PROFESSIONAL INFORMATION FOR QUESARA XR (EXTENDED RELEASE TABLETS)

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

QUESARA XR 150 mg (extended release tablets)

QUESARA XR 200 mg (extended release tablets)

QUESARA XR 300 mg (extended release tablets)

QUESARA XR 400 mg (extended release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

QUESARA XR 150 mg

Each tablet contains quetiapine fumarate 172,68 mg equivalent to 150 mg of quetiapine free base. Contains sugar (lactose monohydrate 74,25 mg).

QUESARA XR 200 mg

Each tablet contains quetiapine fumarate 230,24 mg equivalent to 200 mg of quetiapine free base. Contains sugar (lactose monohydrate 99,0 mg).

QUESARA XR 300 mg

Each tablet contains quetiapine fumarate 345,36 mg equivalent to 300 mg of quetiapine free base. Contains sugar (lactose monohydrate 148,5 mg).

QUESARA XR 400 mg

Each tablet contains quetiapine fumarate 460,48 mg equivalent to 400 mg of quetiapine free base. Contains sugar (lactose monohydrate 198,0 mg).

Excipients:

For a full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Extended release tablet.

QUESARA XR 150 MG

White to off white coloured, capsule shaped, film coated tablets debossed with ‘C 22’ on one side and plain on the other side.

QUESARA XR 200 MG

Yellow coloured, capsule shaped, film coated tablets debossed with ‘C 23’ on one side and plain on the other side.

QUESARA XR 300 MG

Pale yellow coloured, capsule shaped, film coated tablets debossed with ‘C 24’ on one side and plain on the other side.

QUESARA XR 400 MG

White to off white coloured, capsule shaped, film coated tablets debossed with ‘C 25’ on one side and plain on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

QUESARA XR is indicated for the treatment of:

- Schizophrenia
- Preventing relapse in stable schizophrenic patients who have been maintained on **QUESARA XR**
- Bipolar disorder including:
    - Manic episodes associated with bipolar disorder
    - Preventing recurrence in the maintenance treatment of bipolar disorder (manic, mixed or depressive episodes) as monotherapy or in combination with mood stabilisers

4.2 Posology and method of administration

Posology:

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 400-800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of manic episodes associated with bipolar disorder:

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 400-800 mg per day, depending on the clinical response and tolerability of the patient.

For preventing recurrence in maintenance treatment of bipolar disorder:

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

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

*Switching from **QUESARA** immediate-release tablets:*

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

Elderly:

The mean plasma clearance of quetiapine was reduced by 30 – 50 % in elderly patients when compared to younger patients. It should be used with caution in the elderly especially during the initial dosing period. As the recommended starting dose and dose increments for the use of quetiapine in the elderly is 50 mg/day, the use of the **QUESARA XR** range is not suitable for this population.

Children and adolescents:

The safety and efficacy of **QUESARA XR** have not been evaluated in children and adolescents.

Renal and hepatic impairment:

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolized by the liver. It should therefore be used with caution in patients with known hepatic impairment, especially during the initial dosing period. As the recommended starting dose and dose increments for the use of quetiapine in patients with known hepatic impairment is 50 mg/day, the use of **QUESARA XR** range is not suitable for this population.

Method of administration:

Oral

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

4.3 Contraindications

QUESARA XR is contraindicated in:

- Patients who are hypersensitive to quetiapine or to any other component of **QUESARA XR** (see **section 6.1 "List of excipients"**).
- Pregnancy and lactation, as safety has not been demonstrated.
- Safety and efficacy in children and adolescents have not been demonstrated.

- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole antifungal medicines, erythromycin, clarithromycin and nefazodone, is contraindicated.
- Advanced liver and renal function, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

Paediatric population

QUESARA XR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group (see **section 4.3**). Clinical trials with quetiapine, as contained in **QUESARA XR**, have shown that in addition to the known safety profile identified in adults (see **section 4.8**), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.
Furthermore, the long-term safety implications of treatment with **QUESARA XR** on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

Suicide/suicidal thoughts or clinical worsening:

Psychiatric conditions for which **QUESARA XR** is prescribed can be associated with an increased risk of suicide-related events. The 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 the early stages of recovery.
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.
Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and seek medical advice immediately if these symptoms present.

Metabolic risk

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

Neutropenia and agranulocytosis

Severe neutropenia (<0,5 X 10^9/L) without infection has been reported in clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among patients treated with quetiapine during clinical trials as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of medicine 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. **QUESARA XR** 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).

Lipids:

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL have been observed with **QUESARA XR** (see **section 4.8 Undesirable effects**). Lipid changes should be managed as clinically appropriate.

Concomitant illness:

QUESARA XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. **QUESARA XR** may induce orthostatic hypotension, especially during the initial dose-titration period.

