Ebesque® XL

prolonged-release tablets (quetiapine) abbreviated prescribing information

Refer to the Summary of Product Characteristics for full product information.
Presentation: Prolonged-release tablets containing 50, 200, 300 or 400 mg of quetiapine
Indication: Ebesque® XL is indicated in adults for:

- Treatment of schizophrenia, including:
  - Preventing relapse in stable schizophrenic patients who have been maintained on Ebesque® XL
- 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 in patients with bipolar disorder, in patients whose manic or depressive episode has 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 Ebesque® XL.

Dosage and Administration: Refer to SmPC for details and recommendations
Adults: *For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder:* Ebesque® XL should be administered at least 1 hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg from Day 2. If clinically justified the dose may be increased to 800 mg daily. Adjust dose within effective dose range 400 mg to 800 mg o.d., depending on response and tolerability. For maintenance in schizophrenia no dose adjustment is necessary.
Treatment of depressive episodes in bipolar disorder: Ebesque® XL should be administered at bedtime. The total daily dose for the first 4 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. Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, dose reduction to a minimum of 200 mg could be considered.
For preventing recurrence in bipolar disorder: For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Ebesque® XL for acute treatment of bipolar disorder should continue on Ebesque® XL at the same dose administered at bedtime. Ebesque® XL can be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. The lowest effective dose must be used for maintenance therapy.
For add-on treatment of major depressive episodes in MDD: Ebesque® XL should be administered prior to bedtime. Daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.
Switching from quetiapine immediate-release tablets: Patients who are currently being treated with divided doses of immediate release quetiapine tablets may be switched to Ebesque® XL at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.
Older people: Ebesque® XL should be used with caution in older people, especially during the initial dosing period. The rate of dose titration of Ebesque® XL may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. 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 older 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.
Hepatic impairment: Ebesque® XL 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: Ebesque® XL 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.
Administration: Ebesque® XL should be administered once daily, without food (at least 1 hour before a meal). The tablets should be swallowed whole and not split, chewed or crushed.
Contra-indications: Hypersensitivity to the active substance or to any of the excipients of the tablets. Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV- protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone.
Precautions and Warnings: *Paediatric population:* Ebesque® XL is not recommended for use in children and adolescents below 18 years of age. In addition to the known safety profile identified in adults, increased appetite, elevations in serum prolactin, vomiting, rhinitis, syncope, extrapyramidal symptoms and irritability have been found to occur at higher frequencies, and increases in blood pressure and changes in thyroid function tests have been observed. Long-term implications for cognitive and behavioural development are not known. Quetiapine has been associated with an increased incidence of extrapyramidal symptoms (EPS) in children and adolescent patients treated for schizophrenia and bipolar mania.
Suicide/suicidal thoughts or clinical worsening: Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide, which persists until significant remission occurs. Improvement may not occur during the first few weeks or more of treatment and patients should be closely monitored until such improvement occurs. The risk of suicide may increase in the early stages of recovery. 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. Other psychiatric conditions for which Ebesque® XL is prescribed can also be associated with an increased risk of suicide related events, which may be
co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should be observed.
Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. An increased risk of suicidal behaviour with antidepressants has been shown in adult patients younger than 25 years of age with psychiatric disorders.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. 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.
An increased risk of suicide-related events has been observed in adult patients younger than 25 years of age with major depressive episodes in bipolar disorder treated with quetiapine. In patients with MDD, the incidence of suicide-related events observed in adult patients younger than 25 years of age has been found to be greater when treated with quetiapine.
Metabolic Risk: Worsening metabolic profile, including changes in weight, blood glucose and lipids, was observed in clinical trials. Metabolic parameters should be assessed at treatment initiation and regularly during treatment. Changes should be managed as clinically appropriate.
Extrapyramidal symptoms: In adult patients treated for major depressive episodes in bipolar disorder and MDD, treatment has been associated with an increased incidence of EPS. The use of quetiapine has been associated with the development of akathisia, which is most likely to occur within the first few weeks of treatment; in patients who develop symptoms, increasing the dose may be detrimental.
Tardive dyskinesia: Dose reduction or discontinuation of Ebesque® XL should be considered. The symptoms can worsen or even arise after discontinuation of treatment.
Somnolence and dizziness: Quetiapine treatment has been associated with somnolence and related symptoms. Bipolar depression patients and patients with major depressive episodes in MDD 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 has been associated with orthostatic hypotension and related dizziness; patients should be advised to exercise caution until they are familiar with the potential effects of the medication. Use with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or a more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.
