Quetiapine (as fumarate)

Quekline®

25 mg, 100 mg, 200 mg Film-Coated Tablet
Antipsychotic

FORMULATION

Quetiapine (Quekline®) 25 mg tablet

Each peach coloured, round, biconvex, film coated tablet contains quetiapine fumarate equivalent to quetiapine 25 mg.

Quetiapine (Quekline®) 100 mg tablet

Each yellow coloured, round, biconvex film coated tablet contains quetiapine fumarate equivalent to quetiapine 100 mg.

Quetiapine (Quekline®) 200 mg tablet

Each white coloured, round, biconvex film coated tablet contains quetiapine fumarate equivalent to quetiapine 200 mg.

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group

Antipsychotics; Diazepines, oxazepines, thiazepines and oxepines

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 symptoms (EPS) liability of quetiapine compared to typical antipsychotics. 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 for adrenergic α_2 receptors and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic 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 D_2-receptor blockade. It is not known to what extent the Norquetiapine metabolite contributes to the pharmacological activity of quetiapine in humans.

In pre-clinical tests which examine the tendency for EPS, quetiapine has an atypical profile and separates from the standard anti-psychotic drugs. Quetiapine does not produce dopamine D_2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarization blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Pharmacokinetics

The pharmacokinetics of quetiapine and norquetiapine are linear within the approved dosage range.

Absorption

Quetiapine is well absorbed and extensively metabolised following oral administration.

Distribution and metabolism

The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite norquetiapine is 35% of what is seen for quetiapine.

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

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is only seen at concentrations approximately 5 – 50 fold higher than those seen in the dosage range 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other active substances will result in clinically significant inhibition of cytochrome P450 mediated metabolism of the other active substances.

Based on animal-studies it appears that quetiapine may induce cytochrome P450 enzymes. However, in a specific interaction study involving psychotic patients, no increase in the activity of cytochrome P450 after administration of quetiapine was observed.

Elimination

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

Special patient 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/1.73m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis). As quetiapine is extensively metabolised by the liver a higher quetiapine plasma value in patients with hepatic impairment is expected and a dose-adjustment may be necessary in this groups of patients *(see Section Dosage and Administration).*

CLINICAL STUDIES
Not relevant for this product.

NON-CLINICAL INFORMATION
There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. Pigment deposition in the thyroid gland, thyroid follicular cell hypertrophy, a lowering in plasma T_3 levels, decreased haemoglobin concentration, lens opacity and cataracts and a decrease of red and white blood cell count have been observed in laboratory animals.

INDICATIONS
For the treatment of:
- schizophrenia,
- bipolar disorder including:
    - manic episodes associated with bipolar disorder
    - major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

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.
Quetiapine can be administered with or without food.

Route of Administration
For oral use.

Adults
For the treatment of schizophrenia
Quetiapine should be dosed twice a day. The total daily dose for the first 4 days is given in Table 1.

Table 1.

Day	Day 1	Day 2	Day 3	Day 4
Quetiapine	50 mg	100 mg	200 mg	300 mg

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 range 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 manic episodes associated with bipolar disorder
Quetiapine should be dosed twice a day as monotherapy or as adjunct therapy to mood stabilizers, the total daily dose for the first four days is as per Table 2.

Table 2.

Day	Day 1	Day 2	Day 3	Day 4
Quetiapine	100 mg	200 mg	300 mg	400 mg

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 per day.
The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.
For the treatment of depressive episodes in bipolar disorder
Quetiapine should be administered once daily at bedtime. The total daily dose for the first 4 days of therapy is given in Table 3.

Table 3.

Day	Day 1	Day 2	Day 3	Day 4
Quetiapine	50 mg	100 mg	200 mg	300 mg

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. 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. 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. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.
For preventing recurrence in bipolar disorder
For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may then 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.

Children
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 *(see Sections: Warnings and Precautions, Adverse Effects)*.

Elderly
As with other antipsychotics and antidepressants, quetiapine should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on quetiapine 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose. The rate of dose titration of quetiapine 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 quetiapine was reduced by 30% to 50% in elderly patients 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.

Renal impairment

Dose adjustment is not necessary in patients with renal impairment.

Hepatic impairment

Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dosing period.

Patients with hepatic impairment should be started with 25 mg/day. The dose can be increased in increments of 25 - 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

CONTRAINDICATIONS

Quetiapine is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients,
- concomitant administration of cytochrome P450 3A4 inhibitors such as HIV-protease inhibitors, azole- antifungal agents, erythromycin, clarithromycin and nefazodone *(see Section Interactions).*

WARNINGS AND PRECAUTIONS

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

Children and adolescents (10 to 17 years of age)

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 of quetiapine have shown that in addition to the known safety profile identified in adults *(see Section Adverse Effects)*, 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 quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

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

Suicide/suicidal thoughts or clinical worsening

Depression 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. Other psychiatric conditions for which quetiapine are prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders.

