

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Seroquel 100mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg quetiapine (as quetiapine fumarate)

Excipient: Contains lactose

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from Spain, Portugal and Italy

Seroquel 100 mg tablets are yellow, round, biconvex and engraved with Seroquel 100 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Seroquel is indicated for the treatment of:

- Schizophrenia.
- Seroquel is indicated for 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 in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

4.2 Posology and method of administration

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 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.

Children and Adolescents:

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

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), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment 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 (see section 4.8).

Suicide/suicidal thoughts or clinical worsening:

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

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

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

Somnolence:

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Cardiovascular:

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

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 section 4.8).

Extrapyramidal symptoms

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

Tardive Dyskinesia:

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of 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 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Seroquel should be discontinued and appropriate medical treatment given.

Severe Neutropenia:

Severe neutropenia (neutrophil count $<0.5 \times 10^9/L$) has been uncommonly reported in Seroquel clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Seroquel. 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. 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).

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 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).

Hyperglycaemia

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

Lipids

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.

Metabolic Risk

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

QT Prolongation

In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5).

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable. (see section 4.8)

Elderly patients with dementia-related psychosis

Seroquel 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. 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. However 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 of 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.

Dysphagia

Dysphagia (see section 4.8) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

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.

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 Seroquel and preventive measures undertaken.

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.

4.5 Interaction 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 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 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.

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 QT interval.

4.6 Fertility, pregnancy and lactation

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

Neonates exposed to antipsychotics (including Seroquel 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.

The degree to which quetiapine is excreted into human milk is unknown. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking Seroquel.

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 Seroquel are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with 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 ($\geq 1/10,000$, $< 1/1000$) and very rare ($< 1/10,000$).

Blood and lymphatic system disorders

<i>Common:</i>	Leucopenia ¹
<i>Uncommon:</i>	Eosinophilia, Thrombocytopenia
<i>Unknown:</i>	Neutropenia ¹

Immune system disorders

<i>Uncommon:</i>	Hypersensitivity
<i>Very rare:</i>	Anaphylactic reaction ⁶

Endocrine disorders

<i>Common:</i>	Hyperprolactinaemia ¹⁶
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Metabolism and nutritional disorders

<i>Common:</i>	Increased appetite
<i>Very rare:</i>	Diabetes Mellitus ^{1, 5,6}

Psychiatric disorders

Common: Abnormal dreams and nightmares

Nervous system disorders

Very Common: Dizziness^{4,17}, Somnolence^{2,17},
Headache

Common: Syncope^{4,17}
Extrapyramidal symptoms^{1, 13},
Dysarthria

Uncommon: Seizure¹, Restless legs syndrome,
Tardive dyskinesia^{1, 6}

Cardiac disorders

Common: Tachycardia⁴

Eye Disorders

Common: Vision blurred

Vascular disorders

Common: Orthostatic hypotension^{4,17}

Respiratory, thoracic and mediastinal disorder

Common: Rhinitis

Gastrointestinal disorders

Very common: Dry mouth

Common: Constipation, Dyspepsia

Uncommon: Dysphagia⁸

Hepato-biliary disorders

Rare: Jaundice⁶

Very rare: Hepatitis⁶

Skin and subcutaneous tissue disorders

Very rare: Angioedema⁶, Stevens-Johnson
syndrome⁶

Reproductive system and breast disorders

Rare: Priapism, Galactorrhoea

Pregnancy, puerperium and perinatal conditions.

Not known: Drug withdrawal syndrome neonatal (see 4.6)

General disorders and administration site conditions

Very common Withdrawal (discontinuation) symptoms^{1,10}

Common: Mild asthenia, Peripheral oedema, Irritability

Rare: Neuroleptic malignant syndrome¹

Investigations

Very common Elevations in serum triglyceride levels¹¹
Elevations in total cholesterol (predominantly LDL cholesterol)¹²
Decreases in HDL cholesterol¹⁸, Weight gain⁹

Common: Elevations in serum transaminases (ALT, AST)³, Decreased
neutrophil count, Blood glucose increased to hyperglycaemic levels⁷

Uncommon:

Elevations in gamma-GT levels³, Platelet count decreased¹⁴,
 QT Prolongation^{1, 13, 19}

Rare Elevations in blood creatine phosphokinase¹⁵, Venous
 thromboembolism¹

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 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. Exacerbation of pre-existing diabetes has been reported in very rare cases.
6. Calculation of Frequency for these ADR's have been taken from postmarketing data only.
7. Fasting blood glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) or a non fasting blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) on at least one occasion.
8. An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.
9. Based on $>7\%$ increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
10. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
11. Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients < 18 years of age) on at least one occasion.
12. Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients < 18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).
13. See text below
14. Platelets $\leq 100 \times 10^9/L$ on at least one occasion
15. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
16. Prolactin levels (patients > 18 years of age): > 20 mg/L (> 869.56 pmol/L) males; > 30 mg/L (> 1304.34 pmol/L) females at any time

17. May lead to falls
18. HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
19. Incidence of patients who have a QTc shift from <450 msec to \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.

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

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group.

Seroquel treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first two to four weeks of Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel treatment was associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that Seroquel causes clinically relevant hypothyroidism.

Children and adolescents (10 to 17 years of age)

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

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

Metabolism and nutritional disorders

Very common: Increased appetite

Investigations

Very common: Elevations in prolactin¹, increases in blood pressure²

Nervous system disorders

Very common: Extrapyramidal symptoms³

General disorders and administration site conditions

Common: Irritability⁴

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

4.9 Overdose

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of 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.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4, Cardiovascular).

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

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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 (5HT₂) and dopamine D₁- and D₂- receptors.

It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 and serotonin 5HT_{1A} receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effects:

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

In pre-clinical tests predictive of EPS, quetiapine is unlike typical 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. (See section 4.8)

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.

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 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 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 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.

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 sections 4.4 and 4.8).

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 norquetiapine are 35% of that observed for quetiapine. The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do 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 norquetiapine 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 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).

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.

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.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the

safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Calcium Hydrogen Phosphate Dihydrate
Microcrystalline Cellulose
Sodium Starch Glycolate Type A
Lactose Monohydrate
Magnesium Stearate
Hypromellose
Macrogol 400
Titanium Dioxide (E171)
Ferric Oxide, Yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Over-labelled cardboard carton containing six PVC/aluminium blisters (ten tablets per blister).
Pack size: 60 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd.
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/68/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th February 2011

10 DATE OF REVISION OF THE TEXT

May 2012