

PACKAGE INSERT TEMPLATE FOR QUETIAPINE EXTENDED RELEASE TABLET

Brand or Product Name

[Product name] ER Tablet 50mg

[Product name] ER Tablet 200mg

[Product name] ER Tablet 300mg

[Product name] ER Tablet 400mg

Name and Strength of Active Substance(s)

Quetiapine fumarate ...mg equivalent to quetiapine 50mg

Quetiapine fumarate ...mg equivalent to quetiapine 200mg

Quetiapine fumarate ...mg equivalent to quetiapine 300mg

Quetiapine fumarate ...mg equivalent to quetiapine 400mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)]

eg : Tablet - White, circular flat beveled edge extended release tablets marked '50' on one side]

Pharmacodynamics

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. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 and serotonin 5HT_{1A} receptors. Quetiapine has no appreciable affinity at muscarinic or benzodiazepine receptors.

Pharmacodynamic effects

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D₂-receptor blockade.

Pharmacokinetics

Quetiapine is well absorbed following oral administration. Quetiapine is approximately 83% bound to plasma proteins. 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. The kinetics of quetiapine does not differ between men and women.

Quetiapine ER achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}). Quetiapine ER 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 ER administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate IR administered twice daily. The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

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

There are no clinically relevant differences in the observed apparent oral clearance (CL/F) and exposure of quetiapine between subjects with schizophrenia and bipolar disorder.

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.

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approx. 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.

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 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. 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.

Quetiapine ER should be taken at least one hour before a meal.

Indication

Treatment of schizophrenia

Preventing relapse in stable schizophrenic patients who have been maintained on quetiapine ER tablets.

Treatment of moderate to severe manic episodes in the framework of bipolar disorder.

Treatment of major depressive episodes in bipolar disorder.

Prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

Maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex.

The efficacy of quetiapine ER tablets in bipolar disorder was established, in part, on the basis of extrapolation from the established effectiveness of quetiapine IR tablets.

Major depressive disorder

Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies.

Recommended Dosage

Quetiapine ER tablets 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 associated with bipolar disorder

Quetiapine ER tablets should be administered 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. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of depressive episodes associated with bipolar disorder

Quetiapine ER tablets should be administered at bedtime. The 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. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. 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, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

Maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex

While there is no body of evidence available to specifically address how long the patient treated with Quetiapine ER tablets should remain on it, maintenance of efficacy in Bipolar I Disorder was demonstrated with quetiapine IR tablets (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

For preventing recurrence in bipolar disorder

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Quetiapine ER tablets for acute treatment of bipolar disorder should continue on Quetiapine ER tablets at the same dose administered at bedtime. Quetiapine ER tablets 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.

Recurrent major depressive disorder

When treating recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.

Quetiapine ER 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. The usual effective dose in MDD is 150 mg. Further adjustments can be made upwards or downwards within the recommended dose range of 50 mg to 300 mg depending upon the clinical response and tolerability of the patient.

Patients who have not responded to Quetiapine ER after 6 weeks treatment for MDD should have treatment re-evaluated.

For maintenance therapy in MDD in patients who have responded to acute treatment, the effective dose during initial treatment should be continued. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest possible dose needed to maintain remission. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

Long-term safety of Quetiapine ER in MDD has not been systematically evaluated (>52 weeks). Thus, the physician who elects to use Quetiapine ER in the treatment of MDD should use Quetiapine ER for the

shortest time that is clinically indicated. When lengthier treatment is indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks.

Switching from quetiapine immediate-release tablets

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

Elderly

As with other antipsychotics, Quetiapine ER tablets should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of Quetiapine ER tablets 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% to 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 tolerability of the individual patient. In elderly patients with MDD, 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. Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and Adolescents:

The safety and efficacy of Quetiapine ER have not been evaluated in children and adolescents.

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolized by the liver. Therefore, Quetiapine ER 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.

Mode of Administration

Oral

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, azoleantifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated.

Warnings and Precautions

[Specific package insert requirement for quetiapine]

WARNINGS:

Hyperglycemia and Diabetes Mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related events in patients treated

with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

Children and adolescents (10 to 17 years of age)

Quetiapine ER tablets 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 and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

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

Quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania

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.

Somnolence

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression 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.

Cardiovascular

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs.

Seizures

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Extrapyramidal symptoms

Quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder.

Tardive dyskinesia

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine ER should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment.

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. In such an event, Quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia

Severe neutropenia (neutrophil count $<0.5 \times 10^9/L$) has been uncommonly 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, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9/L$. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed $1.5 \times 10^9/L$).

