SEROQUEL XR®

quetiapine fumarate

Extended Release Tablets

Qualitative and Quantitative Composition

SEROQUEL XR 50mg: Each tablet contains quetiapine fumarate delivering a dose of 50 mg of quetiapine free base.

SEROQUEL XR 150 mg: Each tablet contains quetiapine fumarate delivering a dose of 150 mg of quetiapine free base.

SEROQUEL XR 200 mg: Each tablet contains quetiapine fumarate delivering a dose of 200 mg of quetiapine free base.

SEROQUEL XR 300mg: Each tablet contains quetiapine fumarate delivering a dose of 300 mg of quetiapine free base.

SEROQUEL XR 400 mg: Each tablet contains quetiapine fumarate delivering a dose of 400 mg of quetiapine free base.

For Excipients see '*Pharmaceutical particulars'*.

Pharmaceutical Form

Film coated, extended release tablet.

SEROQUEL XR 50 mg tablets are capsule-shaped, peach coloured and engraved with "XR 50" on one side.

SEROQUEL XR 150 mg tablets are capsule-shaped, white coloured and engraved with "XR 150" on one side.

SEROQUEL XR 200 mg tablets are capsule-shaped, yellow coloured and engraved with "XR 200" on one side.

SEROQUEL XR 300 mg tablets are capsule-shaped, pale yellow coloured and engraved with "XR 300" on one side.

SEROQUEL XR 400 mg tablets are capsule-shaped, white coloured and engraved with "XR 400" on one side.

CLINICAL PARTICULARS

Therapeutic indications

SEROQUEL XR is indicated for the treatment of schizophrenia.

SEROQUEL XR is effective in preventing relapse in stable schizophrenic patients who have been maintained on SEROQUEL XR.

SEROQUEL XR is indicated for bipolar disorder:

- manic episodes associated with bipolar I disorder
- depressive episodes associated with bipolar disorder

- preventing recurrence in maintenance treatment of bipolar disorder (manic, mixed or depressive episode) as monotherapy or in combination with lithium or valproate.

SEROQUEL XR is indicated for use as add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy. Prior to initiating treatment, clinicians should consider the safety profile of SEROQUEL XR.

Posology and method of administration

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

Adults

For the treatment of schizophrenia:

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary. The safety of doses above 800 mg/day have not been evaluated.

For the treatment of manic episodes associated with bipolar disorder:

SEROQUEL XR should be administered once daily in the evening.

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient.

For the treatment of depressive episodes associated with bipolar disorder:

SEROQUEL XR should be administered once daily in the evening.

SEROQUEL XR should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). SEROQUEL XR can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with SEROQUEL at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group during short-term treatment (See *Undesirable effects* and *Clinical efficacy*).

For preventing recurrence in maintenance treatment of bipolar disorder:

Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase (See *Clinical efficacy*). Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment (See *Clinical efficacy*).

Patients who have responded to SEROQUEL XR in monotherapy for acute treatment of bipolar disorder should continue on SEROQUEL XR therapy at the same dosing regimen.

SEROQUEL XR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day.

Patients who have responded to SEROQUEL XR in combination therapy to a mood stabilizer (lithium or valproate) for acute treatment of bipolar disorder should continue on SEROQUEL XR therapy at the same dose. The SEROQUEL XR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 400 mg to 800 mg/day.

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

When treating recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.

SEROQUEL XR should be administered once daily in the evening.

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

Patients who have not responded to SEROQUEL XR after 6 weeks treatment for MDD should have treatment re-evaluated (See *Clinical efficacy*).

Switching from SEROQUEL immediate-release tablets:

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

Elderly

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

In elderly patients with major depressive disorder initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8 and then up to 300 mg depending on clinical response and tolerability (See *Pharmacodynamic properties*).

Children and adolescents

SEROQUEL is not indicated for use in children and adolescents below 18 years of age. Data from placebo-controlled clinical trials are set forth in sections '*Special warnings and special precautions for use', 'Undesirable effects', 'Pharmacodynamic properties' and 'Pharmacokinetic Properties'.*

Renal and hepatic impairment

The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver. Therefore, SEROQUEL XR should be used with caution in patients with known hepatic impairment.

