or if you are taking any medicines that may have an impact on the way your heart beats.
- You have low blood pressure
- You have had a stroke, especially if you are elderly
- You have problems with your liver.
- You have ever had a fit (seizure).
- You have diabetes or have a risk of getting diabetes. If you do, your doctor may check your blood sugar levels while you are taking Seroquel.
- You know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- You are an elderly person with dementia (loss of brain function). If you are, Seroquel should not be taken because the group of medicines that Seroquel belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.
- You or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Tell your doctor immediately if you experience any of the following after taking Seroquel::

- A combination of fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called “neuroleptic malignant syndrome).” Immediate medical treatment may be needed.
- Uncontrollable movements, mainly of your face or tongue.
- Dizziness or a severe sense of feeling sleepy. This could increase the risk of accidental injury (fall) in elderly patients.
- Fits (seizures).
- A long-lasting and painful erection (Priapism).

These conditions can be caused by this type of medicine.

Tell your doctor as soon as possible if you have:

- A fever, flu-like symptoms, sore throat, or any other infection, as this could be a result of a very low white blood cell count, which may require Seroquel to be stopped and/or treatment to be given.
- Constipation along with persistent abdominal pain, or constipation which has not responded to treatment, as this may lead to a more serious blockage of the bowel.

### **Thoughts of suicide and worsening of your depression**

If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer. These thoughts may also be increased if you suddenly stop taking your medication. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

### **Weight gain**

Weight gain has been seen in patients taking Seroquel. You and your doctor should check your weight regularly.

### **Children and Adolescents**

Seroquel is not for use in children and adolescents below 18 years of age.

### **Other medicines and Seroquel**

Tell your doctor if you are taking or have recently taken any other medicines .

Do not take Seroquel if you are taking any of the following medicines:

- Some medicines for HIV.
- Azole medicines (for fungal infections).
- Erythromycin or clarithromycin (for infections).
- Nefazodone (for depression).

Tell your doctor if you are taking any of the following medicines:

- Epilepsy medicines (like phenytoin or carbamazepine).
- High blood pressure medicines.
- Barbiturates (for difficulty sleeping).
- Thioridazine or Lithium (other anti-psychotic medicines).
- Medicines that have an impact on the way your heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (drugs to treat infections).
- Medicines that can cause constipation.

Before you stop taking any of your medicines, please talk to your doctor first.

### **Seroquel with food, drink and alcohol**

- Seroquel can be taken with or without food.
- Be careful how much alcohol you drink. This is because the combined effect of Seroquel and alcohol can make you sleepy.
- Do not drink grapefruit juice while you are taking Seroquel. It can affect the way the medicine works.

### **Pregnancy and breast-feeding**

If you are pregnant or breast feeding, think you may be pregnant or planning to have a baby ask your doctor for advice before taking Seroquel. You should not take Seroquel during pregnancy unless this has been discussed with your doctor. Seroquel should not be taken if you are breast-feeding.

The following symptoms which can represent withdrawal may occur in newborn babies of mothers that have used Seroquel in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

### **Driving and using machines**

Your tablets may make you feel sleepy. Do not drive or use any tools or machines until you know how the tablets affect you.

**Seroquel contains lactose**

Seroquel contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

**Effect on Urine Drug Screens**

If you are having a urine drug screen, taking Seroquel may cause positive results for methadone or certain drugs for depression called tricyclic antidepressants (TCAs) when some test methods are used, even though you may not be taking methadone or TCAs. If this happens, a more specific test can be performed.

**3. How to take Seroquel**

Always take Seroquel exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor will decide on your starting dose. The maintenance dose (daily dose) will depend on your illness and needs but will usually be between 150 mg and 800 mg.

- You will take your tablets once a day, at bedtime or twice a day, depending on your illness
- Swallow your tablets whole with a drink of water.
- You can take your tablets with or without food.
- Do not drink grapefruit juice while you are taking Seroquel. It can affect the way the medicine works.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

**Liver problems**

If you have liver problems your doctor may change your dose.

**Elderly people**

If you are elderly your doctor may change your dose.

**Use in children and adolescents**

Seroquel should not be used by children and adolescents aged under 18 years.

**If you take more Seroquel than you should**

If you take more Seroquel than prescribed by your doctor, you may feel sleepy, feel dizzy and experience abnormal heart beats. Contact your doctor or nearest hospital straight away. Keep the Seroquel tablets with you.

**If you forget to take a dose of Seroquel**

If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Seroquel**

If you suddenly stop taking Seroquel, you may be unable to sleep (insomnia), or you may feel sick (nausea), or you may experience headache, diarrhoea, being sick (vomiting), dizziness or irritability. Your doctor may suggest you reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

#### 4. Possible side effects

Like all medicines, Seroquel can cause side effects, although not everybody gets them.

##### **Very common side effects ( may affect more than 1 in 10 people):**

- Dizziness (may lead to falls), headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel) (may lead to falls).
- Discontinuation symptoms (symptoms which occur when you stop taking Seroquel) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness, and irritability. Gradual withdrawal over a period of at least 1 to 2 weeks is advisable.
- Putting on weight.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Changes in the amount of certain fats (triglycerides and total cholesterol)

##### **Common side effects (may affect up to 1 in 10 people):**

- Rapid heartbeat.
- Feeling like your heart is pounding, racing or has skipped beats.
- Constipation, upset stomach (indigestion).
- Feeling weak.
- Swelling of arms or legs.
- Low blood pressure when standing up. This may make you feel dizzy or faint (may lead to falls).
- Increased levels of sugar in the blood.
- Blurred vision.
- Abnormal dreams and nightmares
- Feeling more hungry
- Feeling irritated
- Disturbance in speech and language.
- Thoughts of suicide and worsening of your depression.
- Shortness of breath.
- Vomiting (mainly in the elderly).
- Fever
- Changes in the amount of thyroid hormones in your blood
- Decreases in the number of certain types of blood cells
- Increases in the amount of liver enzymes measured in the blood
- Increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - Men and women to have swelling of breasts and unexpectedly produce breast milk.
  - Women to have no monthly period or irregular periods.

