QUETIAPINE

QTIPINE 25 / QTIPINE 100 / QTIPINE 300

25 mg / 100mg / 300mg Film-Coated Tablet

Antipsychotic

FORMULATION

Each extended-release tablet contains:

Quetiapine Fumarate
equivalent to Quetiapine 25mg
Quetiapine Fumarate
equivalent to Quetiapine 100mg
Quetiapine Fumarate
equivalent to Quetiapine 300mg

PRODUCT DESCRIPTION

Quetiapine Fumarate (Qtipine 25) 25 mg is a brownish red coloured, round, biconvex, film coated tablet plain on both sides.

Quetiapine Fumarate (Qtipine 100) 100 mg is a white to off white, round biconvex, film coated tablet with debossed "1150" on one side and plain on other side.

Quetiapine Fumarate (Qtipine 300) 300 mg is a white to off white, capsule shaped, biconvex, film coated tablet with breakline on both sides.

Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

Its chemical name is 2-[2-(4-Dibenzo [b,f] [1,4]thiazepin-11-yl-1-piperazinyl) ethoxy]ethanol fumarate. Molecular formula is (C21H25N3O2S)2. C4H4O4 and it has a molecular weight of 883.1.

PHARMACOLOGICAL PROPERTIES

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 moderate affinity at adrenergic alpha2 receptors and moderate to high affinity at several muscarinic receptors. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Quetiapine Extended-Release therapeutic efficacy as an antidepressant.

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.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the 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.

Pharmacokinetic properties

Absorption

Quetiapine is well absorbed 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 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 radiolabeled 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 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.

Elimination

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabeled drug was excreted in the urine and 21% in the feces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender

The pharmacokinetics of quetiapine does not differ between men and women.

Elderly

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

Renal impairment

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 $m^{2)}$, but the individual clearance values are within the range for normal subjects.

Hepatic impairment

The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolized by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients.

Children and adolescents (10-17 years of age)

At the steady the pharmacokinetics of the parent compound in children and adolescents, (10-17 years of age) were similar in adults, while AUC and Cmax of the active metabolite, norquetiapine, were higher in children and adolescents than in adults, 45% and 31% respectively. However, when adjusted for weight AUC and Cmax of the parent compound in children and adolescents were lower in adults, 41% and 39% respectively, while the pharmacokinetics of the metabolite, norquetiapine, was similar.

INDICATIONS

Quetiapine Fumarate is indicated for the treatment of:

- schizophrenia
- manic episodes associated with bipolar disorder
- depressive episodes associated with bipolar disorder
- preventing recurrence in bipolar disorder

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 should be administered with or without food and swallowed whole and not split, chewed or crushed.

Adults

For the treatment of schizophrenia

The usual initial dose is 25 mg twice daily on day one, 50 mg twice daily on day two, 100 mg twice daily on day three, and 150 mg twice daily on day four. The dosage is then adjusted according to response to a usual range of 300 to 450 mg daily given in 2 or 3 divided doses, although 150 mg daily may be adequate for some patients. The maximum recommended dose is 750 mg daily.

For the treatment of manic episodes associated with bipolar disorder

The initial dose is 50 mg twice daily on day one, 100 mg twice daily on day two, 150 mg twice daily on day three, and 200 mg twice daily on day four. The dose may then be adjusted to a usual range of 400 to 800 mg daily, although, in some patients, 200mg daily may be adequate. Increments in dosage should be no greater than 200 mg daily.

For the treatment of major depressive episodes in bipolar disorder

Quetiapine fumarate should be administered 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 (Day 3) and 300 mg (Day 4). The dose may then be adjusted to 400mg on Day 5 and up to 600mg by Day 8.

In clinical trials, no additional benefit was seen in the 600mg group compared to the 300mg group. Individual patients may benefit from a 600mg dose.

For preventing recurrence in bipolar disorder

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

Elderly

As with other antipsychotics and antidepressants, Quetiapine fumarate should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of Quetiapine fumarate 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.

Children and Adolescents

For treatment of schizophrenia associated with bipolar disorder (children and adolescents 13 to 17 years of age)

Quetiapine Fumarate should be administered twice daily. However, it may be administered three times daily based on response and tolerability.

The total daily dose for the first five days of therapy is 50mg (Day 1), 100mg (Day 2), 200mg (Day 3), 300mg (Day 4) and 400mg (Day 5). The dose should be adjusted within the effective dose range of 400mg to 800mg a day based on response and tolerability of the individual patient after day 5. Increments in dosage should be no greater than 100 mg daily.

Safety and effectiveness of Quetiapine Fumarate in children less than 13 years of age with bipolar mania have not been established.

For treatment of manic episodes associated with bipolar disorder (children and adolescents 10 to 17 years of age)

Quetiapine Fumarate should be administered twice daily. However, it may be administered three times daily based on response and tolerability.

The total daily dose for the first five days of therapy is 50mg (Day 1), 100mg (Day 2), 200mg (Day 3), 300mg (Day 4) and 400mg (Day 5). The dose should be adjusted within the effective dose range of 400mg to 800mg a day based on response and tolerability of the individual patient after day 5. Increments in dosage should be no greater than 100 mg daily.

Safety and effectiveness of Quetiapine Fumarate in children less than 10 years of age with bipolar mania have not been established.

Renal impairment

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment

Quetiapine is extensively metabolized by the liver. Therefore, Quetiapine Fumarate 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 25mg/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.

CONTRAINDICATION

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

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.

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 a and behavioral development are not known.

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

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 is 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 behavior 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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

Metabolic Risk

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate

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

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. 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. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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.

Seizures

As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine.

Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. 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. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 109/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 109/L).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat) at any time during Quetiapine fumarate therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Weight

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 utilized 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. 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 utilized 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. Lipid changes should be managed as clinically appropriate.

QT Prolongation

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, 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, 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.

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 represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine. This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Pancreatitis

Pancreatitis has been reported in clinical trials and during post marketing experience.

Effects on ability to drive and use machines

Quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

PREGNANCY AND LACTATION

The safety and efficacy of Quetiapine during pregnancy have not been established. Therefore, Quetiapine should be used only if the potential benefit justifies the potential risk.

There have been reports of excretion of Quetiapine into human breast milk, however the degree of excretion was not consistent. Therefore, decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother's health.

DRUG INTERACTIONS

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).

Interaction with Other Medicinal Products and Other Forms Of Interaction

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

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 with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), 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; although a greater effect was seen in some patients. 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.
The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.
Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.
The pharmacokinetics of lithium was not altered when co-administrated with Quetiapine.
There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine.

ADVERSE DRUG EFFECTS

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.
The incidences of ADRs associated with quetiapine therapy, are tabulated below (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group 1995).

Table 1

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Blood and lymphatic system disorders	Decreased Haemoglobin[19]	Leucopenia[1,25] decreased neutrophil count, eosinophils	Neutropenia[1], platelet count decreased[13]	Agranulocytosis[23]		
Immune system disorders			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction[5]	
Endocrine disorders		Hyperprolactinaemia[15], decreases in total T4[21], decreases in free T4[21], decreases in total T3[21], increases in TSH [21]	Decreases in free T3[21], Hypothyroidism[30]			
Metabolism and nutritional	Elevations in serum triglyceride disorders levels [10,27] Elevations in total cholesterol (predominantly LDL cholesterol)[11,27] Decreases in HDL Cholesterol[17,27] Weight gain[8,27]	Increased appetite, blood glucose increased to hyperglycaemic levels [6, 27]	Diabetes Mellitus [1,5] Exacerbation of pre-existing diabetes	Metabolic syndrome[26]		
Psychiatric disorders		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[18]		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
Nervous system disorders	Dizziness [4,16], somnolence[2,16] headache, Extrapyramidal symptoms[1,30]	Dysarthria	Seizure[1], Restless legs syndrome, Tardive dyskinesia[1,5] Syncope[4,16]			
Cardiac disorders		Tachycardia [4,] Palpitations[20]	QT prolongation[1,12] Bradycardia[29]			
Eye Disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension[4,16]				
Respiratory, thoracic and mediastinal disorder		Dyspnoea [20]	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting[22]	Dysphagia[7]	Pancreatitis[1,] Intestinal obstruction/Ileus		
Hepatobiliary disorders		Elevations in serum alanine aminotransferase (ALT)[3,] Elevations in gamma-GT levels[3]	Elevations in serum aspartate aminotransferase (AST)[3]	Hepatitis (with or without jaundice)		
Renal and urinary disorders			Urinary retention			
Pregnancy, puerperium and perinatal conditions						Drug withdrawal syndrome neonatal[28]
Reproductive system and breast disorders				Priapism, galactorrhoea,		
General disorders and administration site conditions	Withdrawal (discontinuation) symptoms[1,9]	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome[1] hypothermia		
Investigations				Elevations in blood creatine phosphokinase[14]		

(1) See **Special warnings and precautions for use**
(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
(3) Asymptomatic elevations (shift from normal to ≥3 X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.
(5) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of quetiapine.
(6) 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.
(7) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
(8) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
(9) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
(10) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.
(11) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
(12) See text below.
(13) Platelets ≤100 x 109/L on at least one occasion.
(14) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
(15) Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time.
(16) May lead to falls.
(17) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
(18) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation
(19) Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was -1.50 g/dL.
(20) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.
(21) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T4, free T4, total T3 and free T3 are defined as <0.8 X LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
(22) Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
(23) Based on shift in neutrophils from > = 1.5 x 109/L at baseline to <0.5 x 109/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 109/L) and infection during all quetiapine clinical trials.

(24) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as ≥1 x 109 cells/L at any time.
(25) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤3 x 109 cells/L at any time.
(26) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
(27) In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies
(28) See Fertility, pregnancy and lactation
(29) 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. 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.

Paediatric Population

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

Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not identified in the adult population

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

System Organ Class	Very Common	Common
Endocrine disorders	Elevations in prolactin[1]	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms[3]	Syncope
Vascular disorders	Increases in blood pressure[2]	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability[3]

(1) Prolactin levels (patients < 18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L.
(2) Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
(3) Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSE AND TREATMENT

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 and hypotension.

Overdose could lead to QT-prolongation, seizures, respiratory depression, urinary retention, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Based on public literature, patients with delerium 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.

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.

STORAGE AND CONDITION

Store at temperatures not exceeding 30°**C.**

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Quetiapine (Qtipine 25) 25 mg Film - Coated Tablet - Alu/Alu Blister Pack x 10's (Box of 100's) - DRP-5721

Quetiapine (Qtipine 300) 300 mg Film - Coated Tablet - Alu-Alu Blister Pack x 10's (Box of 100's) - DRP-5812

Date of First Authorization

October 14, 2011

Quetiapine (Qtipine 100) 100 mg Film - Coated Tablet - Alu/Alu Blister Pack x 10's (Box of 60's) - DR-

Date of First Authorization

mm-dd-yyyy

DATE OF REVISION

April 2017

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
Indrad 382 721 Dist. Mehsana, India

Imported and Distributed by:
TORRENT PHARMA PHILPPINES INC.
Units 3 & 4, 34th Floor, Zuellig Building
Makati Avenue Corner Paseo de Roxas
Makati City, PHILIPPINES