Patients with hepatic or renal impairment should be started on 50 mg/day. The dose should be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

Contraindications

SEROQUEL XR is contraindicated in patients who are hypersensitive to any component of this product.

Special warnings and special precautions for use

As SEROQUEL XR is indicated for the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with MDD, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

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

Suicide/suicidal thoughts or clinical worsening

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

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. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in

approximately 4400 children and adolescents and 77000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine (See *Clinical efficacy*).

Neutropenia and agranulocytosis

Severe neutropenia (<0.5 X 10^9/L) without infection has been uncommonly reported in short-term placebo controlled monotherapy clinical trials with SEROQUEL. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with SEROQUEL. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia.

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

Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L) (See *Undesirable effects*).

Increases in blood glucose and hyperglycemia

Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (See *Undesirable effects*).

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with atypical antipsychotics, including SEROQUEL. Assessment of the association between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia, and the increasing incidence of diabetes mellitus in the general population. Some epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus should be monitored regularly for worsening of glucose control. Appropriate clinical monitoring is advised for patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) and those who develop symptoms of hyperglycemia during treatment with atypical antipsychotics. Patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.

Lipids

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

Metabolic factors

In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

Pancreatitis

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

Concomitant illness

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

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period. This is more common in elderly patients than in younger patients.

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.

Dysphagia

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

Constipation and intestinal obstruction

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

Seizures

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

Tardive dyskinesia and extrapyramidal symptoms (EPS)

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

In placebo-controlled clinical trials for schizophrenia and bipolar mania the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients.

In short-term, placebo-controlled clinical trials for bipolar depression and major depressive disorder, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (See '*Undesirable effects'* for rates of EPS observed in all indications and ages).

Neuroleptic malignant syndrome

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

QT prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (See *Overdose*). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (See *Interaction with other medicinal products and other forms of interaction*).

Cardiomyopathy and myocarditis

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms

(DRESS) are potentially life threatening adverse drug reactions that have been reported during quetiapine exposure. SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, vomiting, have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (See *Undesirable effects*).

Misuse and abuse

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

Children and adolescents (10 to 17 years of age)

SEROQUEL is not indicated for use in children and adolescents below 18 years of age. Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials with SEROQUEL in children and adolescent patients, the same special warnings and special precautions for use that appear above for adults should be considered for pediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate (See *Undesirable effects*).

Long-term safety data including growth, maturation, and behavioural development, beyond 26 weeks of treatment with SEROQUEL, is not available for children and adolescents (10 to 17 years of age).

Elderly patients with dementia

SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis. 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 quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Venous thromboembolism

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.

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 *Interaction with other medicinal products and other forms of interaction, Undesirable effects, Pharmacodynamic properties, Mechanism of Action, and Overdose*).

Interactions

See also '*Interactions with other medicinal products and other forms of interaction'.*

Concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of quetiapine may need to be considered if quetiapine is used concomitantly with a hepatic enzyme inducer.

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 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.

Interactions with other medicinal products and other forms of interaction

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

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval (See *Special warnings and special precautions for use*).

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (See *Special warnings and special precautions*).

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

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium(USAN)) and SEROQUEL (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of quetiapine and thioridazine caused increases in clearance of quetiapine.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, 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, and hence, in each patient, consideration for a higher dose of SEROQUEL XR, depending on clinical response, should be considered. The safety of doses above 800 mg/day has not been established in the clinical trials.

Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin, and other hepatic enzyme inducers (eg, barbiturates, rifampicin etc). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (eg, sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co–administration of ketoconazole resulted in an increase in mean C_{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half–life of quetiapine increased from 2.6 to 6.8 hours. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors).

