QUETIAPINE

VICTUS®

25 mg and 300 mg FILM-COATED TABLET

ANTIPSYCHOTIC

FORMULATION
Each film-coated tablet contains:
Quetiapine (as hemifumarate)..... 25 mg or 300 mg

PRODUCT DESCRIPTION
Quetiapine (Victus) 25 mg is a white, round, biconvex, film-coated tablet.
Quetiapine (Victus) 300 mg is a white, capsule-shaped, biconvex, film-coated tablet.

CLINICAL PHARMACOLOGY
Pharmacodynamics / Mechanism of Action
Quetiapine is an atypical antipsychotic. Quetiapine and its active human plasma metabolite, norquetiapine, interact with a broad range of neurotransmitter receptors in the brain. They exhibit affinity for brain serotonin 5-HT_2 and dopamine D_1 and D_2. It is this combination of receptor antagonism with a higher selectivity of 5HT_2 relative to D_2 receptors which is believed to contribute to the clinical antipsychotic properties and less pronounced extrapyramidal symptoms (EPS) profile of quetiapine.

Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 and serotonin 5HT_1A receptors. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET).
Quetiapine has no appreciable affinity for ß-adrenergic, δ-aminobutyric acid (GABA), benzodiazepine or muscarinic receptors.

Pharmacokinetics
Quetiapine is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The bioavailability of quetiapine is marginally affected by administration with food, with maximum plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) values increased by 25% and 15%, respectively**.** Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10 ± 4 L/kg. It is approximately 83% bound to plasma proteins at therapeutic concentrations. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

After a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Quetiapine is extensively metabolized by the liver**.** The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies showed 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 per day in humans.

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively**.** Quetiapine is mainly excreted as inactive metabolites with approximately 73% of the dose appearing in the urine and 20% in the feces. Less than 1% of the drug is excreted unchanged.

Special Population:
Renal Impairment: Patients with severe renal impairment (CL_{CR}= 10 to 30 mL/min) had a 25% lower mean oral clearance than normal subjects (CL_{CR}>80 mL/min), but plasma quetiapine concentrations in patients with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is not recommended.

Hepatic Impairment: Patients with hepatic impairment had a 30% lower mean quetiapine oral clearance than normal subjects. Higher plasma levels are expected in these patients since quetiapine is extensively metabolized by the liver**.** Dosage adjustment may be necessary**.**

Geriatrics (≥ 65 years old): Quetiapine oral clearance was reduced by 40% in elderly patients compared to young patients. Dosage adjustment may be necessary**.**

INDICATIONS
Schizophrenia
- Treatment of acute and chronic psychoses, including schizophrenia in adolescents (13 to 17 years old) and adults.

Bipolar Disorder
- Acute treatment of manic episodes associated with Bipolar I Disorder, both as monotherapy and as an adjunct to lithium or divalproex in children and adolescents (10 to 17 years old) and adults;
- Acute treatment of depressive episodes associated with Bipolar Disorder in adults;
- Maintenance treatment of Bipolar **I** Disorder, as an adjunct to lithium or divalproex in adults.

DOSAGE AND ADMINISTRATION
Quetiapine can be taken with or without food.
Schizophrenia

Usual Recommended Quetiapine Oral Dose

INITIAL TREATMENT

Adults

Initial Dose: 25 mg two times a day
Increase in increments of 25 to 50 mg divided two or three times on Days 2 and 3 and to a target dose range of 300 to 400 mg by Day 4.

Further dose adjustments, if indicated, should generally occur at intervals of not less than two days, as steady state for quetiapine would not be achieved for approximately 1 to 2 days in the typical patient.

When dose adjustments are necessary, dose increments or decrements of 25 to 50 mg divided two times a day are recommended.

Recommended Dose: From Day 4 onwards, the usual dose is 300 to 450 mg/day. Depending on the clinical response and tolerability of the patient, the dose may be adjusted within 150 to 750 mg/day
Maximum Dose: 750 mg/day

Adolescents (13 to 17 years old)

Initial Dose: Quetiapine should be administered two times a day**.** However, based on response and tolerability, quetiapine may be administered three times a day where needed.
The total daily doses for the initial 5 days of therapy are:

Day	Daily Dose
1	50 mg
2	100 mg
3	200 mg
4	300 mg
5	400 mg

Recommended Dose: After Day 5, the dose should be adjusted within the recommended dose of 400 to 800 mg/day based on response and tolerability**.**
Dosage adjustments should be in increments of no greater than 100 mg per day**.**
Maximum Dose: 800 mg/day

MAINTENANCE TREATMENT

Patients should be periodically reassessed to determine the need for maintenance treatment.

Adults and Adolescents: The effectiveness of quetiapine for longer than 6 weeks has not been evaluated. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission.
Recommended Dose: 400 to 800 mg/day
Maximum Dose: 800 mg/day

Or, as prescribed by the physician.

