**PACKAGE INSERT TEMPLATE FOR QUETIAPINE TABLET**

**Brand or Product Name**
*[Product name]* Tablet 25mg
*[Product name]* Tablet 100mg
*[Product name]* Tablet 200mg
*[Product name]* Tablet 300mg

**Name and Strength of Active Substance(s)**
Quetiapine fumarate ….mg equivalent to quetiapine 25mg
Quetiapine fumarate ….mg equivalent to quetiapine 100mg
Quetiapine fumarate ….mg equivalent to quetiapine 200mg
Quetiapine fumarate ….mg equivalent to quetiapine 300mg

**Product Description**
*[Visual description of the appearance of the product (eg colour, markings etc)*
*eg :Tablet - White, circular flat beveled edge tablets marked '100' 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 ($5HT_2$) 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 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 $\alpha_1$ receptors, with a lower affinity at adrenergic $\alpha_2$ 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 $D_2$-receptor blockade.

**Pharmacokinetics**
*Adults*
Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

*Children and Adolescents*
At steady-state the pharmacokinetics of the parent compound, in children and adolescents (10-17 years of age), were similar to adults. However, when adjusted for dose and weight, AUC and Cmax of the parent compound were 41% and 39% lower, respectively, in children and adolescents than in adults. For the active metabolite, norquetiapine, AUC and $C_{max}$ were 45% and 31% higher, respectively, in children and adolescents than in adults. When adjusted for dose and weight, the pharmacokinetics of the metabolite, norquetiapine, was similar between children and adolescents and adults.

Quetiapine is well absorbed and extensively metabolised following oral administration. 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 are 35% of

that observed for quetiapine. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women. The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

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 with approx. 25% in persons with known hepatic impairment (stable alcoholcirrhosis). 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.

*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.

**Indication**

*Treatment of schizophrenia*

The antipsychotic efficacy of quetiapine was established in short-term (6 weeks) in adults and adolescents (13-17 years) schizophrenic inpatients.

The effectiveness of quetiapine in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use quetiapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

*Treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct to lithium or divalproex*

The efficacy of quetiapine in acute bipolar mania was established in 12 weeks in adults and 3 weeks in pediatric patients (10-17 years).

*Treatment of depressive episodes associated with bipolar disorder*

The efficacy of quetiapine was established in 8 weeks in bipolar I or bipolar II.

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

The efficacy of quetiapine as adjunct maintenance therapy to lithium or divalproex was established in patients with Bipolar I Disorder. The physician who elects to use quetiapine for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

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

**Recommended Dosage**

Schizophrenia

*Adults*

Quetiapine should be administered twice daily, with or without food. Quetiapine should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for quetiapine would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of quetiapine. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety and efficacy doses above 800 mg/day have not been evaluated in clinical trials.

*Adolescents (13-17 years)*

Quetiapine should be administered twice daily. However, based on response and tolerability Quetiapine may be administered three times daily where needed. The total daily dose for the initial five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After day 5, the dose should be adjusted within the recommended dose range of 400 mg/day to 800 mg/day based on response and tolerability. Dosage adjustments should be in increments of no greater than 100 mg/day. Efficacy was demonstrated with Quetiapine at both 400 mg and 800 mg; however, no additional benefit was seen in the 800 mg group.

*Maintenance Treatment*

While there is no body of evidence available to answer the question of how long the patient treated with quetiapine should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on Quetiapine, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

*Reinitiation of Treatment in Patients Previously Discontinued*

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off quetiapine, titration of quetiapine is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off quetiapine for more than one week, the initial titration schedule should be followed.

Acute manic episodes associated with bipolar I disorder

*Adults*

Quetiapine should be administered twice daily, with or without food. As monotherapy or as adjunct therapy to mood stabilizers (lithium or divalproex), 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 per 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.

*Children and Adolescents (10 to 17 years)*

Quetiapine should be administered twice daily. However, based on response and tolerability quetiapine may be administered three times daily where needed. The total daily dose for the initial five days of therapy is 50

mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After day 5, the dose should be adjusted within the recommended dose range of 400 to 600 mg/day based on response and tolerability. Dosage adjustments should be in increments of no greater than 100 mg/day. Efficacy was demonstrated with quetiapine at both 400 mg and 600 mg; however, no additional benefit was seen in the 600 mg group.

