Seropine®XR 300

Quetiapine Fumarate

FORMS AND PRESENTATION
Seropine®XR 300: Extended release tablets: box of 60.

COMPOSITION:
Seropine®XR 300: Each film coated tablet contains quetiapine fumarate equivalent to quetiapine 300 mg.
Excipients: Lactose monohydrate, hypromellose, sodium chloride, povidone, talc, magnesium stearate, titanium dioxide, polyethylene glycol, iron oxide yellow.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines.
ATC code: N05A H04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2-receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2-receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics.
Pharmacodynamic effects
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviorally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

Pharmacokinetic properties
Absorption
Quetiapine is well absorbed following oral administration. It achieves peak quetiapine and norquetiapine 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.
It is recommended that quetiapine XR is taken once daily without food.
Distribution
Quetiapine is approximately 83% bound to plasma proteins.
Biotransformation
Quetiapine is extensively metabolized 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 radiolabeled quetiapine.
Elimination
The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabeled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations
Elderly
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.
Renal impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 m2), but the individual clearance values are within the range for normal subjects.
Hepatic impairment
The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolized by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients.

INDICATIONS
Seropine® XR 300 is indicated for:
• treatment of schizophrenia
• treatment of bipolar disorder:
- For the treatment of moderate to severe manic episodes in bipolar disorder
- For the treatment of major depressive episodes in bipolar disorder
- For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.
• add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy. Prior to initiating treatment, clinicians should consider the safety profile of Seropine® XR 300.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients of this product. Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated.

PRECAUTIONS
As quetiapine 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 MDD have not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy.

Pediatricpopulation
Quetiapine 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. 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).
Suicide/suicidal thoughts or clinical worsening
As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated. 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.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes.
Metabolic risk
Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, 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.
Extrapyramidal symptoms
The use of quetiapine has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment.
Tardive dyskinesia
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment.
Orthostatic hypotension
Quetiapine treatment has been associated with orthostatic hypotension and related dizziness 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. Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.
Sleep apnea syndrome
In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnea, such as those who are overweight/obese or are male, quetiapine should be used with caution.
Seizures
There is no evidence that seizures are associated with quetiapine, but as with other antipsychotics, caution is recommended when treating patients with a history of seizures.
Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase.
Severe neutropenia and agranulocytosis
Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship.
During post-marketing experience, some cases were fatal.
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 quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose.
Weight
Weight gain has been reported in patients who have been treated with quetiapine.
Hyperglycemia
Hyperglycemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor.
Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine. Lipid changes should be managed as clinically appropriate.
QT prolongation
As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia or hypomagnesaemia.
Cardiomyopathy and myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience. In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.
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.
Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable.
Elderly patients with dementia-related psychosis
Quetiapine is not approved for the treatment of dementia-related psychosis.
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.
Dysphagia
Dysphagia has been reported with quetiapine.
Constipation and intestinal obstruction
Constipation and intestinal obstruction have been reported with quetiapine. 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.
Venous thromboembolism (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 post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides, gallstones and alcohol consumption.
Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3.
Lactose
Quetiapine XR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
Effects on ability to drive and use machines
Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

PREGNANCY AND LACTATION

Pregnancy

First trimester: The moderate amount of published data from exposed pregnancies, do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn.

Third trimester: Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding

Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding.

DRUG INTERACTIONS

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

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects. Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. Concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy. In a multiple-dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine, co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure to an average of 13% of the exposure during administration of quetiapine alone. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. 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 quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%. The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine. The pharmacokinetics of lithium were not altered when co-administered with quetiapine. 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. Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

ADVERSE EFFECTS

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

The frequencies of adverse events are ranked according to the following: Very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100, rare (≥1/10,000, <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders: Decreased hemoglobin (very common); leucopenia, decreased neutrophil count, eosinophils increased (common); neutropenia, thrombocytopenia, anemia, platelet count decreased (uncommon); agranulocytosis (rare).

Immune system disorders: Hypersensitivity including allergy skin reactions (uncommon); anaphylactic reaction (very rare).

