APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

QUERO XR 50 mg film coated tablet

QUERO XR 150 mg film coated tablet

QUERO XR 200 mg film coated tablet

QUERO XR 300 mg film coated tablet

QUERO XR 400 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is quetiapine fumarate.

QUERO XR 50 mg: Each prolonged release tablet contains quetiapine fumarate equivalent to quetiapine 50 mg.

Contains sugar (14,21 mg lactose anhydrous per tablet).

QUERO XR 150 mg: Each prolonged release tablet contains quetiapine fumarate equivalent to quetiapine 150 mg.

Contains sugar (42,63 mg lactose anhydrous per tablet).

QUERO XR 200 mg: Each prolonged release tablet contains quetiapine fumarate equivalent to quetiapine 200 mg.

Contains sugar (56,84 mg lactose anhydrous per tablet).

QUERO XR 300 mg: Each prolonged release tablet contains quetiapine fumarate equivalent

to quetiapine 300 mg.

Contains sugar (85,26 mg lactose anhydrous per tablet).

QUERO XR 400 mg: Each prolonged release tablet contains quetiapine fumarate equivalent to quetiapine 400 mg.

Contains sugar (113,68 mg lactose anhydrous per tablet).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

QUERO XR 50 mg: white to off white, film coated, round, biconvex tablet, engraved with ‘50’ on one side.

QUERO XR 150 mg: white to off white, film coated, oblong, biconvex tablet, engraved with ‘150’ on one side.

QUERO XR 200 mg: white to off white, film coated, oblong, biconvex tablet, engraved with ‘200’ on one side.

QUERO XR 300 mg: white to off white, film coated, oblong, biconvex tablet, engraved with ‘300’ on one side.

QUERO XR 400 mg: white to off white, film coated, oval, biconvex tablet, engraved with ‘400’ on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

QUERO XR is indicated for the treatment of:

- Schizophrenia
- prevention of relapse in stable schizophrenic patients who have been maintained on QUERO XR
- bipolar disorder including:
  - treatment of manic episodes associated with bipolar disorder
  - treatment of depressive episodes associated with bipolar disorder
  - prevention of recurrence in the maintenance treatment of bipolar disorder (manic, mixed or depressive episodes), as monotherapy or in combination with mood stabilisers
- major depressive disorder
- preventing relapse in stable major depressive disorder patients who have been maintained on QUERO XR.

4.2 Posology and method of administration

Posology

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

Adults:

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.

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.

Treatment of depressive episodes associated with bipolar disorder:

QUERO XR should be administered once daily in the evening.

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

Antidepressant efficacy was demonstrated with quetiapine at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group during short-term treatment.

Preventing recurrence in maintenance treatment of bipolar disorder:

Patients who have responded to QUERO XR, in combination therapy to a mood stabiliser (lithium or valproate) for acute treatment of bipolar disorder, should continue on QUERO XR therapy at the same dose. The QUERO 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 QUERO XR for acute treatment of bipolar disorder should continue on QUERO XR therapy at the same dosing regimen.

QUERO 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.

For the treatment of major depressive disorder:

QUERO XR should be administered once daily in the evening.

Initial dosing should begin at 50 mg on Day 1 and 2, increased to 150 mg on Day 3 and 4. Further adjustments can be made upwards or downwards within the recommended dose range of 50 - 300 mg depending upon the clinical response and tolerability of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient.

Switching from quetiapine immediate-release tablets:

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

Special populations

Elderly:

QUERO XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of QUERO 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 - 50 % in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance 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.

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

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

Paediatric population

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

Method of administration

QUERO XR is for oral use and should be administered once daily with or without food. The tablets should be swallowed whole and not split, chewed or crushed.

Missed dose

Doctors should advise patients who forget to take QUERO XR, to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

Contraindications to be presented in bullet format where relevant

- Hypersensitivity to quetiapine or to any of the ingredients of QUERO XR (see section 6.1)
- concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (see section 4.5)
- pregnancy and lactation (see section 4.6)
- safety and efficacy in children and adolescents have not been demonstrated
- advanced liver and renal dysfunction, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

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

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

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 quetiapine (as in QUERO XR).