Sleep apnoea syndrome has been reported in patients using **QUESARA XR**. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, **QUESARA XR** should be used with caution.

Dysphagia:

Dysphagia (see **section 4.8**) and aspiration have been reported with **QUESARA XR**. **QUESARA XR** should be used with caution in patients at risk for aspiration pneumonia.

Seizures

Caution is recommended when treating patients with a history of seizures.

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 medicines including **QUESARA XR.** If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of **QUESARA XR** should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see **section 4.5**).

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 **QUESARA XR** has less potential than typical antipsychotic medicines 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.

Neuroleptic Malignant Syndrome (NMS)

NMS has occurred in association with **QUESARA XR.** Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatinine phosphokinase. In such an event, **QUESARA XR** 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. As with other antipsychotics, caution should be exercised when **QUESARA XR** is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when **QUESARA XR** 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 hypomagnesaemia (see **section 4.5**).

Withdrawal:

Acute withdrawal symptoms such as insomnia, nausea, and vomiting have been described after abrupt cessation of antipsychotic medicines including **QUESARA XR**. Gradual withdrawal over a period of at least one to two weeks is advisable. (see **section 4.8**)

Elderly patients with dementia:

QUESARA XR is not approved for the treatment of patients with dementia-related psychosis. In a meta-analysis of atypical antipsychotic medicines, 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 **QUESARA XR** treatment and death in elderly patients with dementia.

Elderly patients with Parkinson's disease (PD)/parkinsonism

A population-based retrospective study of quetiapine for the treatment of patients with MDD, showed an increased risk of death during use of quetiapine in patients aged >65 years. This association was not present when patients with PD were removed from the analysis. Caution should be exercised if quetiapine is prescribed to elderly patients with PD.

Anticholinergic (muscarinic) effects

Norquetiapine, an active metabolite of **QUESARA XR**, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to adverse drugs reactions (ADRs) reflecting anticholinergic effects when **QUESARA XR** is used at recommended doses, when used concomitantly with other medications having anticholinergic effects, and in the setting of overdose. **QUESARA XR** should be used with caution in patients receiving medicines having anticholinergic (muscarinic) effects. **QUESARA XR** 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 **section 4.5, 4.8, 4.9 and 5.1**).

Interactions:

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

During concomitant administration of medicines, 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 **QUESARA XR** 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.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including **QUESARA XR.**

Patients with an established diagnosis of diabetes mellitus, who are started on atypical antipsychotics such as **QUESARA XR**, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics such as **QUESARA XR** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients, who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as **QUESARA XR**, should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as **QUESARA XR** was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Weight

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see **sections 4.8 and 5.1**).

Cardiomyopathy and Myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post marketing experience. Treatment with **QUESARA XR** should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with **QUESARA XR** (see **section 4.8**). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Pancreatitis

Pancreatitis has been reported in clinical trials and during the post marketing experience. Among the post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see **section 4.4: Lipids**), gallstones, and alcohol consumption.

Somnolence and dizziness

QUESARA XR treatment has been associated with somnolence and related symptoms, such as sedation (see **section 4.8**). Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension

QUESARA XR treatment has been associated with orthostatic hypotension and related dizziness (see **section 4.8**) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Misuse and abuse

Cases of misuse and abuse have been reported. Caution may be needed when prescribing **QUESARA XR** to patients with a history of alcohol or substance abuse.

Lactose

QUESARA XR contains lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take **QUESARA XR**.

4.5 Interaction with other medicines and other forms of interaction

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

Caution should be exercised when **QUESARA XR** is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see **section 4.4**).

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

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

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 **QUESARA 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 **QUESARA XR** may be required to maintain control of psychotic symptoms in patients co-administered **QUESARA XR** and phenytoin, and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of **QUESARA XR** may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. 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 **QUESARA XR** given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of **QUESARA XR** of 235 % and 522 %, respectively, with a corresponding decrease in mean oral clearance of 84 %.
The mean half-life of **QUESARA XR** increased from 2,6 - 6,8 hours, but the mean T_{max} was unchanged. Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of **QUESARA XR** 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.

Food interactions:

It is not recommended to consume grapefruit juice while on **QUESARA XR** therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

QUESARA XR is contraindicated in pregnancy as safety has not been demonstrated (see **section 4.3**)

Breastfeeding

QUESARA XR is contraindicated in lactation as safety has not been demonstrated (see **Section 4.3**). Women who are breastfeeding should therefore be advised to stop doing so while taking **QUESARA XR.**

Fertility

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

4.7 Effects on ability to drive and use machines

QUESARA XR may cause somnolence, dizziness or blurred vision which may interfere with activities requiring mental alertness. Therefore patients should be advised not to drive or operate machinery, until individual susceptibility is known.