Lipids

Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine. Lipid increases should be managed as clinically appropriate.

Metabolic Risk

Given the observed changes in weight, blood glucose (see hyperglycemia) and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate.

QT Prolongation

Quetiapine was not associated with a persistent increase in absolute QT intervals. However, with overdose QT prolongation was observed. 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 with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

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 one to two weeks is advisable.

Elderly patients with dementia-related psychosis

Quetiapine ER is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in 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 ER should be used with caution in patients with risk factors for stroke.

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.

Hepatic effects

If jaundice develops, Quetiapine ER should be discontinued.

Concomitant Illness

Dysphagia and aspiration have been reported with Quetiapine ER. Although a causal relationship with aspiration pneumonia has not been established, Quetiapine ER should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism

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 undertaken.

Effect 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.

Interactions with Other Medicaments

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

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. 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).

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. Concomitant administration of quetiapine 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.

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

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.

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

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

Statement on Usage During Pregnancy and Lactation

[Specific package insert requirement for antipsychotic]

Pregnancy and lactation

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

Quetiapine tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The safety and efficacy of quetiapine during human pregnancy have not yet been established. The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking quetiapine.

Adverse Effects / Undesirable Effects

The most commonly reported adverse drug reactions with quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia. As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with quetiapine.

Blood and lymphatic system disorders

Common:	Leucopenia
Uncommon:	Thrombocytopenia
Unknown:	Neutropenia

Immune system disorders

Uncommon:	Hypersensitivity
Very rare:	Anaphylactic reaction

Endocrine disorders

Common:	Hyperprolactinaemia
Very rare:	Inappropriate antidiuretic hormone secretion

Metabolism and nutritional disorders

Common:	Increased appetite
Uncommon:	Hyponatraemia
Very rare:	Diabetes mellitus

Psychiatric disorders

Common:	Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour
Rare:	Somnambulism and other related events

Nervous system disorders

Very Common:	Dizziness, somnolence, headache , extrapyramidal symptoms
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Common: Dysarthria
Uncommon: Seizure, Restless legs syndrome, Tardive dyskinesia , Syncope

Cardiac disorders

Common: Tachycardia, Palpitations
Uncommon: Bradycardia

Eye Disorders

Common: Vision blurred

Vascular disorders

Common: Orthostatic hypotension
Uncommon: Venous thromboembolism

Respiratory, thoracic and mediastinal disorder

Common: Dyspnea
Uncommon: Rhinitis

Gastrointestinal disorders

Very common: Dry mouth
Common: Constipation, dyspepsia , vomiting
Uncommon: Dysphagia
Rare: Intestinal obstruction/Ileus

Hepato-biliary disorders

Rare: Jaundice
Very rare: Hepatitis

Renal and urinary disorders

Uncommon: Urinary retention

Skin and subcutaneous tissue disorders

Very rare: Angioedema, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders

Very rare: Rhabdomyolysis

Reproductive system and breast disorders

Uncommon: Sexual dysfunction
Rare: Priapism, galactorrhoea , breast swelling, menstrual disorder

General disorders and administration site conditions

Very common: Withdrawal (discontinuation) symptoms
Common: Mild asthenia, peripheral oedema, irritability , pyrexia
Rare: Neuroleptic malignant syndrome , hypothermia
Not known : Neonatal withdrawal

Investigations

Very common: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin
Common: Elevations in serum alanine aminotransferase(ALT) , elevations in gamma-GT levels, decreased neutrophil count, eosinophils increased, blood glucose

	increased to hyperglycaemic levels, QT prolongation, decreases in Total T ₄ , decreases in Free T ₄ , decreases in Total T ₃ , increases in TSH
Uncommon:	Elevations in serum aspartate aminotransferase (AST), platelet count decreased, decreases in free T ₃
Rare	Elevations in blood creatine phosphokinase, agranulocytosis

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.

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Quetiapine treatment was associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that Quetiapine causes clinically relevant hypothyroidism.

Children and adolescents (10 to 17 years of age)

The same ADRs described above for adults should be considered for children and adolescents. The following table summarises 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.

Metabolism and nutritional disorders

Very common: Increased appetite

Investigations

Very common: Elevations in prolactin, increases in blood pressure

Nervous system disorders

Common: Syncope

General disorders and administration site conditions

Common: Irritability

Respiratory, thoracic, and mediastinal disorders

Common: Rhinitis

Gastrointestinal disorders

Very Common: Vomiting

Overdose and Treatment

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams. In postmarketing experience, there have been very rare reports of overdose of quetiapine alone, resulting in death or coma or QT-prolongation.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

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

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. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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

Storage Conditions

Store below°C

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]