In some cases, a prior increase in body weight has been reported

which may be a predisposing factor.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Weight should be monitored regularly.

Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.

Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing.

In some cases, hyperglycaemia was resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Suicide/suicidal thoughts or clinical worsening:

An increased risk of suicidal thoughts, self-harm and suicide (suicide-related events) are all associated with depression. Until significant remission occurs, this risk with continue.

Patients should be closely monitored until an improvement occurs, since such an improvement may not happen during the first few weeks or more of therapy. The risk of

suicide may increase in the early stages of treatment.

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

An increased risk of suicide-related events can also be associated with other psychiatric disorders for which QUERO XR is prescribed, which may be co-morbid with major depressive disorder. When treating patients with other psychiatric disorders the same precautions should be observed.

Patients who exhibit a significant degree of suicidal ideation before starting treatment with QUERO XR, and those with a history of suicide-related events, are at increased risk of suicidal thoughts or suicide attempts. These patients should be monitored closely during therapy.

Close supervision of patients and in particular those at high risk, especially in early treatment and following dose changes, should be undertaken. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine, as compared to those treated with placebo (3,0 % vs. 0 %, respectively).

In clinical studies of patients with MDD, the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2,1 % (3/144) for quetiapine and

1,3 % (1/75) for placebo. A population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 - 64 years without a history of self-harm during use of quetiapine with other antidepressants.

Severe neutropenia and agranulocytosis:

Severe neutropenia (neutrophil count <0,5 x 10^9/litre) without infection has been uncommonly reported in quetiapine clinical trials. There have been reports of agranulocytosis (severe neutropenia with infection) among patients treated with quetiapine, as contained in QUERO XR, during clinical trials, as well as post-marketing reports. Most cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine.

There was no apparent dose relationship. During post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood 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 /litre.

Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 x 10^9/litre) (see section 5.1).

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy, or sore throat) at any time during QUERO XR therapy. Such patients should have a WBC count and an

absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Lipids:

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

Metabolic risk:

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

Orthostatic hypotension:

Quetiapine, as contained in QUERO 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 medicine. QUERO XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. QUERO XR may induce orthostatic hypotension especially during the initial dose-titration period. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Seizures:

No data is available about the incidence of seizures in patients with a history of seizure disorder.

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

Tardive dyskinesia and extrapyramidal symptoms:

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medicines, including quetiapine. There is a potential for QUERO XR to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of QUERO XR should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).

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 medicines to induce tardive dyskinesia in schizophrenia and bipolar mania patients.

An increased incidence of extrapyramidal symptoms (EPS) are associated with quetiapine, as contained in QUERO XR, treatment in patients treated for major depressive episodes in bipolar disorder and major depressive disorder.

The development of akathisia, characterised by distressing restlessness and the need to move often accompanied by the inability to sit down or standstill, has been associated with the use of quetiapine, as contained in QUERO XR. These symptoms usually occur during the first few weeks of therapy. It is not advised to increase the dose of QUERO XR in patients

who experience these side-effects.

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome has been associated with QUERO XR treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, QUERO XR should be discontinued and appropriate medical treatment given.

Serotonin syndrome

Concomitant administration of QUERO XR and other serotonergic medicines, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

QT prolongation:

Studies indicate quetiapine, as contained in QUERO XR, was not associated with a persistent increase in absolute QT intervals.

However, QT prolongation has been reported with quetiapine at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, caution should be exercised when QUERO XR is prescribed in patients with cardiovascular disease or

family history of QT prolongation. Also, caution should be exercised when QUERO XR is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5).

Withdrawal:

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

Somnolence and dizziness:

QUERO XR treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). Onset is usually within the first 3 days of treatment and predominantly of mild to moderate intensity. If patients with bipolar depression or MDD patients with major depressive episodes experience somnolence of severe intensity, they 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.

Sleep apnoea syndrome:

Sleep apnoea syndrome has been reported in patients using QUERO 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, QUERO XR should be used with caution.