##### **Uncommon side effects (may affect up to 1 in 100 people):**

- Fits or seizures
- Allergic reactions that may include raised lumps (weals), swelling of the skin and swelling around the mouth.
- Unpleasant sensations in the legs (also called restless legs syndrome).
- Difficulty swallowing.
- Uncontrollable movements, mainly of your face or tongue.
- Sexual dysfunction.
- Diabetes
- Change in electrical activity of the heart seen on ECG (QT prolongation)

- A slower than normal heart rate which may occur when starting treatment and which may be associated with low blood pressure and fainting.
- Difficulty in passing urine.
- Fainting (may lead to falls)
- Stuffy nose
- Decrease in the amount of red blood cells
- Decrease in the amount of sodium in the blood

**Rare side effects (may affect up to 1 in 1,000 people):**

- A combination of high temperature (fever), sweating, stiff muscles, feeling very drowsy or faint (a disorder called “neuroleptic malignant syndrome).”
- Yellowing of the skin and eyes (jaundice).
- Inflammation of the liver (hepatitis).
- A long-lasting and painful erection (priapism).
- Swelling of breasts and unexpected production of breast milk (galactorrhoea).
- Menstrual disorder.
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- Walking, talking, eating or other activities while you are asleep.
- Body temperature decreased (hypothermia).
- Inflammation of the pancreas
- A condition (called “metabolic syndrome”) where you may have a combination of 3 or more of the following: an increase in fat around your abdomen, a decrease in “good cholesterol” (HDL-C), an increase in a type of fat in your blood called triglycerides, high blood pressure and an increase in your blood sugar.
- Combination of fever, flu-like symptoms, sore throat, or any other infection with very low white blood cell count, a condition called agranulocytosis.
- Bowel obstruction.
- Increased blood creatine phosphokinase (a substance from the muscles)

**Very rare side effects (may affect up to 1 in 10,000 people):**

- Severe rash, blisters, or red patches on the skin.
- A severe allergic reaction (called anaphylaxis) which may cause difficulty in breathing or shock.
- Rapid swelling of the skin, usually around the eyes, lips and throat (angioedema).
- A serious blistering condition of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)
- Inappropriate secretion of a hormone that controls urine volume.
- Breakdown of muscle fibers and pain in muscles (rhabdomyolysis).
- Worsening of pre-existing diabetes.

**Not known (frequency cannot be estimated from the available data)**

- Skin rash with irregular red spots (erythema multiforme).
- Serious, sudden allergic reaction with symptoms such as fever and blisters on the skin and peeling of the skin (toxic epidermal necrolysis).
- Symptoms of withdrawal may occur in newborn babies of mothers that have used Seroquel during their pregnancy.

The class of medicines to which Seroquel belongs can cause heart rhythm problems, which can be serious and in severe cases may be fatal.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, changes in the amount of thyroid hormones

in your blood, increased liver enzymes, decreases in the number of certain types of blood cells, decrease in the amount of red blood cells, increased blood creatine phosphokinase (a substance in the muscles), decrease in the amount of sodium in the blood and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:

- Men and women to have swelling of breasts and unexpectedly produce breast milk.
- Women to have no monthly period or irregular periods.

Your doctor may ask you to have blood tests from time to time.

### **Side effects in children and adolescents**

The same side effects that may occur in adults may also occur in children and adolescents.

The following side effects have been seen more often in children and adolescents or have not been seen in adults:

#### **Very Common side effects (may affect more than 1 in 10 people):**

- Increase in the amount of a hormone called prolactin, in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - Boys and girls to have swelling of breasts and unexpectedly produce breast milk
  - Girls to have no monthly period or irregular periods
- Increased appetite
- Vomiting
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Increase in blood pressure

#### **Common side effects (may affect up to 1 in 10 people):**

- Feeling weak, fainting (may lead to falls).
- Stuffy nose.
- Feeling irritated.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

### **5. How to store Seroquel**

- Keep this medicine out of the reach and sight of children.
- Do not use Seroquel after the expiry date which is stated on the container after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

### What Seroquel contains

- The active substance is quetiapine. Seroquel tablets contain 25 mg, 100 mg, 150 mg, 200 mg or 300mg of quetiapine (as quetiapine fumarate).

The other ingredients are:

Tablet core : povidone, calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycollate Type A, lactose monohydrate, magnesium stearate

Tablet coating: hypromellose, macrogol, titanium dioxide (E171). The 25 mg, 100 mg and 150 mg tablet also contain iron oxide yellow (E172) and the 25 mg contain iron oxide red (E172).

### What Seroquel looks like and contents of the pack

Seroquel 25 mg film-coated tablets are peach coloured, round biconvex and engraved with SEROQUEL 25 on one side

Seroquel 100 mg film-coated tablets are yellow, round biconvex and engraved with SEROQUEL 100 on one side

Seroquel 150 mg film-coated tablets are pale yellow, round biconvex and engraved with SEROQUEL 150 on one side

Seroquel 200 mg film-coated tablets are white, round biconvex and engraved with SEROQUEL 200 on one side

Seroquel 300 mg film-coated tablets are white, capsule-shaped and engraved with SEROQUEL on one side and 300 on the other side

Pack sizes of 20, 30, 50, 60 and 100 tablets are registered for all strengths. In addition, for 25 mg tablets pack size of 6 tablets is registered. For 100 mg, 150 mg, 200 mg and 300 mg tablets pack sizes of 10, 90 are registered. For 150 mg and 300 mg tablets pack sizes of 120, 180 and 240 tablets are registered. For 3-Day Starterpack pack size of 8 tablets is registered and for 4-Day Starterpack pack size of 10 tablets is registered. Not all pack sizes may be available.

### Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

### This medicinal product is authorised in the Member States of the EEA under the following names:

COUNTRY	TRADE NAME
Austria	Seroquel
Belgium	Seroquel
Cyprus	Seroquel
Denmark	Seroquel
Estonia	Seroquel
Finland	Seroquel
Germany	Seroquel® 25 mg Filmtabletten, Seroquel® 100 mg Filmtabletten,

	Seroquel® 200 mg Filmtabletten, Seroquel® 300 mg Filmtabletten
Greece	Seroquel
Iceland	Seroquel
Ireland	Seroquel
Italy	Seroquel
Latvia	Seroquel
Lithuania	Seroquel
Luxembourg	Seroquel
Malta	Seroquel
Netherlands	Seroquel
Norway	Seroquel
Portugal	Seroquel
Romania	Seroquel
Slovenia	Seroquel
Spain	Seroquel
Sweden	Seroquel
United Kingdom	Seroquel

<[See Annex I - To be completed nationally]> *[For referral procedures, as appropriate]*

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>



**SUMMARY OF PRODUCT CHARACTERISTICS,  
LABELLING AND PACKAGE LEAFLET**

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 50 mg prolonged-release tablets  
Seroquel XR 150 mg prolonged-release tablets  
Seroquel XR 200 mg prolonged-release tablets  
Seroquel XR 300 mg prolonged-release tablets  
Seroquel XR 400 mg prolonged-release tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Seroquel XR 50 mg contains 50 mg quetiapine (as quetiapine fumarate)  
Excipient : 119 mg lactose (anhydrous) per tablet  
Seroquel XR 150 mg contains 150 mg quetiapine (as quetiapine fumarate)  
Excipient : 71 mg lactose (anhydrous) per tablet  
Seroquel XR 200 mg contains 200 mg quetiapine (as quetiapine fumarate)  
Excipient : 50 mg lactose (anhydrous) per tablet  
Seroquel XR 300 mg contains 300 mg quetiapine (as quetiapine fumarate)  
Excipient : 47 mg lactose (anhydrous) per tablet  
Seroquel XR 400 mg contains 400 mg quetiapine (as quetiapine fumarate)  
Excipient : 15 mg lactose (anhydrous) per tablet

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Prolonged-release tablet

Seroquel XR 50 mg tablets are peach-coloured and engraved with “XR 50” on one side  
Seroquel XR 150 mg tablets are white and engraved with “XR 150” on one side  
Seroquel XR 200 mg tablets are yellow and engraved with “XR 200” on one side  
Seroquel XR 300 mg tablets are pale yellow and engraved with “XR 300” on one side  
Seroquel XR 400 mg tablets are white and engraved with “XR 400” on one side

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Seroquel XR is indicated for:

- treatment of Schizophrenia
- treatment of bipolar disorder:
  - For the treatment of moderate to severe manic episodes in bipolar disorder
  - For the treatment of major depressive episodes in bipolar disorder
  - For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.
- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see Section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of SEROQUEL XR (see Section 4.4).

## 4.2 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 XR should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

### **Adults:**

#### **For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder**

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

#### **For the treatment of major depressive episodes in bipolar disorder**

Seroquel XR should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

#### **For preventing recurrence in bipolar disorder**

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Seroquel XR for acute treatment of bipolar disorder should continue on Seroquel XR at the same dose administered at bedtime. Seroquel XR dose can be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy.

#### **For add-on treatment of major depressive episodes in MDD:**

Seroquel XR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine - see Section 5.1) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

#### **Switching from Seroquel immediate-release tablets:**

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

#### **Elderly:**

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

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting

from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

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

***Paediatric Population:***

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

### **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**

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

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see Section 5.1).

***Paediatric population***

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 with 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, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) 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 with 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, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania, and bipolar depression (see section 4.8).

***Suicide/suicidal thoughts or clinical worsening:***

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

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 adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo.

***Metabolic Risk***

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also 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 and major depressive disorder (see sections 4.8 and 5.1).

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:***

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).

***Somnolence and dizziness:***

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 and major depressive disorder, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. 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.

***Orthostatic Hypotension***

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see Section 4.8) 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.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially 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 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 creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

***Severe Neutropenia and agranulocytosis:***

Severe neutropenia (neutrophil count  $<0.5 \times 10^9/L$ ) has been 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, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count  $<1.0 \times 10^9/L$ . Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed  $1.5 \times 10^9/L$ ) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

**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 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 Sections 4.8 and 5.1).

**Hyperglycaemia:**

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.

**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).

**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.

**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) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

### ***Constipation and intestinal obstruction***

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8 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. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

### ***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.

### ***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 section 4.4), gallstones, and alcohol consumption.

### ***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.

### ***Lactose:***

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

## **4.5 Interaction 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 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.

In a 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).

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

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.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

#### *First trimester*

The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

### Third trimester

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.

### Breastfeeding

Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel XR therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

### Fertility

The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (see section 5.3 preclinical data).

## 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 ( $\geq 10\%$ ) are somnolence, dizziness, headache, 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 (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

**Table 1 ADRs associated with quetiapine therapy**

The frequencies of adverse events are ranked according to the following: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1000$ ), very rare ( $< 1/10,000$ ), and not known (cannot be estimated from the available data).

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders	Decreased haemoglobin <sup>22</sup>	Leucopenia <sup>1, 28</sup> , decreased neutrophil count, eosinophils increased <sup>27</sup>	Thrombocytopenia, Anaemia, platelet count decreased <sup>13</sup>	Agranulocytosis <sup>26</sup>		Neutropenia <sup>1</sup>
Immune system disorders			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction <sup>5</sup>	