Bipolar Disorder

Usual Recommended Quetiapine Oral Dose

INITIAL TREATMENT

Adults

Acute Treatment of Manic Episodes in Bipolar I Disorder

Initial Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), quetiapine should be initiated in two times a day with total daily doses of:

Day	Daily Dose
1	100 mg
2	200 mg
3	300 mg
4	400 mg
5	Up to 600 mg
6	Up to 800 mg

Further dose adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day**.**

Recommended Dose: The dose may then be adjusted according to response and tolerance to a usual range of 400 to 800 mg/day**.** In some patients, 200 mg/day may be adequate.
Maximum Dose: 800 mg/day

Children and Adolescents (10 to 17 years old)

Acute Treatment of Manic Episodes in Bipolar I Disorder

Initial Dose: Quetiapine should be administered two times a day**.** However, based on response and tolerability, quetiapine may be administered three times a day where needed.
The total daily doses for the initial 5 days of therapy are:

Day	Daily Dose
1	50 mg
2	100 mg
3	200 mg
4	300 mg
5	400 mg

Recommended Dose: 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 per day**.**
Maximum Dose: 600 mg/day

Usual Recommended Quetiapine Oral Dose

INITIAL TREATMENT

Adults

Acute Treatment of Depressive Episodes in Bipolar I Disorder

Initial Dose: Quetiapine should be administered once a day at bedtime to reach a usual target dose of 300 mg/day by Day 4.

Day	Daily Dose
1	50 mg
2	100 mg
3	200 mg
4	300 mg

Dose adjustments should be made depending on the clinical response and tolerability of the patient.

In individual patients, in the event of tolerance concerns, dose reduction to a minimum of 200 mg could be considered.

Recommended Dose: 300 mg/day
Maximum Dose: 300 mg/day

Children and Adolescents (10 to 17 years old)

N/A

MAINTENANCE TREATMENT

Patients should be periodically reassessed to determine the need for maintenance treatment. Antipsychotics should be slowly tapered and discontinued unless they are required to control persistent psychosis or provide prophylaxis against recurrence.

Recommended Dose: Administer two times a day totaling 400 to 800 mg/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. It is important that the lowest effective dose is used for maintenance treatment.
Maximum Dose: 800 mg/day

The effectiveness of quetiapine for longer than 3 weeks has not been evaluated in controlled clinical trials of children and adolescents.

It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission.

Or, as prescribed by the physician.

Recommended Dosing in Special Populations:
Elderly and patients who are debilitated or who have a predisposition to hypotensive reactions:
A lower starting dose (50 mg per day), slower rate of dose titration and a lower target dose are recommended in these patients. When indicated, dose escalation should be performed with caution in these patients. The dose can be increased in increments of 50 mg/day depending on the clinical response and tolerability of the individual patient.
Hepatic Impairment:
Patients with hepatic impairment should be started on 25 mg/day**.**
The dose should be increased daily in increments of 25 to 50 mg per day to an effective dose, depending on the clinical response and tolerability of the patient.
Reinitiation of Treatment in Patients Previously Discontinued:
Although there are no data on reinitiation of treatment, it is recommended that when restarting patients who have had an interval of < 1 week off quetiapine, titration is not required and the maintenance dose may be reinitiated.
When restarting therapy of patients who have been off quetiapine for > 1 week, the initial titration schedule should be followed.
Switching from Antipsychotics:
There are no data on switching patients with schizophrenia from other antipsychotics to quetiapine, or concerning concomitant use with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others.
In all cases, the period of overlapping antipsychotic use should be minimized.
When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate quetiapine therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically**.**

CONTRAINDICATIONS
- Hypersensitivity to quetiapine or any ingredient of the product

WARNINGS AND PECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Quetiapine is not approved for the treatment of patients with Dementia-Related Psychosis.

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive quetiapine or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond 24 years old; there was a reduction in risk with antidepressants compared to placebo in adults ≥ 65 years old. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Quetiapine is not approved for use in pediatric patients < 10 years old.

General
Screening Patients for Bipolar Disorder: Bipolar disorder may initially present as a major depressive episode. Treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder**.** Adequately screen patients with depressive symptoms if they are at risk for bipolar disorder before starting antidepressant treatment. Include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, depression) during such screening. It should be noted that quetiapine is approved for use in treating adult bipolar depression.
Body Temperature Regulation: Appropriate care is advised when prescribing quetiapine to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant drugs with anticholinergic activity, or being subject to dehydration.
Withdrawal: Acute withdrawal symptoms such as nausea, vomiting and insomnia have rarely been reported, after abrupt cessation of atypical antipsychotic drugs including quetiapine. Gradual withdrawal is advised.