Depressive episodes associated with bipolar disorder

Quetiapine should be administered once daily at bedtime, with or without food. Quetiapine should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). Quetiapine can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8. Antidepressant efficacy was demonstrated with Quetiapine at 300 mg and 600 mg however no additional benefit was seen in the 600 mg group.

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

*Adults*

Maintenance of efficacy in Bipolar I Disorder was demonstrated with quetiapine (administered twice daily totalling 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

*Children and Adolescents (10 to 17 years)*

The effectiveness of quetiapine for longer than 3 weeks has not been evaluated in controlled clinical trials of children and adolescents. While there is no body of evidence available to answer the question of how long the patient treated with quetiapine should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Preventing recurrence in bipolar disorder

For preventing recurrence of manic, mixed or depressive 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 be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

*Elderly*

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

*Pediatric Use*

In general, the adverse reactions observed in children and adolescents during the clinical trials were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults. Orthostatic hypotension occurred more frequently in adults (4-7%) compared to children and adolescents (< 1%).

*Schizophrenia*

The efficacy and safety of quetiapine in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated. Safety and effectiveness of quetiapine in pediatric patients less than 13 years of age with schizophrenia have not been established.

*Maintenance*

The safety and effectiveness of quetiapine in the maintenance treatment of bipolar disorder has not been established in pediatric patients less than 18 years of age. The safety and effectiveness of quetiapine in the

maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients.

*Bipolar Mania*
The efficacy and safety of quetiapine in the treatment of mania in children and adolescents ages 10 to 17 years with Bipolar I disorder was demonstrated. Safety and effectiveness of quetiapine in pediatric patients less than 10 years of age with bipolar mania have not been established.

*Bipolar Depression*
Safety and effectiveness of quetiapine in pediatric patients less than 18 years of age with bipolar depression have not been established. Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10 to 17 years of age) and adults. When adjusted for weight, the AUC and $C_{max}$ of quetiapine were 41% and 39% lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight.

*Renal impairment*
Dosage 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 known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

**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.

*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 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 X $10^9$/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X $10^9$/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 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 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.

*Special Considerations in Treating Pediatric (Schizophrenia and Bipolar I Disorder )*
Pediatric schizophrenia and bipolar I disorder are serious mental disorders, however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes psychological, educational and social interventions.

*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 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 |

*Metabolism and nutritional disorders*

| | |
|---|---|
| Common: | Increased appetite |
| Very rare: | Diabetes mellitus |

*Psychiatric disorders*

| | |
|---|---|
| Common: | Abnormal dreams and nightmares |
| Rare: | Somnambulism and other related reactions |

*Nervous system disorders*

| | |
|---|---|
| Very Common: | Dizziness, somnolence, headache , extrapyramidal symptoms |
| Common: | Dysarthria |
| Uncommon: | Seizure, restless legs syndrome, tardive dyskinesia, syncope |

*Cardiac disorders*

| | |
|---|---|
| Common: | Tachycardia , palpitations |
| Uncommon: | Bradycardia |

*Eye Disorders*

| | |
|---|---|
| Common: | Vision blurred |

*Renal and urinary disorders*

| | |
|---|---|
| Uncommon: | Urinary retention |

*Vascular disorders*

| | |
|---|---|
| Common: | Orthostatic hypotension |

*Respiratory, thoracic and mediastinal disorder*

| | |
|---|---|
| Common: | Dyspnoea |
| 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 |

*Skin and subcutaneous tissue disorders*

| | |
|---|---|
| Very rare: | Angioedema, Stevens-Johnson syndrome |

*Reproductive system and breast disorders*

| | |
|---|---|
| Rare: | Priapism, galactorrhoea |

*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, elevations in serum prolactin, 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 $T_4$ and free $T_4$. 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 $T_4$, irrespective of the duration of treatment. Smaller decreases in total $T_3$ and reverse $T_3$ 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 ]*