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
<i>Endocrine disorders</i>		Hyperprolactinaemia <sup>15</sup> , decreases in total T <sub>4</sub> <sup>24</sup> , decreases in free T <sub>4</sub> <sup>24</sup> , decreases in total T <sub>3</sub> <sup>24</sup> , increases in TSH <sup>24</sup>	Decreases in free T <sub>3</sub> <sup>24</sup> , Hypothyroidism <sup>21</sup>		Inappropriate antidiuretic hormone secretion	
<i>Metabolism and nutritional disorders</i>	Elevations in serum triglyceride levels <sup>10,30</sup> Elevations in total cholesterol (predominantly LDL cholesterol) <sup>11,30</sup> Decreases in HDL cholesterol <sup>17,30</sup> , Weight gain <sup>8,30</sup>	Increased appetite, blood glucose increased to hyperglycaemic levels <sup>6,30</sup>	Hyponatraemia <sup>19</sup> , Diabetes Mellitus <sup>1,5</sup>	Metabolic syndrome <sup>29</sup>	Exacerbation of pre-existing diabetes	
<i>Psychiatric disorders</i>		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour <sup>20</sup>		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
<i>Nervous system disorders</i>	Dizziness <sup>4,16</sup> , somnolence <sup>2,16</sup> , headache, Extrapyramidal symptoms <sup>1,21</sup>	Dysarthria	Seizure <sup>1</sup> , Restless legs syndrome, Tardive dyskinesia <sup>1,5</sup> , Syncope <sup>4,16</sup>			
<i>Cardiac disorders</i>		Tachycardia <sup>4</sup> , Palpitations <sup>23</sup>	QT prolongation <sup>1,12,18</sup> Bradycardia <sup>32</sup>			
<i>Eye Disorders</i>		Vision blurred				
<i>Vascular disorders</i>		Orthostatic hypotension <sup>4,16</sup>		Venous thromboembolism <sup>1</sup>		
<i>Respiratory, thoracic and mediastinal disorder</i>		Dyspnoea <sup>23</sup>	Rhinitis			
<i>Gastrointestinal disorders</i>	Dry mouth	Constipation, dyspepsia, vomiting <sup>25</sup>	Dysphagia <sup>7</sup>	Pancreatitis <sup>1</sup> , Intestinal obstruction/Ileus		

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
<i>Hepato-biliary disorders</i>		Elevations in serum alanine aminotransferase (ALT) <sup>3</sup> . Elevations in gamma-GT levels <sup>3</sup>	Elevations in serum aspartate aminotransferase (AST) <sup>3</sup>	Jaundice <sup>5</sup> Hepatitis		
<i>Skin and subcutaneous tissue disorders</i>					Angioedema <sup>5</sup> , Stevens-Johnson syndrome <sup>5</sup>	Toxic Epidermal Necrolysis, Erythema Multiforme
<i>Musculoskeletal and connective tissue disorders</i>					Rhabdomyolysis	
<i>Renal and urinary disorders</i>			Urinary retention			
<i>Pregnancy, puerperium and perinatal conditions</i>						Drug withdrawal syndrome neonatal <sup>31</sup>
<i>Reproductive system and breast disorders</i>			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
<i>General disorders and administration site conditions</i>	Withdrawal (discontinuation) symptoms <sup>1,9</sup>	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome <sup>1</sup> , hypothermia		
<i>Investigations</i>				Elevations in blood creatine phosphokinase <sup>14</sup>		

(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 (shift from normal to > 3X 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 section 4.4).

(5) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of quetiapine.

(6) Fasting blood glucose  $\geq 126$  mg/dL ( $\geq 7.0$  mmol/L) or a non fasting blood glucose  $\geq 200$  mg/dL ( $\geq 11.1$  mmol/L) on at least one occasion.

(7) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

(8) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(9) 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.

- (10) Triglycerides  $\geq 200$  mg/dL ( $\geq 2.258$  mmol/L) (patients  $\geq 18$  years of age) or  $\geq 150$  mg/dL ( $\geq 1.694$  mmol/L) (patients  $< 18$  years of age) on at least one occasion
- (11) Cholesterol  $\geq 240$  mg/dL ( $\geq 6.2064$  mmol/L) (patients  $\geq 18$  years of age) or  $\geq 200$  mg/dL ( $\geq 5.172$  mmol/L) (patients  $< 18$  years of age) on at least one occasion. An increase in LDL cholesterol of  $\geq 30$  mg/dL ( $\geq 0.769$  mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL ( $\geq 1.07$  mmol/L).
- (12) See text below
- (13) Platelets  $\leq 100 \times 10^9/L$  on at least one occasion
- (14) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
- (15) Prolactin levels (patients  $> 18$  years of age):  $> 20$   $\mu\text{g/L}$  ( $> 869.56$  pmol/L) males;  $> 30$   $\mu\text{g/L}$  ( $> 1304.34$  pmol/L) females at any time.
- (16) May lead to falls.
- (17) HDL cholesterol:  $< 40$  mg/dL (1.025 mmol/L) males;  $< 50$  mg/dL (1.282 mmol/L) females at any time.
- (18) Incidence of patients who have a QTc shift from  $< 450$  msec to  $\geq 450$  msec with a  $\geq 30$  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.
- (19) Shift from  $> 132$  mmol/L to  $\leq 132$  mmol/L on at least one occasion.
- (20) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see Sections 4.4 and 5.1).
- (21) See Section 5.1
- (22) Decreased haemoglobin to  $\leq 13$  g/dL (8.07 mmol/L) males,  $\leq 12$  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.
- (23) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
- (24) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T<sub>4</sub>, free T<sub>4</sub>, total T<sub>3</sub> and free T<sub>3</sub> are defined as  $< 0.8 \times \text{LLN}$  (pmol/L) and shift in TSH is  $> 5$  mIU/L at any time.
- (25) Based upon the increased rate of vomiting in elderly patients ( $\geq 65$  years of age).
- (26) Based on shift in neutrophils from  $\geq 1.5 \times 10^9/L$  at baseline to  $< 0.5 \times 10^9/L$  at any time during treatment and based on patients with severe neutropenia ( $< 0.5 \times 10^9/L$ ) and infection during all quetiapine clinical trials (See Section 4.4).
- (27) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as  $> 1 \times 10^9$  cells/L at any time.
- (28) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as  $\leq 3 \times 10^9$  cells/L at any time.
- (29) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
- (30) 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 Section 4.4).
- (31) See Section 4.6.
- (32) May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event 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.