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

Pregnancy and lactation

The safety and efficacy of quetiapine during human pregnancy have not been established. Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported (See '*Pre-clinical safety data, Reproduction studies'*, for animal reproductive toxicology data). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

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

Non-teratogenic effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

Effect on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, dizziness, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

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

Table 1 Undesirable Effects

Frequency	System Organ Class	Event
Very Common (≥10%)	Gastrointestinal disorders	Dry mouth
	General disorders and administration site conditions	Withdrawal (discontinuation) symptoms[1, 10]
	Investigations	Elevations in serum triglyceride levels[11] Elevations in total cholesterol (predominantly LDL cholesterol)[12] Decreases in HDL cholesterol [1,18] Weight gain[3] Decreased haemoglobin[20]

Frequency	System Organ Class	Event
	Nervous system disorders	Dizziness [1, 5, 17] Somnolence [2, 17] Extrapyramidal symptoms[1, 16]
Common (≥1% - <10 %)	Blood and lymphatic system disorders	Leukopenia [1, 25]
	Cardiac disorders	Tachycardia [1, 5] Palpitations [21]
	Eye disorders	Vision blurred
	Gastrointestinal disorders	Constipation Dyspepsia Vomiting [23]
	General disorders and administration site conditions	Mild asthenia Peripheral edema Irritability Pyrexia
	Investigations	Elevations in serum alanine aminotransferase (ALT)[4] Elevations in gamma-GT levels [4] Neutrophil count decreased [1, 7] Eosinophils increased [24] Blood glucose increased to hyperglycaemic level [1,8] Elevations in serum prolactin[15] Decreases in Total T_4 [22] Decreases in Free T_4 [22] Decreases in Total T_3 [22] Increases in TSH [22]
	Nervous system disorders	Dysarthria
	Metabolism and nutrition disorders	Increased appetite
	Respiratory, thoracic, and mediastinal disorders	Dyspnea [21]
	Vascular disorders	Orthostatic hypotension [1, 5, 17]
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥0.1% - <1%)	Cardiac disorders	Bradycardia [26] QT prolongation[16,19]
	Gastrointestinal disorders	Dysphagia [1, 9]
	Immune system disorders	Hypersensitivity

Frequency	System Organ Class	Event
	Investigations	Elevations in serum aspartate aminotransferase (AST)[4] Platelet count decreased[14] Decreases in free T_3 [22]
	Nervous system disorders	Seizure [1] Restless legs syndrome Tardive dyskinesia[1] Syncope [1, 5, 17] Confusional state
	Respiratory, thoracic, and mediastinal disorders	Rhinitis
	Renal and urinary disorders	Urinary retention
Rare (≥0.01% - <0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome [1] Hypothermia
	Hepatobiliary disorders	Hepatitis (with or without jaundice)[29]
	Investigations	Elevations in blood creatine phosphokinase[13] Agranulocytosis[27]
	Psychiatric disorders	Somnambulism and other related events such as sleep-related eating disorder
	Reproductive system and breast disorders	Priapism Galactorrhoea
	Gastrointestinal disorders	Intestinal obstruction/Ileus
Very rare (<0.01%)	Immune system disorders	Anaphylactic reaction[6]
	Musculoskeletal and connective tissue disorders	Rhabdomyolysis
Not known	General disorders and administration site conditions	Neonatal withdrawal[28]
	Skin and subcutaneous disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP) Erythema multiforme (EM) Cutaneous vasculitis
	Gastrointestinal disorders	Bezoar[30]

[1] See *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 quetiapine.

[3] Based on ≥7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment.

[4] Asymptomatic elevations (shift from normal to ≥ 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.

[5] As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.

[6] The inclusion of anaphylactic reaction is based on post-marketing reports.

[7] In all short-term placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥ 1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count < 1.5 X 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count <1.0 x 10^9/L, among patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <0.5 X 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo treated patients and the incidence ≥0.5 - <1.0 X 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients.

[8] Fasting blood glucose ≥126mg/dL or a non-fasting blood glucose ≥200mg/dL on at least one occasion.

[9] An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

[10] In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (eg, insomnia, nausea, headache, diarrhea, vomiting, dizziness, and irritability) did not exceed 5.3 % in any treatment group and usually resolved after 1 week post-discontinuation.

[11] Triglycerides ≥200 mg/dL (patients ≥18 years of age) or ≥150 mg/dL (patients <18 years of age) on at least one occasion.