***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 anti-cholinergic effects, when QUERO XR is used at recommended doses, when used concomitantly with other medicines having anti-cholinergic effects, and in the setting of overdose. QUERO XR should be used with caution in patients receiving medicines having anti-cholinergic (muscarinic) effects. QUERO 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 sections 4.5, 4.8 and 4.9).

Dysphagia:

Dysphagia and aspiration have been reported with QUERO XR.

Although a causal relationship with aspiration pneumonia has not been established, QUERO XR should be used with caution in patients at risk for aspiration pneumonia.

Cardiomyopathy and myocarditis:

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience. Treatment with QUERO XR 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) which can be life threatening or fatal have been reported very rarely with quetiapine treatment.

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. Most of these reactions occurred within 4 weeks after initiation of quetiapine therapy, some DRESS reactions occurred within 6 weeks after initiation of quetiapine therapy. If signs and symptoms suggestive of these severe skin reactions appear, QUERO XR should be withdrawn immediately and alternative treatment should be considered.

Constipation and intestinal obstruction:

Constipation represents a risk factor for intestinal obstruction.

Constipation and intestinal obstruction have been reported with QUERO XR. This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medicines 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 QUERO XR and preventive measures undertaken.

Pancreatitis:

Pancreatitis has been reported, 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, gallstones and alcohol consumption.

Misuse and abuse:

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

Hepatic effects:

Concomitant use of QUERO XR with a strong hepatic enzyme inducer, such as carbamazepine or phenytoin, substantially decreases quetiapine plasma concentrations, which could affect the efficacy of QUERO XR therapy. In patients receiving a hepatic enzyme inducer, initiation of QUERO XR treatment should only occur if the doctor considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Weight:

Weight gain has been reported in patients who have been treated with QUERO XR, and should be monitored and managed as clinically appropriate.

Lactose anhydrous:

QUERO XR 50, 150, 200, 300 and 400 mg contains 14,21 mg, 42,63 mg, 56,84 mg, 85,26 mg and 113,68 mg lactose anhydrous per tablet, respectively. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take QUERO XR.

Additional information on special populations

Elderly patients with dementia-related psychosis:

QUERO XR is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical 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 quetiapine treatment and death in elderly patients with dementia.

Elderly patients with Parkinson's Disease (PD)/parkinsonism:

A population-based retrospective study of quetiapine, (as contained in QUERO XR), 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 QUERO XR is prescribed to elderly patients with PD.

Paediatric population

QUERO 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).

Studies have shown that in addition to the known safety profile identified in adults treated with quetiapine (see section 4.8), certain adverse events either:

- increased in frequency in children and adolescents when compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope)
- may have different implications for children and adolescents (extrapyramidal symptoms and irritability)
- have been reported in children and adolescents, but not identified in adults, such as increases in blood pressure and changes in thyroid function tests.

Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania and bipolar depression (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine, as contained in QUERO XR. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of QUERO XR with CYP3A4 inhibitors is contraindicated (see section 4.3).

It is also not recommended to consume grapefruit juice while on QUERO XR therapy.

QUERO XR should be used with caution in combination with serotonergic medicines such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Concomitant use of QUERO XR with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of QUERO XR may need to be considered if used concomitantly with a hepatic enzyme inducer.
In patients receiving a hepatic enzyme inducer, initiation of QUERO XR therapy should only occur after careful consideration of the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4).

Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450 %.

QUERO XR should be used with caution when combined with other centrally acting medicines and alcohol, due to the primary central nervous system effects of quetiapine.

Caution should be exercised when treating patients receiving other medicines having anti-

cholinergic (muscarinic) effects (see section 4.4).

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 QUERO 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.

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of QUERO XR and thioridazine caused an increased clearance of quetiapine by approximately 70%.

The pharmacokinetics of QUERO XR were not altered following co-administration with cimetidine.

The pharmacokinetics of lithium were not altered when co-administered with QUERO XR.
In a 6-week, randomised, study of lithium and quetiapine (prolonged release) versus placebo and quetiapine (prolonged release) in adult patients with acute mania, a higher incidence of

extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.
A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

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

Caution should be exercised when QUERO XR is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

QUERO XR is contraindicated during pregnancy as safety has not been demonstrated (see

section 4.3).

