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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SEROQUEL®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Seroquel 25 mg tablets: Each tablet contains 25 mg quetiapine (as 28.78 mg quetiapine fumarate).

Seroquel 100 mg tablets: Each tablet contains 100 mg quetiapine (as 115.13 mg quetiapine fumarate).

Seroquel 200 mg tablets: Each tablet contains 200 mg quetiapine (as 230.26 mg quetiapine fumarate).

Seroquel 300 mg tablets: Each tablet contains 300 mg quetiapine (as 345.39 mg quetiapine fumarate).

For Excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis

Suicidal Thoughts and Behavior

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families

and caregivers of the need for close observation and communication with the prescriber

SEROQUEL is not approved for use in pediatric patients under 18 years of age

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of schizophrenia.

Treatment of manic episodes associated with bipolar disorder.

Treatment of major depressive episodes in bipolar disorder.

Seroquel is not indicated for the prevention of recurrence of manic or depressive episodes.

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 should be administered twice daily, with or without food.

Adults

For the treatment of schizophrenia : the total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder: as monotherapy or as adjunct therapy to mood stabilizers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

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

For the treatment of depressive episodes in bipolar disorder: Seroquel should be administered once daily at bedtime as this may reduce the likelihood of daytime sedation. 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. Depending on the patient's response Seroquel may be titrated up to 600 mg daily. Antidepressant efficacy was demonstrated at 300 mg and 600 mg/day, however no additional benefit was seen in the 600 mg group above 300 mg daily during short-term treatment.(see section 5.1)

When treating depressive episodes in bipolar disorder, treatment should be prescribed by physicians experienced in treating bipolar disorder.

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.

Children and adolescents

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

Renal Impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic Impairment:

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

4.3 Contraindications

SEROQUEL is contraindicated in patients who are hypersensitive to any component 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 special precautions for use

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

Children and adolescents (10 to 17 years of age):

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. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), 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 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 and bipolar mania and bipolar depression (see section 4.8 Undesirable effects).

Suicide/suicidal thoughts or clinical worsening:

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

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

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

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 disorder. The same precautions observed when treating patients with major depressive disorder 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).

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

Concomitant illness

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

Sever Neutropenia and agranulocytosis:

Severe neutropenia ($<0.5 \times 10^9/L$) without infection has been uncommonly reported in Short-term placebo controlled monotherapy clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases).

Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with Seroquel. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors.

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

Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9/L$. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed $1.5 \times 10^9/L$). (see Section 5.1).

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

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 utilised antipsychotic guidelines (see Section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties).

Increases in blood glucose and Hyperglycaemia:

Increases in blood glucose and 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 and cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid increases should be managed as clinically appropriate.

Metabolic Risk

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

Pancreatitis

Pancreatitis has been reported in clinical trials and during the post marketing experience, however a causal relationship has not been established. Among the post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see Section 4.4 Lipids), gallstones, and alcohol consumption.¹

Dysphagia:

Dysphagia (See section 4.8 Undesirable effects) and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been

established, quetiapine should be used with caution in patients at risk for aspiration pneumonia.

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.

Cardiovascular disease:

SEROQUEL should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

SEROQUEL may induce orthostatic hypotension, this is more common in elderly patients than in younger patients especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs.

A slower titration regimen could be considered in patients with underlying cardiovascular disease.

QT Prolongation

In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. However, with overdose (see section 4.9) QT prolongation was observed. 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 with medicines known to increase QTc interval, and 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.

Seizures:

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with SEROQUEL or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (See also *Section 4.8 Undesirable Effects*).

Extrapyramidal symptoms:

In placebo controlled clinical trials quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder.(see section 4.8).

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

As with other antipsychotics, there is a potential for SEROQUEL to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of SEROQUEL should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see Section 4.8).

Neuroleptic malignant syndrome:

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

Withdrawal:

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable (see Section 4.8 Undesirable effects)

Elderly Patients with Dementia:

SEROQUEL is not approved for the treatment of patients with 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. Seroquel should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo controlled SEROQUEL studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in SEROQUEL-treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do

not establish a causal relationship between SEROQUEL treatment and death in elderly patients with dementia.