[12] Cholesterol ≥240 mg/dL (patients ≥18 years of age) or ≥ 200 mg/dL (patients <18 years of age) on at least one occasion.

[13] Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

[14] Platelets ≤100 x 10^9/L on at least one occasion.

[15] Prolactin levels (patients ≥18 years of age): > 20 µg/L males; > 30 µg/L females at any time

[16] See text below

[17] May lead to falls

[18] HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.

[19] Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.

[20] Decreased haemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. In short term placebo-controlled trials, decreased haemoglobin to ≤13 g/dL males, ≤12 g/dL females on at least one occasion occurred in 8.3% of quetiapine patients compared to 6.2% of placebo patients. In the long-term randomised withdrawal trials, the time to onset of decreased haemoglobin is variable and the trend in the incidence of decreased haemoglobin declines with longer exposure.

[21] These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.

[22] 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 X LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.

[23] Based upon the increased rate of vomiting in elderly patients (≥65 years of age).

[24] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as $\geq 1 \times 10^9$cells/L at any time.

[25] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as $\leq 3X10^9$cells/L at any time.

[26] 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.

[27] Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia ($<0.5 \times 10^9$/L) and infection.

[28] See section *'Pregnancy and lactation'*.

[29] SERM Clinical Overview, 2014-March. Hepatic Events. GEL locator: [CNS.000-377-593].

[30] Observed only in overdose. See section *'Overdose'*.

Extrapyramidal symptoms

The following clinical trials (monotherapy and combination therapy) 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 short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for SEROQUEL XR and 3.2% for placebo. In a short-term placebo controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for SEROQUEL XR and 2.3% for placebo. In two placebo-controlled short-term adjunct therapy clinical trials for the treatment of MDD utilising between 150 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.1% for SEROQUEL XR and 4.2% for placebo. In long-term studies of schizophrenia, bipolar disorder and major depressive disorder the aggregated exposure adjusted 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 T_4: 3.4 % for quetiapine versus 0.6 % for placebo; free T_4: 0.7% for quetiapine versus 0.1% for placebo; total T_3: 0.54 % for quetiapine versus 0.0% for placebo and free T_3: 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 T and TSH was 0.0 % for both quetiapine and placebo and 0.1% for quetiapine versus

0.0 % for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, 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.

Based on clinical data with SEROQUEL the following table summarises ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Table 2 Undesirable effects in children and adolescents

Frequency	System Organ Class	Event
Very Common (≥10%)	Metabolism and nutrition disorders	Increased appetite
	Investigations	Elevations in serum prolactin[1]
		Increases in blood pressure[2]
	Gastrointestinal Disorders	Vomiting
Common (1% - <10 %)	Respiratory, thoracic, and mediastinal disorders	Rhinitis
	Nervous system disorders	Syncope

1. Prolactin levels (patients < 18 years of age): >20 μg/L males; > 26 μg/L females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

Weight gain in children and adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group. Twenty one percent of SEROQUEL-treated patients and 7% of placebo-treated patients gained ≥ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group. Twelve percent of SEROQUEL-treated patients and 0% of placebo treated patients gained ≥ 7 % of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with SEROQUEL. After 26 weeks of treatment, the

mean increase in body weight was 4.4 kg. Forty five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

In one 8-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the mean increase in body weight was 1.4 kg in the SEROQUEL XR group and 0.6 kg in the placebo group. 13.7 % of SEROQUEL XR-treated patients and 6.8% of placebo-treated patients gained ≥ 7 % of their body weight.

Extrapyramidal symptoms in children and adolescent population:

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 SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (eg, akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) was generally low and 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 SEROQUEL and 1.1% for placebo.

In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar depression in which efficacy was not established, the aggregated incidence of extrapyramidal symptoms was 1.1% for SEROQUEL XR and 0.0% for placebo.

Post-market adverse reactions

Hepatic failure, including fatalities, has also been reported very rarely during the post-marketing period.

Overdose

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone.

In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma.

In post marketing experience there were cases reported of QT prolongation with overdose.

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

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

Management of overdose

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

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.