Animal studies have shown reproductive toxicity (see section 5.3).

Breastfeeding

The degree to which quetiapine is excreted into human milk is unknown. Women who are breastfeeding should therefore be advised to avoid breastfeeding while taking QUERO XR (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

QUERO XR may cause somnolence, which may affect a patient's judgement, their ability to think and their motor skills. Patients should therefore be cautioned about their ability to operate machinery and drive whilst taking QUERO XR.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions (ADRs) with QUERO XR are somnolence, dizziness, headache, dry mouth, withdrawal symptoms, asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia, elevations in serum triglyceride levels, elevations in

total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

Weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with QUERO XR.

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequent Less frequent	Decreased haemoglobin, leucopenia, decreased neutrophil count, eosinophils increased Agranulocytosis, anaemia, eosinophilia, thrombocytopenia, platelet count decreased, neutropenia, pancytopenia
Immune system disorders	Frequent Frequency unknown	Hypersensitivity Anaphylactic reaction*
Endocrine disorders	Frequent Less frequent	Hyperprolactinaemia, decreases in total T_4, decreases in free T_4, decreases in total T_3, increases in TSH Decreases in free T_3, hypothyroidism, inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders	Frequent Less frequent	Increased appetite, blood glucose increased to hyperglycaemic levels, elevations in serum triglyceride levels and total cholesterol (predominantly LDL), decreases in HDL cholesterol Hyponatraemia, hyperglycaemia, diabetes, exacerbation of pre-existing diabetes, metabolic syndrome
Psychiatric disorders	Frequent Less frequent	Abnormal dreams and nightmares, mania, suicidal ideation and suicidal behaviour Somnambulism and related reactions such as sleep related eating disorder and sleep talking
Nervous system disorders	Frequent Less frequent	Dizziness, dysarthria, somnolence, syncope, extrapyramidal symptoms, Restless leg syndrome, seizure, tardive dyskinesia, confusional state
Eye disorders	Frequent	Blurred vision
Cardiac disorders	Frequent Less frequent Frequency unknown	Palpitations, tachycardia Bradycardia, QT prolongation Cardiomyopathy, myocarditis
Vascular disorders	Frequent Less frequent Frequency unknown	Orthostatic hypotension Venous thromboembolism Stroke, hypertension

Respiratory, thoracic and mediastinal disorders	Frequent Frequency unknown	Dyspnoea, rhinitis Hyperventilation, respiratory alkalosis, acute respiratory failure
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Dry mouth, constipation, dyspepsia, vomiting Dysphagia, pancreatitis, intestinal obstruction/Ileus Abdominal pain
Hepatobiliary disorders	Frequent Less frequent Frequency unknown	Elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels Elevations in serum aspartate aminotransferase (AST) Jaundice, hepatitis
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Angioedema, Stevens-Johnson syndrome Toxic Epidermal Necrolysis, erythema multiforme, drug-rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), cutaneous vasculitis
Musculoskeletal, connective tissue and bone disorders	Less frequent	Rhabdomyolysis
Renal and urinary disorders	Frequent Less frequent	Urinary tract infection Urinary retention
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Drug withdrawal syndrome neonatal

Reproductive system and breast disorders	Less frequent	Sexual dysfunction, priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administrative site conditions	Frequent Less frequent	Asthenia, peripheral oedema, withdrawal symptoms, headache, irritability, pyrexia Neuroleptic malignant syndrome, hypothermia
Investigations	Frequent Less frequent	Weight gain Elevations in blood creatine phosphokinase, elevations in gamma-GT levels, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol

*Post-marketing

a. Description of selected adverse reactions

Somnolence may occur upon initiation of treatment and resolve with continuous administration of therapy.

The following side effects may occur in the early weeks of treatment: orthostatic hypotension associated with dizziness, tachycardia, syncope, increase in body weight from baseline, bradycardia associated with hypotension and/or syncope.

The incidence of discontinuation symptoms include insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability decreased significantly after 1-week post-discontinuation.