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. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

Extrapyramidal symptoms

In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder *(see Section Adverse Effects)*.

The use of quetiapine has been associated with the development of akathisia, characterised 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 *(see Section Adverse Effects)*.

Somnolence

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation *(see Section Adverse Effects)* or falls. Somnolence usually occurs during the first two weeks of treatment and generally resolves with the continued administration of quetiapine. 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.

Dizziness

Quetiapine treatment has also been associated with orthostatic hypotension and related dizziness, tachycardia and, in some patients, syncope *(see Section Adverse Effects)* which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Cardiovascular disease

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. A slower titration regimen could be considered in patients with underlying cardiovascular disease.

QT prolongation

In clinical trials and use in recommended dosing schedule, 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 *(see Section Adverse Effects)* and in overdose *(see Section Overdosage)*. 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, hypokalaemia or hypomagnesaemia *(see Section Interactions)*.

Seizures

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures *(see Section Adverse Effects)*.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine *(see Section Adverse Effects).* 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 *(see Section Adverse Effects)*. There was no apparent dose relationship. During post-marketing experience, resolution of leukopenia 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 1.5×10^9/L).

Concomitant use with hepatic enzyme inducers

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 *(see Section Interactions)*. In patients receiving a hepatic enzyme inducer, initiation of quetiapine 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).

Weight gain

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines *(see Section Adverse Effects)*.

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases *(see Section Adverse Effects).* In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia (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 *(see Section Adverse Effects).* Lipid changes should be managed as clinically appropriate.

Metabolic risk

Given the observed changes in weight, blood glucose *(see Hyperglycaemia)* and lipids seen in clinical studies, patients (including those with normal baseline values) may experience worsening of their metabolic risk profile, which should be managed as clinically appropriate *(see Section Adverse Effects)*.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. The incidence of these reactions had decreased significantly after 1 week post discontinuation. Gradual withdrawal over a period of at least one to two weeks is advisable *(see Section Adverse Effects).*

Elderly patients with dementia-related psychosis

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

In a meta-analysis of atypical antipsychotics it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations

for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Hepatic effects

If jaundice develops, quetiapine should be discontinued *(see Section Adverse Effects)*.

Dysphagia

Dysphagia *(see Section Adverse Effects)* has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

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 undertaken.

Pancreatitis

Pancreatitis has been reported in clinical trials and during the post marketing experience. Among the 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 *(see Lipids),* gallstones, and alcohol consumption.

Combination with valproate semisodium or lithium

Quetiapine data in combination with valproate semisodium 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 *(see Section Interactions)*.

Elevations in serum transaminases

Asymptomatic elevations (shift from normal to > 3x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine *(see Section Adverse Effects)*. These elevations were usually reversible on continued quetiapine treatment.

Dyspnoea and palpitations

Reports of dyspnoea and palpitation often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease *(see Section Adverse Effects).*

Lactose

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ability to perform tasks that require judgement, motor or cognitive skills

Patients should be advised not to drive or operate machinery, until individual susceptibility to this is known. Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness.

DRUG INTERACTIONS

Centrally acting medicinal products, alcohol, neuroleptic medicines

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

CYP3A4 inhibitor

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 *(see Section Contraindications)*.

Carbamazepine, phenytoin - hepatic enzyme inducers

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur which can influence 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) *(see Section Warnings and Precautions)*.

Imipramine, fluoxetine

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).

Risperidone, haloperidol, thioridazine

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%.

Cimetidine

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

Lithium

The pharmacokinetics of lithium were not altered when co-administered with quetiapine *(see Section Warnings and Precautions)*.

Valproic acid

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.

Products that can prolong the QT-interval

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.
Methadone and tricyclic antidepressants
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.
Food and beverages
It is not recommended to consume grapefruit juice while on quetiapine therapy.

PREGNANCY AND LACTATION

Fertility
There are no relevant data available.
Pregnancy
Quetiapine should only be used during pregnancy if the benefits justify the potential risks.
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined, though. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed.
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.
Lactation
Women who are breast-feeding should be advised to avoid breast-feeding while taking quetiapine. There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent.