4.8 Undesirable effects

The most frequent reported adverse reactions with **QUESARA XR** are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, dyspepsia, Weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema have been associated with **QUESARA XR**.

Table 1 ADRs associated with QUESARA XR therapy

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Frequent	Leucopoenia[1] [28], decreased haemoglobin, decreased neutrophil count, eosinophils increased[27]
	Less frequent	Eosinophilia, neutropenia[1], thrombocytopenia,

		anaemia, platelet count decreased[13], agranulocytosis[26]
Immune system disorders	Less frequent	Hypersensitivity, angioedema, anaphylactic reaction[5]
Endocrine disorders	Frequent	Hyperprolactinaemia[15], decreases in total T_4[24], decreases in free T_4[24], decreases in total T_3[24], increases in TSH[24]
	Less frequent	Hypothyroidism[21], decreases in free T_3[24]
Metabolism and nutrition disorders	Frequent	Increased appetite, elevations in serum triglyceride levels[10, 30]. Elevations in total cholesterol (predominantly LDL cholesterol)[11,30], decreases in HDL cholesterol[17, 30], weight gain[8, 30], blood glucose increased to hyperglycaemic levels[6, 30]
	Less frequent	Hyponatraemia[19], diabetes mellitus[1,5], exacerbation of pre-existing diabetes, metabolic syndrome[29]
Psychiatric disorders	Frequent	Abnormal dreams and nightmares, suicidal ideation and suicidal behaviour[20]
	Less frequent	Somnambulism and related reactions such as sleep talking and sleep related eating disorder.
	Frequency unknown	Anxiety
Nervous system disorders	Frequent	Dizziness[4,16], somnolence[2,16], syncope[4, 16], extrapyramidal symptoms[1, 21], dysarthria, headache
	Less frequent	Seizure[1], restless legs syndrome, tardive dyskinesia[1, 5], syncope[4,16]
Cardiac disorders	Frequent	Tachycardia[4], palpitations[23]
	Less frequent	QT prolongation[1,12,18], bradycardia[32]

	Frequency unknown	Chest pain, hypertension
Eye disorders	Frequent	Blurred vision
	Frequency unknown	Dry eyes
Vascular disorders	Frequent	Orthostatic hypotension[4, 16]
	Less frequent	Venous thromboembolism[1]
	Frequency unknown	Stroke[33]
Respiratory, thoracic and mediastinal disorders	Frequent	Rhinitis, dyspnoea[23]
Gastrointestinal disorders	Frequent	Dry mouth, constipation, dyspepsia, vomiting[25]
	Less frequent	Dysphagia[7], pancreatitis[1], intestinal obstruction /ileus
	Frequency unknown	Abdominal pain, diarrhoea
Hepatobiliary disorders	Frequent	Elevation in serum alanine aminotransferase (ALT)[3],elevations in gamma-GT levels
	Less frequent	Elevations in serum aspartate aminotransferase (AST)[3], jaundice[5], hepatitis
Skin and subcutaneous tissue disorders	Less frequent	Stevens-Johnson syndrome[5]
	Frequency unknown	Toxic epidermal necrolysis, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Less frequent	Rhabdomyolysis
	Frequency unknown	Myalgia
Renal and urinary disorders	Frequent	Urinary tract infection
	Less frequent	Urinary retention
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	Less frequent	Priapism, galactorrhoea, breast swelling, menstrual disorder, sexual dysfunction

General disorders and administration site conditions	Frequent	Headache, withdrawal (discontinuation) symptoms[1, 9], mild asthenia, peripheral oedema, irritability, pyrexia
	Less frequent	Neuroleptic malignant syndrome[1], hypothermia
	Frequency unknown	Back pain, ear pain
Investigations	Frequent	Elevations in serum triglyceride levels; Elevations in total cholesterol (predominantly LDL cholesterol), Decreases in HDL Cholesterol, Weight gain, Elevations in serum transaminases (ALT, AST); Decreased neutrophil count; Increased blood glucose to hyperglycaemic level; Elevations in serum prolactin
	Less frequent	Elevations in gamma-GT levels; Platelet count decreased, Elevations in blood creatine phosphokinase[14]

(1) See **section 4.4.**

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

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

(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (see **section 4.4**).

(5) Calculation of Frequency for these ADR's has only been taken from post-marketing data with the immediate release formulation of quetiapine.

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

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

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

(9) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(10) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.

(11) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).

(12) See text below.

(13) Platelets ≤100 x 109/L on at least one occasion.

(14) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(15) Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time.

(16) May lead to falls.

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

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

(19) Shift from >132 mmol/L to ≤132 mmol/L on at least one occasion.

(20) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see **sections 4.4 and 5.1**).

(21) See **section 5.1.**

(22) Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was -1.50 g/dL.

(23) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.

(24) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T4, free T4, total T3 and free T3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.