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anticholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anticholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma. (See Sections 4.5 Interaction with other medicinal products, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties, Mechanism of Action, and 4.9 Overdose).

Lactose:

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

Interactions

See also section 4.5

Concomitant use of Seroquel with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of Seroquel therapy. In patients receiving an hepatic enzyme inducer, initiation of Seroquel treatment should only occur if the physician considers that the benefits of Seroquel 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).

During concomitant administration of drugs, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of quetiapine **Error! Bookmark not defined.** should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

The concomitant use of quetiapine with central nervous system depressant medications (eg. benzodiazepines) should be used with caution as concomitant use has the potential to increase adverse effects such as somnolence, drowsiness and sedation. This is particularly important in those with risk factors for a history of sleep apnoea.

Body Temperature Regulation:

Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to

extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Additional information:

Seroquel 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.

Hepatic effects:

If jaundice develops, Seroquel should be discontinued

4.5 Interactions with other medicinal products and other forms of interaction

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

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 take quetiapine together with grapefruit juice.

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 Seroquel therapy.

Co-administration of Seroquel 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 Seroquel treatment should only occur if the physician considers that the benefits of Seroquel 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 also 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 Seroquel 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 Seroquel.

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.

The pharmacokinetics of sodium valproate and Seroquel were not altered to a clinically relevant extent when co-administered.

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

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

Caution should be exercised treating patients receiving other medications having anticholinergic (muscarinic) effects (see Section 4.4 Special warnings and special precautions).

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 Pregnancy and lactation

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.

Breast-feeding

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.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Seroquel.

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

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).

Blood and lymphatic system disorders

Very Common: Decreased haemoglobin²²

Common: Leucopenia^{1,28} decreased neutrophil count, eosinophils increased²⁷⁷

Uncommon: Thrombocytopenia, Anaemia, Platelet count decreased¹³

Rare: Agranulocytosis²⁶

Unknown Neutropenia¹

Immune system disorders

Uncommon: Hypersensitivity (including allergic skin reactions)

Very rare: Anaphylactic reaction⁵

Endocrinic disorders:

Common: Hyperprolactinaemia¹⁵, decreases in Total T₄²⁴, decreases in Free T₄²⁴, decreases in Total T₃²⁴, increases in TSH²⁴

Uncommon: Decrease in free T₃²⁴, Hypothyroidism²¹

Very rare: Inappropriate antidiuretic hormone secretion

Metabolism and nutritional disorders

<i>Very Common:</i>	Elevations in serum triglyceride levels ^{10,30} , Elevations in total cholesterol (predominantly LDL cholesterol) ^{11,30} , Decreases in HDL cholesterol ^{17,30} , Weight gain ^{8,30}
<i>Common:</i>	Increase appetite, Blood glucose increased to hyperglycaemic levels ^{7,31}
<i>Uncommon:</i>	Hyponatraemia ²⁰ , Diabetes Mellitus ^{1, 5,6}
<i>Rare:</i>	Metabolic syndrome ³⁰
Very Rare	Exacerbation of pre-existing diabetes

Nervous system disorders

<i>Very Common:</i>	Dizziness ^{4,16} , somnolence ^{2,16} , headache, Extrapyrimal symptoms ^{1,21}
<i>Common:</i>	Dysarthria
<i>Uncommon:</i>	Seizure ¹ , Restless legs syndrome, Tardive dyskinesia ^{1, 5} , Syncope ^{4,16}

Cardiac disorders

<i>Common:</i>	Palpitations ²³ , Tachycardia ⁴
<i>Uncommon:</i>	QT prolongation ^{1,12, 18} ,Bradycardia ³²

Eye Disorders

<i>Common:</i>	Vision blurred
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Vascular disorders

<i>Common:</i>	Orthostatic hypotension ^{4,16}
<i>Rare:</i>	Venous thromboembolism ¹

Respiratory, thoracic and mediastinal disorder

<i>Common:</i>	Dyspnea ²³ Rhinitis
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Gastrointestinal disorders