Seizures: Caution is recommended when treating patients with a history of seizures.
Neuroleptic malignant syndrome: Neuroleptic malignant syndrome has been associated with antipsychotic treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. Ebesque® XL should be discontinued and appropriate medical treatment given.
Severe neutropenia and agranulocytosis: Severe neutropenia has been reported in clinical trials. Post marketing, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed.
Interactions: See "Interactions", below, regarding patients receiving a hepatic enzyme inducer.
Weight: Gain has been reported and should be monitored and managed as clinically appropriate in accordance with antipsychotic guidelines.
Hyperglycaemia: Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases. A prior increase in body weight may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with antipsychotic guidelines. Patients treated with any antipsychotic agent should be observed for symptoms of hyperglycaemia, 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. Lipid changes should be managed as clinically appropriate.
QT prolongation: Caution should be exercised in patients with cardiovascular disease or family history of QT prolongation. Caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in older people, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.
Cardiomyopathy and Myocarditis: Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience; however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.
Withdrawal: Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least 1 to 2 weeks is advisable.
Older patients with dementia-related psychosis: Ebesque® XL is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen with some atypical antipsychotics in the dementia population; the mechanism is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Ebesque® XL should be used with caution in patients with risk factors for stroke.
Dysphagia: Dysphagia has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.
Constipation and Intestinal Obstruction: Constipation and intestinal obstruction have been reported with quetiapine, including fatal cases in patients with an increased risk of intestinal obstruction and in patients for which no information on constipation is present.
Venous Thromboembolism (VTE): Cases of 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 Ebesque® XL and preventive measures undertaken.
Pancreatitis: Pancreatitis has been reported in clinical trials and post-marketing. Among post-marketing reports, many patients had risk factors for 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: Ebesque® XL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take Ebesque® XL.
Interactions: Ebesque® XL should be used with caution in combination with other centrally acting medicinal products and alcohol. Concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of Ebesque® XL treatment should only occur if the physician considers that the benefits 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. The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine or fluoxetine, the antipsychotics risperidone or haloperidol, or cimetidine. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine of around 70%. The pharmacokinetics of lithium or sodium valproate were not altered when co-administered with quetiapine. A higher incidence of extrapyramidal related events (particularly tremor), somnolence and weight gain was observed in a clinical study in adult patients with acute mania with lithium and quetiapine versus placebo and quetiapine. A higher incidence of leucopenia and neutropenia was observed in a retrospective study of children and adolescents with valproate and quetiapine versus valproate alone and versus quetiapine alone.
Formal interaction studies with commonly used cardiovascular medicinal products have not been performed. Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.
Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.
Side-effects: Refer to SmPC for full list. The most commonly reported Adverse Drug Reactions (ADRs) (≥10%) are: somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglycerides, elevations in total cholesterol (predominantly LDL cholseterol), decreases of HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms. Other commonly reported ADRs are, leucopenia, decreased neutophil count, increased eosinophils hyperprolactinaemia, decreases in total and free T_4, decreases in total T_3, increases in TSH, increased appetite, blood glucose increased to hyperglycaemic levels, abnormal dreams and nightmares, suicidal ideation and suicidal behaviour, dysarthria, tachycardia, palpitations, vision blurred, orthostatic hypotension, dyspnea, constipation, dyspepsia, vomiting, elevations in serum ALT and GT, mild asthenia, peripheral oedema, irritability and pyrexia. Less commonly reported are: thrombocytopenia, anaemia, decreased platelet count, hypersensitivity (including allergic skin reaction), decreases in free T_3, hypothyroidism, hyponatraemia, diabetes mellitus, seizure, restless legs syndrome, tardive dyskinesia, syncope, QT prolongation, bradycardia, rhinitis, dysphagia, elevations in serum AST, urinary retention and sexual dysfunction. Rarely reported: agranulocytosis, anaphylactic reaction, inappropriate antidiuretic hormone secretion, metabolic syndrome, somnambulism and related reactions such as sleep talking and sleep related eating disorder, venous thromboembolism, pancreatitis, intestinal obstruction/ileus, jaundice, hepatitis, angioedema, Stevens-Johnson syndrome, rhabdomyolysis, priapism, galactorrhoea, breast swelling, menstrual disorder, neuroleptic malignant syndrome, hypothermia and elevations in blood creatine phosphokinase. Not known: neutropenia, exacerbation of pre-existing diabetes, toxic epidermal necrolysis, erythema multiforme and drug withdrawal syndrome neonatal.

Price (pack size 60): 50mg - £31.80, 200mg - £53.16, 300mg - £79.90, 400mg - £106.31.

Legal category: POM.
Further Information: For full prescribing information see Summary of Product Characteristics.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to Medical Services Information - enquiries@medinformation.co.uk

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