### Paediatric population

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.

**Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not 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 ( $< 1/10,000$ ).

<b>SOC</b>	<b>Very Common</b>	<b>Common</b>
<i>Endocrine disorders</i>	Elevations in prolactin <sup>1</sup>	
<i>Metabolism and nutritional disorders</i>	Increased appetite	
<i>Nervous system disorders</i>	Extrapyramidal symptoms <sup>3, 4</sup>	Syncope
<i>Vascular disorders</i>	Increases in blood pressure <sup>2</sup>	
<i>Respiratory, thoracic and mediastinal disorders</i>		Rhinitis
<i>Gastrointestinal disorders</i>	Vomiting	
<i>General disorders and administration site conditions</i>		Irritability <sup>3</sup>

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 >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.
4. See section 5.1

#### Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#).**

## **4.9 Overdose**

### Symptoms

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. Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4, Orthostatic Hypotension).

### **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.

Based on public literature, patients with delirium and agitation and a clear anticholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring), This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines

ATC code: N05A H04

#### **Mechanism of action:**

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5HT<sub>2</sub>) and dopamine D<sub>1</sub>- and D<sub>2</sub>- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT<sub>2</sub> relative to D<sub>2</sub>- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha<sub>1</sub> receptors, moderate affinity at adrenergic alpha<sub>2</sub> receptors and moderate to high affinity at several muscarinic receptors. Inhibition of NET and partial agonist action at 5HT<sub>1A</sub> sites by norquetiapine may contribute to Seroquel XR's therapeutic efficacy as an antidepressant.

#### **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 D<sub>2</sub>-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<sub>2</sub>-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D<sub>2</sub>-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve Cebus monkeys after acute and chronic administration. (See Section 4.8)

#### **Clinical efficacy:**

##### **Schizophrenia**

The efficacy of Seroquel XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Seroquel immediate release-to-Seroquel XR switching study in clinically stable outpatients with schizophrenia. The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Seroquel XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

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



In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XR for 16 weeks, Seroquel XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XR treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with Seroquel XR for up to 9 months (median 7 months). In particular, reports of adverse events related to EPS and weight gain did not increase with longer-term treatment with Seroquel XR.

### **Bipolar Disorder**

In the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of Seroquel XR was further demonstrated with significance versus placebo in an additional 3 week study. Seroquel XR was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day Seroquel XR showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine, with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Seroquel IR 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 IR 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 quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

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.

## Major depressive episodes in MDD

Two short-term (6 week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Seroquel XR 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see below).

The following studies were conducted with Seroquel XR as monotherapy treatment, however Seroquel XR is only indicated for use as add-on therapy:

In three out of four short term (up to 8 weeks) monotherapy studies, in patients with major depressive disorder, Seroquel XR 50 mg, 150 mg and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (LS mean change vs. placebo of 2-4 points).

In a monotherapy relapse prevention study, patients with depressive episodes stabilised on open-label Seroquel XR treatment for at least 12 weeks were randomised to either Seroquel XR once daily or placebo for up to 52 weeks. The mean dose of Seroquel XR during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for Seroquel XR treated patients and 34.4% for placebo-treated patients.

In a short-term (9 week) study non-demented elderly patients (aged 66 to 89 years) with major depressive disorder, Seroquel XR dosed flexibly in the range of 50 mg to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study patients randomised to Seroquel XR received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The mean dose of Seroquel XR was 160 mg/day. Other than the incidence of extrapyramidal symptoms (see section 4.8 and 'Clinical Safety' below) the tolerability of Seroquel XR once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomized patients over 75 years of age was 19%.

### 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, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

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  $\geq 7\%$  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.

A 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania indicated that the combination of SEROQUEL XR with lithium leads to more adverse events (63% versus 48% in SEROQUEL XR in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the SEROQUEL XR with lithium add-on group (12.7%) compared to the SEROQUEL XR with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain ( $\geq 7\%$ ) at the end of treatment compared to patients in the placebo add-on group (4.7%).

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<sub>4</sub> 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 T<sub>4</sub>, 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/day) 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.

## Paediatric population

### Clinical efficacy

The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n=222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was -5.21 for Seroquel 400 mg/day and -6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement  $\geq 50\%$ ) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was -8.16 for Seroquel 400 mg/day and -9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as  $\geq 30\%$  reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XR in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

### Clinical safety

In the short-term pediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain  $\geq 7\%$  of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 12.5% vs. 6% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended post-treatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

### Long-term safety

A 26-week open-label extension to the acute trials (n=380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see sections 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

## 5.2 Pharmacokinetic properties

### Absorption:

Quetiapine is well absorbed following oral administration. Seroquel XR achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (T<sub>max</sub>). 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 and dose-proportional for doses up to 800 mg administered once daily. When Seroquel XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (Seroquel immediate release) administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C<sub>max</sub>) is 13% lower at steady state. When Seroquel XR is compared to Seroquel immediate release, the norquetiapine metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the Seroquel XR C<sub>max</sub> and AUC of approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C<sub>max</sub> or AUC of quetiapine. It is recommended that Seroquel XR is taken once daily without food.

### Distribution:

Quetiapine is approximately 83% bound to plasma proteins.

### Biotransformation:

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.

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. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

### Elimination:

The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabelled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. 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 pharmacokinetics of quetiapine does 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/1.73 m<sup>2</sup>), but the individual clearance values are within the range for normal subjects.

#### Hepatic impairment:

The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcoholcirrhosis). 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 section 4.2).

#### **Paediatric population**

Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine (Seroquel) twice daily. At steady-state, the dose-normalized plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C<sub>max</sub> in children was at the higher end of the range observed in adults. The AUC and C<sub>max</sub> for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for Seroquel XR in children and adolescents.

### **5.3 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<sub>3</sub> 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 section 5.1).