ADVERSE EFFECTS

Clinical Trial Data and Post Marketing Data
The most commonly reported Adverse Drug Reactions (ADRs) 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, leukopenia, neutropenia and peripheral oedema, have been associated with quetiapine.
Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).
Blood and lymphatic system disorders
Very common: haemoglobin decreased
Common: leukopenia *(see Section Warnings and Precautions)*, neutrophil count decreased, eosinophil count increased
Uncommon: thrombocytopenia, anaemia, platelet count decreased
Rare: agranulocytosis
Unknown: neutropenia *(see Section Warnings and Precautions)*
Immune system disorders
Uncommon: hypersensitivity (including allergic skin reactions)
Very rare: anaphylactic reaction[3]
Endocrine disorders
Common: hyperprolactinaemia, thyroxine decreased, thyroxine free decreased, tri-iodothyronine decreased, blood thyroid stimulating hormone increased
Uncommon: tri-iodothyronine free decreased, hypothyroidism
Very rare: inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders
Very common: blood triglycerides increased, blood cholesterol increased (predominantly LDL cholesterol), high density lipoprotein decreased, weight increased (based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment) *(see Section Warnings and Precautions)*
Common: increased appetite, blood glucose increased to hyperglycaemic levels[1]
Uncommon: hyponatraemia, diabetes mellitus[3] *(see Section Warnings and Precautions)*
Rare: metabolic syndrome
Psychiatric disorders
Common: abnormal dreams, nightmare, suicidal ideation, suicidal behaviour
Rare: somnambulism and related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders
Very common: dizziness *(see Section Warnings and Precautions)*, somnolence *(see Section Warnings and Precautions),* headache
Common: syncope *(see Section Warnings and Precautions)*, extrapyramidal symptoms *(see Section Warnings and Precautions)*, dysarthria
Uncommon: seizure *(see Section Warnings and Precautions)*, restless legs syndrome, tardive dyskinesia[3] *(see Section Warnings and Precautions)*
Eye disorders

Common: vision blurred
Cardiac disorders
Common: tachycardia *(see Section Warnings and Precautions)*, palpitations *(see Section Warnings and Precautions)*
Uncommon: QT prolongation *(see Section Warnings and Precautions),* bradycardia[(2)]
Vascular disorders
Common: orthostatic hypotension *(see Section Warnings and Precautions)*
Rare: embolism venous *(see Section Warnings and Precautions)*
Respiratory, thoracic and mediastinal disorders
Common: rhinitis, dyspnoea *(see Section Warnings and Precautions)*
Gastrointestinal disorders
Very common: dry mouth
Common: constipation, dyspepsia, vomiting
Uncommon: dysphagia
Rare: pancreatitis
Hepatobiliary disorders
Common: transaminases increased (ALT, AST), gamma-glutamyltransferase increased *(see Section Warnings and Precautions)*
Rare: jaundice[(3)], hepatitis *(see Section Warnings and Precautions)*
Skin and subcutaneous tissue disorders
Very rare: angioedema[(3)], Stevens-Johnson syndrome[(3)]
Unknown: toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders
Very rare: rhabdomyolysis
Pregnancy, puerperium and perinatal conditions
Unknown: drug withdrawal syndrome neonatal (*see Section Pregnancy and Lactation*)
Reproductive system and breast disorders
Uncommon: sexual dysfunction
Rare: priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions
Very common: withdrawal syndrome *(see Section Warnings and Precautions)*
Common: mild asthenia, peripheral oedema, irritability, pyrexia
Rare: neuroleptic malignant syndrome *(see Section Warnings and Precautions)*, hypothermia
Investigations
Rare: blood creatine phosphokinase increased (not associated with neuroleptic malignant syndrome)
[(1)]Fasting blood glucose ≥126mg/dL(≥7.0 mmol/L) or a non fasting blood glucose ≥200mg/dL (≥11.1 mmol/L) on at least one occasion
[(2)]May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.
[(3)]Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of Quetiapin
Class effects
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.
Children and adolescents (10 to 17 years of age)
The same ADRs described above for adults should be considered for children and adolescents.
The ADRs below occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or have not been identified in the adult population.
Metabolism and nutritional disorders
Very common: increased appetite
Nervous system disorders
Very common: extrapyramidal disorder
General disorders and administration site conditions
Common: irritability[(4)]
Investigations
Very common: prolactin increased, blood pressure increased
[(4)]The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

OVERDOSAGE AND TREATMENT

Symptoms and signs
Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 g, and in post-marketing on doses as low as 6 g of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 g. In post marketing experience, there have been reports of overdose of quetiapine alone resulting in death or coma. Additionally, the following events have been reported in the setting of monotherapy overdose with quetiapine: QT prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation.
Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose *(see Section Warnings and Precautions: Cardiovascular)*.
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 and hypotension.

Treatment
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. 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 at temperatures not exceeding 30°C.

AVAILABILITY
Quetiapine (*Quekline®*) *25 mg tablet*: 10 tablets per blister (Box of 30's)
Quetiapine (*Quekline®*) *100 mg tablet*: 10 tablets per blister (Box of 30's)
Quetiapine (*Quekline®*) *200 mg tablet*: 10 tablets per blister (Box of 30's)

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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For Healthcare Professionals only