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

(26) Based on shift in neutrophils from > = 1.5 x 109/L at baseline to <0.5 x 109/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 109/L) and infection during all quetiapine clinical trials (see **section 4.4**).

(27) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as ≥1 x 109 cells/L at any time.

(28) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤3 x 109 cells/L at any time.

(29) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.

(30) In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see **section 4.4**).

(31) **QUESARA XR** is contraindicated in pregnancy (see **sections 4.3 and 4.6**).

(32) May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.

(33) Based on one retrospective non-randomised epidemiological study.

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

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment.

Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of **QUESARA XR**.

Extrapyramidal symptoms (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity and tremor) are not dose related.

Thyroid Levels:

QUESARA XR treatment was associated with 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 2 to 4 weeks of **QUESARA XR** treatment, with no further reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of **QUESARA XR** 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 any indication that **QUESARA XR** causes clinically relevant hypothyroidism.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com. By reporting side effects, you can help provide more information on the safety of **QUESARA XR**.

4.9 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 **QUESARA XR** alone resulting in death or coma.

In post marketing experience, there were cases reported of QT prolongation with overdose (see **section 4.4 and 4.8**).

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see **section 4.4 and 4.8**).

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

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.

Close medical supervision and monitoring should be continued until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Central nervous system depressants: Miscellaneous structure.

ATC code: N05AH04

Quetiapine is an atypical antipsychotic medicine. 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 dopamine D2 receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic alpha1

receptors, with a lower affinity at adrenergic alpha2 and serotonin 5HT1A receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

In animal models, 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 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 super-sensitivity 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 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.

5.2 Pharmacokinetic properties

Absorption

Quetiapine is absorbed and extensively metabolised following oral administration.

Quetiapine extended-release achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}).

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

Quetiapine extended-release 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 quetiapine extended-release administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate administered twice daily.

When quetiapine extended-release administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate administered twice daily, the area under the quetiapine plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13 % lower. When quetiapine extended-release administered once daily is compared to the same total daily

dose of the immediate release formulation of quetiapine administered once daily, the quetiapine extended-release AUC is equivalent; and C_{max} is 59 % lower. The AUC and C_{max} for the metabolite norquetiapine are 37 % and 18 % lower than the immediate-release quetiapine fumarate, respectively.

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 quetiapine extended-release C_{max} and AUC of 44-52 % and 20-22 %, 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 quetiapine extended-release can be taken with or without food.

Distribution

Quetiapine is approximately 65 to 83 % bound to plasma proteins.

Biotransformation

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

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 5-50 fold higher than those observed at a dose range of 300-800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine extended-release with other medicines will result in clinically significant medicine inhibition of cytochrome P450 mediated metabolism of the other medicine.

Elimination

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5 % excreted in the urine.

Special populations

Gender

The kinetics of quetiapine does not differ between men and women.

Elderly

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

Renal impairment

The mean plasma clearance of quetiapine is reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment

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 **section 4.2**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains microcrystalline cellulose, lactose monohydrate, sodium citrate dihyrdrate, ethylcellulose, povidone, isopropyl alcohol, magnesium stearate. **QUESARA XR 150 mg** and **400 mg** tablets are

coated with coating made up of hypromellose, titanium dioxide (Colour Index No. 77891), polyethylene glycol 400.

In addition **QUESARA XR 200 mg** and **300 mg** contain iron oxide yellow (Colour Index No. 77492)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the manufacturing date for HDPE container pack of QUESARA XR 150 mg, 200 mg, 300 mg and 400 mg and for blister pack of QUESARA XR 200 mg and 400 mg.

48 months from the manufacturing date for blister pack of QUESARA XR 150 mg and 36 months for blister pack of QUESARA XR 300 mg.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

QUESARA XR 150, 200, 300 and 400 mg:

Blister Pack:

Tablets are packed in white opaque PVC/PVdC 250/60 PVC film coated with 60 gsm PVdC as the forming material and plain 25 µm, aluminium foil, 6-8 gsm HSL, as the lidding material. Each blister contains 10 tablets.

Pack size: 60’s – Each carton contains 6 blisters of 10 tablets each.

HDPE Container Pack:

Tablets are packed in white, opaque, round 40 ml/60 ml/100 ml/120 ml HDPE bottle closed with a white child resistant closure with pulp and heat seal.

Pack size: 60’s - One HDPE container contains 60 tablets

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

QUESARA XR 150 mg: 48/2.6.5/0076

QUESARA XR 200 mg: 48/2.6.5/0077

QUESARA XR 300 mg: 48/2.6.5/0078

QUESARA XR 400 mg: 48/2.6.5/0079

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 May 2021

10. DATE OF REVISION OF THE TEXT

10 December 2025



PM0051-02