In an embryofoetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **Core**

Cellulose, microcrystalline

Sodium citrate

Lactose monohydrate

Magnesium stearate

Hypromellose 2208

**Coating**

Hypromellose 2910

Macrogol 400

Titanium dioxide (E171)

Iron oxide, yellow (E172) (50, 200 and 300 mg tablets)

Iron oxide, red (E172) (50 mg tablets)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Polychlorotrifluoroethylene and polyvinylchloride with aluminium blister

<b>Tablet Strength</b>	<b>Carton (pack) contents</b>	<b>Blisters</b>
<b>50 mg, 150 mg 200 mg, 300 mg and 400 mg tablets</b>	10 tablets	1 blister of 10 tablets
	30 tablets	3 blisters of 10 tablets
	50 tablets	10 blisters of 5 tablets
	50 tablets	5 blisters of 10 tablets
	60 tablets	6 blisters of 10 tablets
	100 tablets	10 blisters of 10 tablets
	100 tablets	100 blisters of 1 tablet

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER****8. MARKETING AUTHORISATION NUMBER(S)****9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION****10. DATE OF REVISION OF THE TEXT**

## **LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND LABEL FOR BOTTLE**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 50 mg prolonged-release tablets  
quetiapine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 50 mg quetiapine (as fumarate)

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 prolonged-release tablets  
30 prolonged-release tablets  
50 prolonged-release tablets  
60 prolonged-release tablets  
100 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Do not split, chew or crush the tablets.  
Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**16. INFORMATION IN BRAILLE**

Seroquel XR 50 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 50 mg prolonged-release tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND LABEL FOR BOTTLE**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 150 mg prolonged-release tablets  
quetiapine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 150 mg quetiapine (as fumarate)

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 prolonged-release tablets  
30 prolonged-release tablets  
50 prolonged-release tablets  
60 prolonged-release tablets  
100 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Do not split, chew or crush the tablets.  
Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

{Name and Address}  
<{tel}>  
<{fax}>  
<{e-mail}>

**12.     MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13.     BATCH NUMBER**

Lot

**14.     GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**16.     INFORMATION IN BRAILLE**

Seroquel XR 150 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 150 mg prolonged-release tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND LABEL FOR BOTTLE**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 200 mg prolonged-release tablets  
quetiapine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 200 mg quetiapine (as fumarate)

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 prolonged-release tablets  
30 prolonged-release tablets  
50 prolonged-release tablets  
60 prolonged-release tablets  
100 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Do not split, chew or crush the tablets.  
Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**16. INFORMATION IN BRAILLE**

Seroquel XR 200 mg



**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 200 mg prolonged-release tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND LABEL FOR BOTTLE**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 300 mg prolonged-release tablets  
quetiapine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 300 mg quetiapine (as fumarate)

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 prolonged-release tablets  
30 prolonged-release tablets  
50 prolonged-release tablets  
60 prolonged-release tablets  
100 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Do not split, chew or crush the tablets.  
Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**16. INFORMATION IN BRAILLE**

Seroquel XR 300 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 300 mg prolonged-release tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND LABEL FOR BOTTLE**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 400 mg prolonged-release tablets  
quetiapine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 400 mg quetiapine (as fumarate)

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 prolonged-release tablets  
30 prolonged-release tablets  
50 prolonged-release tablets  
60 prolonged-release tablets  
100 prolonged-release tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Do not split, chew or crush the tablets.  
Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**16. INFORMATION IN BRAILLE**

Seroquel XR 400 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Seroquel XR 400 mg prolonged-release tablets  
quetiapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**PACKAGE LEAFLET**



## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Seroquel XR 50 mg, 150 mg, 200 mg, 300 mg, 400 mg prolonged-release tablets

quetiapine

#### **Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See Section 4.

#### **In this leaflet:**

1. What Seroquel XR is and what it is used for
2. What you need to know before you take Seroquel XR
3. How to take Seroquel XR
4. Possible side effects
5. How to store Seroquel XR
6. Contents of the pack and other information

#### **1. What Seroquel XR is and what it is used for**

Seroquel XR contains a substance called quetiapine. This belongs to a group of medicines called anti-psychotics. Seroquel XR can be used to treat several illnesses, such as:

- Bipolar depression and major depressive episodes in major depressive disorder: where you feel sad. You may find that you feel depressed, feel guilty, lack energy, lose your appetite or can't sleep.
- Mania: where you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Schizophrenia: where you may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed.

When Seroquel XR is being taken to treat major depressive episodes in major depressive disorder, it will be taken in addition to another drug being used to treat this illness.

Your doctor may continue to prescribe Seroquel XR even when you feel better.

#### **2. What you need to know before you take Seroquel XR**

##### **Do not take Seroquel XR:**

- If you are allergic (hypersensitive) to quetiapine or any of the other ingredients of Seroquel XR (see section 6: Further information)
- If you are taking any of the following medicines:
  - some medicines for HIV
  - azole medicines (for fungal infections)
  - erythromycin or clarithromycin (for infections)
  - nefazodone (for depression)

Do not take Seroquel XR if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Seroquel XR.

## Warnings and Precautions

Talk to your doctor or pharmacist before taking Seroquel XR if:

- You, or someone in your family, have or have had any heart problems, for example heart rhythm problems, weakening of the heart muscle or inflammation of the heart or if you are taking any medicines that may have an impact on the way your heart beats.
- You have low blood pressure.
- You have had a stroke, especially if you are elderly.
- You have problems with your liver.
- You have ever had a fit (seizure).
- You have diabetes or have a risk of getting diabetes. If you do, your doctor may check your blood sugar levels while you are taking Seroquel XR.
- You know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- You are an elderly person with dementia (loss of brain function). If you are, Seroquel XR should not be taken because the group of medicines that Seroquel XR belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.
- You or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Tell your doctor immediately if you experience any of the following after taking Seroquel XR:

- A combination of fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called “neuroleptic malignant syndrome).” Immediate medical treatment may be needed.
- Uncontrollable movements, mainly of your face or tongue.
- Dizziness or a severe sense of feeling sleepy. This could increase the risk of accidental injury (fall) in elderly patients.
- Fits (seizures).
- A long-lasting and painful erection (Priapism).

