Seropine®

Quetiapine Fumarate

FORMS AND PRESENTATION

Seropine® 25: Film coated tablets. Box of 60.
Seropine® 100: Film coated tablets. Box of 60.
Seropine® 200: Film coated tablets. Box of 60.
Seropine® 300: Film coated tablets. Box of 60.

COMPOSITION

Seropine® 25: Each film coated tablet contains quetiapine fumarate equivalent to Quetiapine 25mg.
Seropine® 100: Each film coated tablet contains quetiapine fumarate equivalent to Quetiapine 100mg.
Seropine® 200: Each film coated tablet contains quetiapine fumarate equivalent to Quetiapine 200mg.
Seropine® 300: Each film coated tablet contains quetiapine fumarate equivalent to Quetiapine 300mg.
Excipients: Lactose monohydrate, sodium starch glycolate, di basic calcium phosphate dihydrate, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow (for Seropine® 25 & 100), iron oxide red (for Seropine® 25).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: 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 (5HT2) and dopamine D1- and D2-receptors. It is this combination of receptor antagonism, with a higher selectivity for 5HT2 relative to D2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant.
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviorally or electro physiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade.

Pharmacokinetic properties

Absorption

Quetiapine is well absorbed and extensively metabolized following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. 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.

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 feces.

Elimination

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

INDICATIONS

Seropine® 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.

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

The safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Pediatric population

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. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults, 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.

Suicide/suicidal thoughts or clinical worsening

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

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.

Somnolence and dizziness

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

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. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

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

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo.

Neuroleptic malignant syndrome

Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis

Severe neutropenia (neutrophil count <0.5 x 109/L) has been reported in quetiapine clinical trials. 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. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma.

Weight

Weight gain has been reported in patients treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines.

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. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine.

QT prolongation

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema Multiform (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.
Most of these reactions occurred within 4 to 6 weeks after initiation of quetiapine therapy. If signs and symptoms of these severe skin reactions appear, quetiapine should be withdrawn immediately and alternative treatment should be considered.

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.
Quetiapine should be used with caution in patients with risk factors for stroke.

Elderly patients with Parkinson's disease (PD)

Caution should be exercised if quetiapine is prescribed to elderly patients with PD.

Dysphagia

Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. 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 drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures should be undertaken.

Additional information

Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited.

Lactose and sodium

Quetiapine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Misuse and abuse

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

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
Quetiapine should only be used if the benefits justify the potential risks.
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

Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue quetiapine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS

Given the primary central nervous system effects of quetiapine, it 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. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

PI070/3

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. 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%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician 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).
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 or lithium.
Caution should be exercised when quetiapine is used concomitantly with medicinal products 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 quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

ADVERSE EFFECTS

Very common: (≥1/10)
- Decreased hemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females
- Elevations in serum triglyceride and LDL cholesterol levels
- Decreases in HDL cholesterol
- Weight gain
- Dizziness, somnolence
- Headache
- Extrapyramidal symptoms
- Dry mouth
- Withdrawal (discontinuation) symptoms

Common: (≥1/100, <1/10)
- Leucopenia, decreased neutrophil count, Eosinophils increased
- Hyperprolactinemia
- Decrease in total T4, decrease in free T4, decrease in total T3, increase in TSH
- Increased appetite, blood glucose increased to hyperglycemic levels
- Abnormal dreams and nightmares, Suicidal ideation and suicidal behavior
- Dysarthria, Tachycardia, Palpitations
- Vision blurred
- Orthostatic hypotension
- Dyspnea, Constipation, dyspepsia, vomiting
- Elevations in serum alanine aminotransferase (ALT), Elevations in gamma-GT levels
- Mild asthenia, peripheral oedema, irritability, pyrexia

Uncommon: (≥1/1000, <1/100)
- Neutropenia, Thrombocytopenia, Anemia, platelet count decreased
- Hypersensitivity (allergic skin reactions)
- Decreases in free T3, Hypothyroidism
- Hyponatremia, Diabetes Mellitus, Exacerbation of pre-existing diabetes
- Seizure, Restless legs syndrome, Tardive dyskinesia, Syncope
- QT prolongation, Bradycardia
- Rhinitis
- Dysphagia
- Elevations in serum aspartate aminotransferase (AST)
- Urinary retention, sexual dysfunction

Rare: (≥1/10,000, <1/1000)
- Agranulocytosis
- Metabolic syndrome
- Somnambulism and related reactions
- Venous thromboembolism
- Pancreatitis, Intestinal obstruction/Ileus
- Jaundice, Hepatitis
- Priapism, galactorrhea, breast swelling, menstrual disorder
- Neuroleptic malignant syndrome, hypothermia
- Elevations in blood creatine phosphokinase

Very rare: (<1/10,000)
- Anaphylactic reaction
- Inappropriate antidiuretic hormone secretion
- Angioedema, Stevens-Johnson syndrome
- Rhabdomyolysis

Not known:
- Cardiomyopathy and myocarditis
- Stroke
- Toxic Epidermal Necrolysis, Erythema Multiforme, Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Cutaneous vasculitis
- Drug withdrawal syndrome neonatal

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

Very common: (≥1/10)
Elevations in prolactin, Increased appetite, Extrapyramidal symptoms, increases in blood pressure, vomiting

Common: (≥1/100, <1/10)
Syncope, Rhinitis, Irritability

DOSAGE AND ADMINISTRATION

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.
It can be administered with or without food.

Adults

For the treatment of schizophrenia, the total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards, the dose should be titrated to the usual effective dose of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.
For the treatment of moderate to severe manic episodes in bipolar disorder the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day.
For the treatment of major depressive episodes in bipolar disorder, it should be taken once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day3) 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 of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Seropine® for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

Elderly

As with other antipsychotics, Seropine® should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of Seropine® was reduced by 30 - 50% in elderly subjects when compared to younger patients.
Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Pediatric population

Seropine® 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.

Renal impairment

Dosage adjustment is not necessary for patients with renal impairment.

Hepatic impairment

Seropine® is extensively metabolized by the liver. Therefore, it should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

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

STORAGE CONDITIONS

Store below 25°C.
Keep in original pack in intact conditions.

Marketing Authorization Holder and Manufacturer
Benta S.A.L.
Dbayeh – Lebanon

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