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).

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 are usually reversible on continued quetiapine treatment.
An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Side-effects generally reported as a result of overdose with quetiapine, as contained in QUERO XR, include drowsiness, sedation, tachycardia, anti-cholinergic effects and hypotension. There have been very rare reports of quetiapine alone resulting in death or coma.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death.

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

Management of overdose:

There is no specific antidote to quetiapine, as contained in QUERO XR. In cases of severe signs, the possibility of multiple medicine involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1 - 2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG

aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

Whilst the prevention of absorption in overdose has not been investigated, the administration of activated charcoal should be considered.

In cases of quetiapine overdose refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

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

In case of overdose with QUERO XR there is a delayed peak sedation and peak pulse and prolonged recovery.

In case of a QUERO XR overdose gastric bezoar formation has been reported and appropriate diagnostic imaging is recommended to further guide patient management. Endoscopic pharmacobezoar removal has been performed successfully in some cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; diazepines, oxazepines and thiazepines

ATC code: N05A H04

Pharmacological classification: A 2.6.5 Central nervous system depressants: Miscellaneous structures

Mechanism of action

Quetiapine is an atypical antipsychotic medicine which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin (5HT2) receptors in the brain than it does for dopamine D1 and D2 receptors in the brain. Quetiapine also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors, but 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 well absorbed following oral administration. Peak quetiapine and norquetiapine plasma concentrations are achieved 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.

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 prolonged release C_{max} and AUC of approximately 50 % and 20 % respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that quetiapine prolonged release is taken once daily without food.

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

Distribution:

Approximately 83 % of quetiapine is bound to plasma proteins.

Biotransformation:

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5 % of unchanged medicine-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.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In*

vitro CYP inhibition is observed only at concentrations approximately 5- to 50-fold higher than those observed at a dose range of 300 - 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other medicines will result in clinically significant medicine inhibition of cytochrome P450 mediated metabolism of the other medicine. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination:

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73 % of a radiolabelled medicine was excreted in the urine and 21 % in the faeces, with less than 5 % of the total radioactivity representing unchanged medicine-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5 % excreted in the urine.

Linearity/non-linearity:

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. The kinetics of quetiapine does not differ between men and women.

Pharmacokinetics in special patient groups

Elderly:

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

Renal impairment:

The mean plasma clearance of quetiapine was reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73m2), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5 % excreted in the urine.

Hepatic impairment:

The mean quetiapine plasma clearance decreases with approximately 25 % in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients.

Gender:

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

Paediatric population

Pharmacokinetic data were sampled in 9 children aged 10 - 12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10 - 17 years of age) were, in general, similar to adults, though C_{max} in children was at the higher end of the range observed in adults.

The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62 % and 49 % in children (10 - 12 years), respectively and 28 % and 14 % in adolescents (13 - 17 years), respectively, compared to adults.

No information is available for quetiapine extended release in children and adolescents.

5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies.
In laboratory animals at a clinically relevant exposure level, the following deviations were seen, which as yet have not been confirmed in long-term clinical research.
In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys, thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs, lens opacity and cataracts have been observed.
In an embryofoetal toxicity study in rabbits, the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans, at the maximal therapeutic dose. The relevance of this finding for humans is unknown.
In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crystalline maltose

Lactose anhydrous

Magnesium stearate

Methacrylic acid –ethyl acrylate copolymer

Talc

Triethyl citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep in the outer carton until required for use.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

White, opaque, PVC-PCTFE/aluminium blister strips, or white, opaque, HDPE bottles with child resistant polypropylene cap and induction seal liner containing either 10, 30 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

QUERO XR 50 mg: A49/2.6.5/0280

QUERO XR 150 mg: A49/2.6.5/0281

QUERO XR 200 mg: A49/2.6.5/0282

QUERO XR 300 mg: A49/2.6.5/0283

QUERO XR 400 mg: A49/2.6.5/0284

9. DATE OF FIRST AUTHORISATION

11 May 2021

10. DATE OF REVISION OF THE TEXT

04 August 2025