These conditions can be caused by this type of medicine.

Tell your doctor as soon as possible if you have:

- A fever, flu-like symptoms, sore throat, or any other infection, as this could be a result of a very low white blood cell count, which may require Seroquel XR to be stopped and/or treatment to be given.
- Constipation along with persistent abdominal pain, or constipation which has not responded to treatment, as this may lead to a more serious blockage of the bowel.

### Thoughts of suicide and worsening of your depression

If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer. These thoughts may also be increased if you suddenly stop taking your medication. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

### Weight gain

Weight gain has been seen in patients taking Seroquel XR. You and your doctor should check your weight regularly.

### **Children and Adolescents**

Seroquel XR is not for use in children and adolescents below 18 years of age.

### **Other medicines and Seroquel XR**

Tell your doctor if you are taking or have recently taken any other medicines .

Do not take Seroquel XR if you are taking any of the following medicines:

- Some medicines for HIV.
- Azole medicines (for fungal infections).
- Erythromycin or clarithromycin (for infections).
- Nefazodone (for depression).

Tell your doctor if you are taking any of the following medicines:

- Epilepsy medicines (like phenytoin or carbamazepine).
- High blood pressure medicines.
- Barbiturates (for difficulty sleeping).
- Thioridazine or Lithium (other anti-psychotic medicines).
- Medicines that have an impact on the way your heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (drugs to treat infections).
- Medicines that can cause constipation.

Before you stop taking any of your medicines, please talk to your doctor first.

### **Seroquel XR with food, drink and alcohol**

- Seroquel XR can be affected by food and you should therefore take your tablets at least one hour before a meal or prior to bedtime.
- Be careful how much alcohol you drink. This is because the combined effect of Seroquel XR and alcohol can make you sleepy.
- Do not drink grapefruit juice while you are taking Seroquel XR. It can affect the way the medicine works.

### **Pregnancy and breast-feeding**

If you are pregnant or breast feeding, think you may be pregnant or planning to have a baby ask your doctor for advice before taking Seroquel XR. You should not take Seroquel XR during pregnancy unless this has been discussed with your doctor. Seroquel XR should not be taken if you are breast-feeding.

The following symptoms which can represent withdrawal may occur in newborn babies of mothers that have used Seroquel in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

### **Driving and using machines**

Your tablets may make you feel sleepy. Do not drive or use any tools or machines until you know how the tablets affect you.

**Seroquel XR contains lactose**

Seroquel XR contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

**Effect on Urine Drug Screens**

If you are having a urine drug screen, taking Seroquel may cause positive results for methadone or certain drugs for depression called tricyclic antidepressants (TCAs) when some test methods are used, even though you may not be taking methadone or TCAs. If this happens, a more specific test can be performed.

**3. How to take Seroquel XR**

Always take Seroquel XR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor will decide on your starting dose. The maintenance dose (daily dose) will depend on your illness and needs but will usually be between 150 mg and 800 mg.

- You will take your tablets once a day.
- Do not split, chew or crush the tablets.
- Swallow your tablets whole with a drink of water.
- Take your tablets without food (at least one hour before a meal or at bedtime, your doctor will tell you when).
- Do not drink grapefruit juice while you are taking Seroquel XR. It can affect the way the medicine works.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

**Liver problems**

If you have liver problems your doctor may change your dose.

**Elderly people**

If you are elderly your doctor may change your dose.

**Use in children and adolescents**

Seroquel XR should not be used by children and adolescents aged under 18 years.

**If you take more Seroquel XR than you should**

If you take more Seroquel XR than prescribed by your doctor, you may feel sleepy, feel dizzy and experience abnormal heart beats. Contact your doctor or nearest hospital straight away. Keep the Seroquel XR tablets with you.

**If you forget to take a dose of Seroquel XR**

If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Seroquel XR**

If you suddenly stop taking Seroquel XR, you may be unable to sleep (insomnia), or you may feel sick (nausea), or you may experience headache, diarrhoea, being sick (vomiting), dizziness or irritability. Your doctor may suggest you reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

#### 4. Possible side effects

Like all medicines, Seroquel XR can cause side effects, although not everybody gets them.

##### **Very common side effects (may affect more than 1 in 10 people):**

- Dizziness (may lead to falls), headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel) (may lead to falls).
- Discontinuation symptoms (symptoms which occur when you stop taking Seroquel) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness, and irritability. Gradual withdrawal over a period of at least 1 to 2 weeks is advisable.
- Putting on weight.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Changes in the amount of certain fats (triglycerides and total cholesterol)

##### **Common side effects (may affect up to 1 in 10 people):**

- Rapid heartbeat.
- Feeling like your heart is pounding, racing or has skipped beats.
- Constipation, upset stomach (indigestion).
- Feeling weak.
- Swelling of arms or legs.
- Low blood pressure when standing up. This may make you feel dizzy or faint (may lead to falls).
- Increased levels of sugar in the blood.
- Blurred vision.
- Abnormal dreams and nightmares
- Feeling more hungry
- Feeling irritated
- Disturbance in speech and language.
- Thoughts of suicide and worsening of your depression.
- Shortness of breath.
- Vomiting (mainly in the elderly).
- Fever
- Changes in the amount of thyroid hormones in your blood
- Decreases in the number of certain types of blood cells
- Increases in the amount of liver enzymes measured in the blood
- Increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - Men and women to have swelling of breasts and unexpectedly produce breast milk.
  - Women to have no monthly period or irregular periods.

##### **Uncommon side effects (may affect up to 1 in 100 people):**

- Fits or seizures
- Allergic reactions that may include raised lumps (weals), swelling of the skin and swelling around the mouth.
- Unpleasant sensations in the legs (also called restless legs syndrome).
- Difficulty swallowing.
- Uncontrollable movements, mainly of your face or tongue.
- Sexual dysfunction.
- Diabetes
- Change in electrical activity of the heart seen on ECG (QT prolongation)
- A slower than normal heart rate which may occur when starting treatment and which may be associated with low blood pressure and fainting.