SEROQUEL XR overdose may lead to gastric bezoar formation and an appropriate diagnostic imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass. Endoscopic pharmacobezoar removal has been performed successfully in many cases.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group : Antipsychotics

Therapeutic classification : N05A H04

Pharmacodynamic properties

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to dopamine D_2 receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to SEROQUEL's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes which may explain anti-cholinergic (muscarinic) effects.

Pharmacodynamic effects

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

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

Clinical efficacy

Schizophrenia

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled SEROQUEL IR-to-SEROQUEL XR switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. SEROQUEL XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

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

In a long-term study in stable schizophrenic patients who had been maintained on SEROQUEL XR for 16 weeks, SEROQUEL XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the SEROQUEL XR treatment group compared to 68.2% for placebo. The mean dose was 669 mg.

Bipolar mania

In a clinical trial, SEROQUEL XR has been shown to be effective as monotherapy in reducing manic symptoms in patients with bipolar mania at doses between 400 and 800 mg/day. The effect of SEROQUEL XR was significant at Day 4 and was maintained through the end of the trial (Week 3).

In clinical trials, SEROQUEL has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week

median dose of SEROQUEL in responders, was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

Bipolar depression

In a clinical trial, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, SEROQUEL XR has been shown to be effective in patients with bipolar depression at doses of 300 mg/day. SEROQUEL XR was superior to placebo in reduction of MADRS total score. The antidepressant effect of SEROQUEL XR was significant at Day 8 (Week 1) and was maintained through the end of the trial (Week 8).

In four clinical trials, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, SEROQUEL has been shown to be effective in patients with bipolar depression at doses of 300 and 600 mg/day, however, no additional benefit was seen with the 600 mg dose during short-term treatment.

In all four studies, SEROQUEL was superior to placebo in reduction of MADRS total score. The antidepressant effect of SEROQUEL was significant at Day 8 (Week 1) and was maintained through the end of the studies (Week 8). Treatment with either SEROQUEL 300 or 600 mg at bedtime reduced depressive symptoms and anxiety symptoms in patients with bipolar depression. There were fewer episodes of treatment emergent mania with either dose of SEROQUEL than with placebo. In 3 out of 4 studies, for the 300 mg and 600 mg dose group, statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10 and in 2 out of 3 studies, for the 300 mg dose group, overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF).

In two bipolar depression clinical trials with SEROQUEL in adult patients, maintenance of antidepressant efficacy was evaluated. These trials included an 8-week placebo-controlled acute phase, followed by a placebo-controlled continuation phase of at least 26 weeks but up to 52-weeks in duration. Patients were required to be stable at the end of the acute phase in order to be in the randomized into continuation phase. In both trials, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event (depressed, mixed or manic). The risk reduction from the pooled trials was 49%. The risk of a mood event for SEROQUEL versus placebo was reduced by 41% for the 300-mg dose and by 55% for the 600-mg dose.

Preventing recurrence in maintenance treatment of bipolar disorder

The efficacy of SEROQUEL in the monotherapy treatment for recurrence prevention was established in 1 placebo-controlled trial in 1226 patients who met DSM-IV criteria for Bipolar I Disorder. The trial included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilised on SEROQUEL for a minimum of 4 weeks in order to be randomized. In the randomization phase, patients either continued treatment with SEROQUEL (300 to 800 mg per day: average dose 546 mg per day) or were to receive lithium or placebo for up to 104 weeks. SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed, or depressive), the primary endpoint. The risk reductions were 74%, 73%, and 75% for mood, manic and depressive events, respectively.

The efficacy of SEROQUEL in the combination treatment for recurrence prevention was established in 2 placebo-controlled trial in 1326 patients who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilised on SEROQUEL in combination with mood stabilizer (lithium or valproate) for a minimum of 12 weeks in order to be randomized. In the randomisation phase, patients either continued treatment with SEROQUEL (400 to 800 mg per day average dose 507 mg per day) in combination with mood stabiliser or received placebo in combination with mood stabiliser for up to 104 weeks. SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressive), the primary endpoint. The risk reductions were 70%, 67%, and 74% for mood, manic and depressive events, respectively.