<i>Very common:</i>	Dry mouth,
<i>Common:</i>	Constipation, dyspepsia, Vomiting ²⁵
<i>Uncommon:</i>	Dysphagia ⁷
<i>Rare:</i>	Pancreatitis ¹ , Intestinal obstruction/Ileus

Hepato-biliary disorders

Common: Elevations in serum transaminases alanine aminotransferase (ALT)³, Elevations in gamma-GT levels³

Uncommon Elevations in serum aspartate aminotransferase (AST)³

Rare: Jaundice⁵ Hepatitis (with or without Jandice)

Skin and subcutaneous tissue disorders

Very rare: Angioedema⁵, Stevens-Johnson syndrome⁵

Unknown: Toxic Epidermal Necrolysis, Erythema Multiforme

Musculoskeletal and connective tissue disorders

Very rare: Rhabdomyolysis

<i>Pregnancy, puerperium and perinatal conditions</i>	
<i>Unknown:</i>	Drug withdrawal syndrome neonatal ³¹

Renal and urinary disorders

<i>Uncommon:</i>	Urinary retention
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Reproductive system and breast disorders

Uncommon: Sexual dysfunction

Rare: Priapism, Galactorrhoea breast swelling, menstrual disorder

General disorders and administration site conditions

Very common Withdrawal (discontinuation) symptoms^{1,9}

Common: Mild asthenia, peripheral oedema, Irritability, Pyrexia

Rare: Neuroleptic malignant syndrome¹
Hypothermia

Psychiatric disorders

Common: Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour²⁰

Rare: Somnambulism and related reactions such as sleep talking and sleep related eating disorder

Investigations

Rare: Elevations in blood creatine phosphokinase¹⁴

- (1) See Section 4.4 Special Warnings and Special Precautions for Use.
- (2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of Seroquel.
- (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 Seroquel. These elevations were usually reversible on continued Seroquel treatment.
- (4) As with other antipsychotics with alpha1 adrenergic blocking activity, Seroquel 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 ≥ 126 mg/dL (≥ 7.0 mmol/L) or a non fasting blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) on at least one occasion.
- (7) An increase in the rate of dysphagia with SEROQUEL 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.
- (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 ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients <18 years of age) on at least one occasion.
- (11) Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).
- (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 μ g/L >869.56 pmol/L) males; >30 μ 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 ≥ 450 msec with a ≥ 30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
- (19) Shift from >132 mmol/L to <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 (Pharmacodynamic properties).
 - (22) Decreased haemoglobin to ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin 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 any time 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 (≥ 65 years of age).
 - (26) Based on shift in neutrophils from $> = 1.5 \times 10^9/L$ 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 any time post-baseline in all trials. Shifts in eosinophils are defined as $> 1 \times 10^9$ at any time.
 - (28) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined $\leq 3 \times 10^9$ 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.

Extrapyramidal Symptoms

The following clinical trials (monotherapy and combination therapy) in adult patients included treatment with SEROQUEL and SEROQUEL XR.

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary,

psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. In long-term studies of schizophrenia and bipolar disorder the aggregated incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

Thyroid Levels

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T4: 3.4 % for quetiapine versus 0.6 % for placebo; free T4: 0.7% for quetiapine versus 0.1% for placebo; total T3: 0.54 % for quetiapine versus 0.0% for placebo and free T3: 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T3 and TSH was 0.0 % for both quetiapine and placebo and 0.1% for quetiapine versus 0.0 % for placebo for shifts in T4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. In eight patients, where TBG was measured, levels of TBG were unchanged.

Children and adolescents (10 to 17 years of age)

The same ADRs described above for adults should be considered for children and adolescents. The following table summarises ADRs that occur in a higher frequency category in children and adolescent patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).	
<i>Endocrine disorders</i>	
Very Common	Elevations in prolactin ¹
<i>Metabolism and nutritional disorders</i>	
<i>Very common:</i>	Increased appetite
<i>Nervous system disorders</i>	
Very Common	Extrapyramidal symptoms ^{3, 4}
<i>Common</i>	Syncope
<i>Vascular disorders</i>	
Very Common	Increases in blood pressure ²

General disorders and administration site conditions	
Common:	Irritability ³
Respiratory, thoracic and mediastinal disorder	
Common:	Rhinitis
Gastrointestinal disorders	
Very Common:	Vomiting

(1) Prolactin levels (patients < 18 years of age): >20 µg/L >869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level>100 µg/L.