- Difficulty in passing urine.
- Fainting (may lead to falls)
- Stuffy nose
- Decrease in the amount of red blood cells
- Decrease in the amount of sodium in the blood

**Rare side effects (may affect up to 1 in 1,000 people):**

- A combination of high temperature (fever), sweating, stiff muscles, feeling very drowsy or faint (a disorder called “neuroleptic malignant syndrome).”
- Yellowing of the skin and eyes (jaundice).
- Inflammation of the liver (hepatitis).
- A long-lasting and painful erection (priapism).
- Swelling of breasts and unexpected production of breast milk (galactorrhoea).
- Menstrual disorder.
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- Walking, talking, eating or other activities while you are asleep.
- Body temperature decreased (hypothermia).
- Inflammation of the pancreas
- A condition (called “metabolic syndrome”) where you may have a combination of 3 or more of the following: an increase in fat around your abdomen, a decrease in “good cholesterol” (HDL-C), an increase in a type of fat in your blood called triglycerides, high blood pressure and an increase in your blood sugar.
- Combination of fever, flu-like symptoms, sore throat, or any other infection with very low white blood cell count, a condition called agranulocytosis.
- Bowel obstruction.
- Increased blood creatine phosphokinase (a substance from the muscles)

**Very rare side effects (may affect up to 1 in 10,000 people):**

- Severe rash, blisters, or red patches on the skin.
- A severe allergic reaction (called anaphylaxis) which may cause difficulty in breathing or shock.
- Rapid swelling of the skin, usually around the eyes, lips and throat (angioedema).
- A serious blistering condition of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)
- Inappropriate secretion of a hormone that controls urine volume.
- Breakdown of muscle fibers and pain in muscles (rhabdomyolysis).
- Worsening of pre-existing diabetes.

**Not known (frequency cannot be estimated from the available data)**

- Skin rash with irregular red spots (erythema multiforme)
- Serious, sudden allergic reaction with symptoms such as fever and blisters on the skin and peeling of the skin (toxic epidermal necrolysis)
- Symptoms of withdrawal may occur in newborn babies of mothers that have used Seroquel XR during their pregnancy

The class of medicines to which Seroquel XR belongs can cause heart rhythm problems, which can be serious and in severe cases may be fatal.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, changes in the amount of thyroid hormones in your blood, increased liver enzymes, decreases in the number of certain types of blood cells, decrease in

the amount of red blood cells, increased blood creatine phosphokinase (a substance in the muscles), decrease in the amount of sodium in the blood and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:

- Men and women to have swelling of breasts and unexpectedly produce breast milk.
- Women to have no monthly period or irregular periods.

Your doctor may ask you to have blood tests from time to time.

### **Side effects in children and adolescents**

The same side effects that may occur in adults may also occur in children and adolescents.

The following side effects have been seen more often in children and adolescents or have not been seen in adults:

#### **Very Common side effects (may affect more than 1 in 10 people):**

- Increase in the amount of a hormone called prolactin, in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - Boys and girls to have swelling of breasts and unexpectedly produce breast milk
  - Girls to have no monthly period or irregular periods
- Increased appetite
- Vomiting
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Increase in blood pressure

#### **Common side effects (may affect up to 1 in 10 people):**

- Feeling weak, fainting (may lead to falls).
- Stuffy nose.
- Feeling irritated.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Seroquel XR**

- Keep this medicine out of the reach and sight of children.
- Do not use Seroquel XR after the expiry date which is stated on the container after EXP. The expiry date refers to the last day of that month.
- Seroquel XR does not require any special storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

### What Seroquel XR contains

- The active substance is quetiapine. Seroquel XR tablets contain 50 mg, 150 mg, 200 mg, 300 mg or 400 mg of quetiapine (as quetiapine fumarate).
- The other ingredients are:

Tablet core: microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose.

Tablet coating: hypromellose, macrogol, titanium dioxide (E171). The 50 mg, 200 mg and 300 mg tablets also contain iron oxide yellow (E172) and the 50 mg tablets contain iron oxide red (E172).

### What Seroquel XR looks like and contents of the pack

All prolonged-release tablets are capsule shaped and marked with XR and the strength. 50 mg tablets are peach coloured; 150 mg tablets are white coloured, 200 mg tablets are yellow coloured; 300 mg tablets are pale yellow coloured and 400 mg tablets are white coloured.

Pack sizes of 10, 30, 50, 60 and 100 tablets are registered for all strengths. Not all pack sizes may be available.

### Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address }

<{tel}>

<{fax}>

<{e-mail}>

### This medicinal product is authorised in the Member States of the EEA under the following names:

COUNTRY	TRADE NAME
Austria	Seroquel XR
Belgium	Seroquel XR
Cyprus	Seroquel XR
Czech Republic	Seroquel Prolong
Denmark	Seroquel Prolong
Estonia	Seroquel XR
Finland	Seroquel Prolong
France	Xeroquel LP
Germany	Seroquel Prolong® 50 mg Retardtabletten, Seroquel Prolong® 150 mg Retardtabletten, Seroquel Prolong® 200 mg Retardtabletten, Seroquel Prolong® 300 mg Retardtabletten, Seroquel Prolong® 400 mg Retardtabletten
Greece	Seroquel XR
Hungary	Seroquel XR
Iceland	Seroquel Prolong



Ireland	Seroquel XR
Italy	Seroquel compresse a rilascio prolungato
Latvia	Seroquel XR
Lithuania	Seroquel XR
Luxembourg	Seroquel XR
Malta	Seroquel XR
Netherlands	Seroquel XR
Norway	Seroquel Depot
Portugal	Seroquel SR
Romania	Seroquel XR
Slovakia	Seroquel XR
Slovenia	Seroquel SR
Spain	Seroquel Prolong
Sweden	Seroquel Depot
United Kingdom	Seroquel XL

**This leaflet was last approved in {MM/YYYY}.**