Endocrine disorders: Hyperprolactinemia, decreases in total T4, decreases in free T4, decreases in total T3, increases in TSH (common); decreases in free T3, hypothyroidism (uncommon); inappropriate antidiuretic hormone secretion (very rare).

Metabolism and nutritional disorders: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain (very common); increased appetite, blood glucose increased to hyperglycemic levels (common); hyponatremia, diabetes mellitus, exacerbation of pre-existing diabetes (uncommon); metabolic syndrome (rare).

Psychiatric disorders: Abnormal dreams and nightmares, suicidal ideation and suicidal behavior (common); somnambulism and related reactions such as sleep talking and sleep related eating disorder (rare).

Nervous system disorders: Dizziness, somnolence, headache, extrapyramidal symptoms (very common); dysarthria (common); seizures, restless legs syndrome, tardive dyskinesia, syncope (uncommon).

Cardiac disorders: Tachycardia, palpitations (very common); QT prolongation bradycardia (uncommon); cardiomyopathy and myocarditis (not known).

Eye disorders: Vision blurred (common).

Vascular disorders: Orthostatic hypotension (common); venous thromboembolism (rare); stroke (not known).

Respiratory, thoracic and mediastinal disorders: Dyspnea (common); rhinitis (uncommon).

Gastrointestinal disorders: Dry mouth (very common); constipation, dyspepsia, vomiting (common); dysphagia (uncommon); pancreatitis, intestinal obstruction/ileus (rare).

Hepato-biliary disorders: Elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels (common); elevations in serum aspartate aminotransferase (AST) (uncommon); Jaundice Hepatitis (rare).

Skin and subcutaneous tissue disorders: Angioedema, Stevens-Johnson syndrome (very rare); Toxic Epidermal Necrolysis, Erythema Multiforme, Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Cutaneous vasculitis (not known).

Musculoskeletal and connective tissue disorders: Rhabdomyolysis (very rare).

Renal and urinary disorders: Urinary retention (uncommon).

Pregnancy, puerperium and perinatal conditions: Drug withdrawal syndrome neonatal (not known).

Reproductive system and breast disorders: Sexual dysfunction (uncommon); priapism, galactorrhea, breast swelling, menstrual disorder (rare).

General disorders and administration site conditions: Withdrawal symptoms (very common); mild asthenia, peripheral oedema, irritability, pyrexia (common); neuroleptic malignant syndrome, hypothermia (rare).

Investigations: Elevation in blood creatine phosphokinase (rare).

Pediatric population

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

Table 1 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not identified in the adult population

SOC	Very Common	Common
Endocrine disorders	Elevations in prolactin	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms	Syncope
Vascular disorders	Increases in blood pressure	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability

DOSAGE AND ADMINISTRATION

Seropine®XR 300 should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder

Seropine®XR 300 should be administrated at least one hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically justified the dose may be increased to 800 mg daily.

For the treatment of major depressive episodes in bipolar disorder

Seropine®XR 300 should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Seropine®XR 300 for acute treatment of bipolar disorder should continue on Seropine®XR 300 at the same dose administered at bedtime. Seropine®XR 300 dose can be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy.

For add-on treatment of major depressive episodes in MDD

Seropine®XR 300 should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine) and at 50 mg/day in short-term monotherapy trials.

Switching from Seropine immediate-release tablets

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

Elderly

As with other antipsychotics and antidepressants, Seropine®XR 300 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient. In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

Renal impairment

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment

Quetiapine is extensively metabolized by the liver. Therefore, Seropine®XR 300 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.

OVERDOSAGE

Symptoms

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

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. 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. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible, to perform within one hour of ingestion. 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. In case of overdose with extended-release quetiapine there is a delayed peak sedation and peak pulse and prolonged recovery compared with IR quetiapine overdose. In case of a quetiapine extended-release overdose gastric bezoar formation has been reported and appropriate diagnostic imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass.

Endoscopic pharmacobezoar removal has been performed successfully in some cases.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

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