Major depressive disorder

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

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

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

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

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

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

Clinical safety

Suicide/suicidal thoughts or clinical worsening

In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events was 0.8% for both quetiapine (76/9327) and for placebo (37/4845).

In these trials of patients with schizophrenia the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥25 years of age, and 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients < 18 years of age.

In these trials of patients with bipolar mania the incidence of suicide related events was 0% for both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo 6/503 in patients ≥25 years of age, and 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients < 18 years of age.

In these trials of patients with bipolar depression the incidence of suicide related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24 and 1.8% for both quetiapine (19/1616) and placebo (11/622) in patients ≥25 years of age. There has been one trial conducted in patients 10-17 years of age in which efficacy was not established. The incidence of suicide related events was 1.0% (1/92) for quetiapine and 0% (0/100) for placebo. In this study there were two additional events in two patients that occurred during an extended post-treatment follow-up phase of the study; one of these patients was on quetiapine at the time of the event (See *Special Warnings and Special Precautions for Use*).

In these trials of patients with major depressive disorder the incidence of suicide related events was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo in patients 18-24 and 0.6% (11/1798) for quetiapine and 0.7% for placebo (7/1054) in patients ≥ 25 years of age. There have been no trials conducted in patients <18 years of age with major depressive disorder.

Cataracts/lens opacities

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

Pharmacokinetic properties

General

Quetiapine is well absorbed and extensively metabolised following oral administration. 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 pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine does not differ between men and women.

SEROQUEL XR achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}). SEROQUEL XR displays dose-proportional pharmacokinetics for doses

of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for SEROQUEL XR administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate (SEROQUEL IR) administered twice daily. The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

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

There are no clinically relevant differences in the observed apparent oral clearance (CL/F) and exposure of quetiapine between subjects with schizophrenia and bipolar disorder.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2) but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Metabolism

Quetiapine is extensively metabolised by the liver with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean plasma clearance of quetiapine is reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis). Since quetiapine is extensively metabolised by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients (See *Posology and method of administration*).

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 dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of SEROQUEL XR with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the SEROQUEL XR C_{max} and AUC of 44% to 52% and 20% to 22%, respectively, for the 50-mg and 300-mg tablets. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. This increase in exposure is not clinically significant, and therefore SEROQUEL XR can be taken with or without food.

Pre-clinical safety data

Acute toxicity studies

Quetiapine has low acute toxicity. Findings in mice and rats after oral (500 mg/kg) or intraperitoneal (100 mg/kg) dosing were typical of an effective neuroleptic agent and included decreased motor activity, ptosis, loss of righting reflex, fluid around the mouth and convulsions.

Repeat-dose toxicity studies

In multiple-dose studies in rats, dogs and monkeys, anticipated central nervous system effects of an antipsychotic drug were observed with quetiapine (eg, sedation at lower doses and tremor, convulsions or prostration at higher exposures).

Hyperprolactinaemia, induced through the dopamine D_2 receptor antagonist activity of quetiapine or its metabolites, varied between species but was most marked in the rat, and a range of effects consequent to this were seen in the 12-month study, including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females.

Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey.

Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.

Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects.

Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/kg/day, nor in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man (See Pharmacodynamic properties).

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies.

Carcinogenicity studies

In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia.

In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Reproduction studies

Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.

Quetiapine had no teratogenic effects.

Mutagenicity studies

Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen.

PHARMACEUTICAL PARTICULARS

List of excipients

Core	*Coating*
Microcrystalline Cellulose (Ph Eur) Sodium Citrate (Ph Eur) Lactose Monohydrate (Ph Eur) Magnesium Stearate (Ph Eur) Hypromellose (Ph Eur)	Hypromellose (Ph Eur) Macrogol 400 (Ph Eur) Titanium Dioxide (E171) Ferric Oxide, Yellow (E172) (50mg, 200mg and 300mg tablets) Ferric Oxide, Red (E172) (50mg tablets)

Incompatibilities

None known.

Special precautions for storage

Do not store above 30 ℃.

Shelf life

Please refer to expiry date on the outer carton.

Pack size

Please refer to the outer carton for pack size.

Product Owner

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Central, Hong Kong

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