(2) Based on shifts above clinically significant thresholds (adapted from the National Institute of Health criteria) or increases>20mmHg for systolic or>10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

(3) Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

(4) See section 5.1

4.9 Overdose

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e. drowsiness and sedation, tachycardia and hypotension and anticholinergic effects⁸.

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 *Special warnings and special precautions for use*).

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of Seroquel alone. However, survival has also been reported following acute overdoses of up to 30 grams. In postmarketing experience, there have been very rare reports of overdose of Seroquel alone resulting in death or coma, or QT-prolongation.

Management

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are

recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

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 (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative 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

Pharmacotherapeutic group: Antipsychotics

Therapeutic classification: N05A H04

5.1 Pharmacodynamic properties

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interacts with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibits affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to dopamine D₂ receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of SEROQUEL.

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

Pharmacodynamic effect

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

In pre-clinical tests predictive of EPS, quetiapine is unlike standard antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D₂ receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D₂ receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The results of these tests predict that SEROQUEL should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia. (See Section 4.8)

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

Clinical efficacy

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.

In four placebo-controlled trials, evaluating doses of SEROQUEL up to 800 mg for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

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.

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

In 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 and approximately 85% of the responders were in the dose range of 400 to 800 mg per 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 XL versus placebo and SEROQUEL XL 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, 5HT₂- and D₂-receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

The 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.

In 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 neutrophil count $<1.5 \times 10^9/L$, was 1.72% in patients treated with Seroquel compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count $\geq 1.5 \times 10^9/L$), the incidence of at least one occurrence of neutrophil count $<0.5 \times 10^9/L$ was 0.21% in patients treated with Seroquel and 0% in placebo treated patients and the incidence $\geq 0.5 - <1.0 \times 10^9/L$ was 0.75% in patients treated with Seroquel and 0.11% in placebo-treated patients.

Cataracts/lens opacities

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

Children and adolescents (10 to 17 years of age)

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.

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

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 Section 4.4 Special warnings and special precautions for use and Section 4.8 Undesirable effects).

Extrapyramidal Symptoms

In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

Weight Gain

In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained $\geq 7\%$ of their body weight. When adjusting for normal growth over 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.

Suicide/Suicidal thoughts or Clinical worsening

In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 Pharmacokinetic properties

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

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

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

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

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted

in the urine and 21% in the faeces. The mean 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). *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is observed only at concentrations approximately 5 to 50-fold higher than those observed at 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.

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/1.73m²), 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).

Children and adolescents (10 to 17 years of age)

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_{max} in children was at the higher end of the range observed in adults. The AUC and C_{max} 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 T₃ 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

<i>Core</i>	<i>Coating</i>
Povidone	Hypromellose (Methylhydroxypropyl cellulose)
Calcium hydrogen phosphate dihydrate	Macrogol 400
Microcrystalline cellulose	Titanium dioxide (E171)
Sodium starch glycollate Type A	Ferric oxide, yellow (E172) (25 mg and 100 mg tablets)
Lactose monohydrate	Ferric oxide, red (E172) (25 mg tablets)
Magnesium stearate	

6.2 Incompatibilities

None known.

6.3 Special precautions for storage

Do not store above 30°C.

6.4 Nature and contents of container

Seroquel 100: Packs of 8, 10, 30, 50, 60, 90, 100

Seroquel 25 Packs of 6, 8, 20, 30, 50, 60, 100

Seroquel 200 Packs of 30, 50, 60, 90, 100

Seroquel 300 Packs of 10, 30

Not all pack sizes may be marketed.

6.5 Instructions for use, handling and disposal

None stated.

7 MANUFACTURER

AstraZeneca U.K. Ltd
Macclesfield, U.K.

8 LICENSE HOLDER AND IMPORTER

Astrazeneca (Israel) Ltd.
PO Box 4070
Ra'anana 43656