Cardiovascular Effects
Orthostatic Hypotension: Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties.
Quetiapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive drugs). The risk of hypotension and syncope may be minimized by limiting the initial dose to 25 mg two times a day**.** If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.
Increases in Blood Pressure in Children and Adolescents: Placebo-controlled trials in children and adolescents with schizophrenia or bipolar mania showed increases at any time in systolic blood pressure (≥ 20 mmHg) of 15.2% for quetiapine and 5.5% for placebo. The incidence of increases at any time in diastolic blood pressure (≥10 mmHg) was 40.6% for quetiapine and 24.5% for placebo. It is recommended that blood pressure in children and adolescents should be measured at the beginning of, and periodically during treatment.
QT Prolongation: Post marketing cases reported QT prolongation in patients who overdosed on quetiapine (see **Overdose and Treatment**), in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval (see **Interactions with Other Medicaments**).
Quetiapine should be avoided in circumstances that may increase the risk of occurrence of *torsades de pointes* and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong QT_c interval; and (4) presence of congenital prolongation of the QT interval.
Exercise caution when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g., cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

Endocrine and Metabolic Effects
Cholesterol and Triglyceride Elevations: Very common cases of elevations in serum triglyceride levels (≥ 2.258 mmol/L on at least one occasion), elevations in total cholesterol (predominantly LDL cholesterol; ≥ 6.2064 mmol/L on at least one occasion), and decreases in HDL cholesterol (< 1.025 mmol/L males; < 1.282 mmol/L females at any time) have been observed during treatment with quetiapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using quetiapine is recommended.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and occasional reports of diabetes have been seen with quetiapine use. Patients who are at risk for developing diabetes (e.g., obesity and a family history of diabetes) should have appropriate clinical monitoring of blood sugar**.** Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyuria, polyphagia, and weakness) during atypical antipsychotic therapy should undergo fasting blood glucose testing. In some cases, hyperglycemia resolved when the atypical antipsychotic was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation.
Weight Gain: Increases in weight have been observed with quetiapine use. Patients receiving quetiapine should receive regular monitoring of weight.
Hyperprolactinemia: Like other drugs that antagonize dopamine D_2 receptors, quetiapine elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic gonadotropin-releasing hormone (GnRH), resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.
Hypothyroidism: Clinical trials with quetiapine demonstrated dose-related decreases in thyroid hormone levels. The reduction in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range was maximal in the first 6 weeks of treatment and maintained without adaptation or progression during more chronic therapy**.** In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. Both thyroid-stimulating hormone (TSH) and free T4, in addition to clinical assessment, should be measured as baseline and at follow-up.

Gastrointestinal Effects
Antiemetic Effect: Consistent with its dopamine antagonist effects, quetiapine may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage of other drugs, or may mask symptoms of disease such as brain tumor or intestinal obstruction.
Dysphagia and Aspiration Pneumonia: The use of antipsychotic drugs has been associated with esophageal dysmotility and aspiration. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Quetiapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Genitourinary Effects
Priapism: Rare cases of priapism have been reported with antipsychotic use, such as quetiapine. This adverse reaction did not appear to be dose-dependent and did not correlate with the duration of treatment. Severe priapism may require surgical intervention.

Hematologic Effects
Leukopenia, Neutropenia and Agranulocytosis: There have been reports of leukopenia/neutropenia (including severe neutropenia) and agranulocytosis temporally related to atypical antipsychotic agents, including quetiapine.
Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue quetiapine at the first sign of a decline in WBC in the absence of other causative factors.
Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur**.** Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue quetiapine and have their WBC followed until recovery**.**
Venous Thromboembolism: Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic agents, including quetiapine. When prescribing quetiapine, all potential risk factors for VTE should be identified and preventive measures undertaken.

Hepatic/Pancreatic Effects
Transaminase Elevations: There have been reports of asymptomatic, transient and reversible elevations in serum transaminases (primarily alanine transaminase or ALT).
Pancreatitis: Pancreatitis has been reported with the use of quetiapine. Many patients had risk factors which were known to be associated with pancreatitis such as increased triglycerides, gallstones, and alcohol consumption.

Neurologic and Psychiatric Effects
Cerebrovascular Adverse Reactions (including stroke) in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled trials with antipsychotic drugs in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Quetiapine is not approved for the treatment of patients with dementia-related psychosis.
Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported rarely in patients receiving antipsychotic agents, including quetiapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.
Reintroduction of drug therapy should be carefully considered if a patient requires antipsychotic therapy following recovery from NMS. The patient should be carefully monitored since recurrences of NMS have been reported.
Tardive Dyskinesia: Antipsychotic agents including quetiapine may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary and dyskinetic movements. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.
Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate.
If signs and symptoms of tardive dyskinesia appear in a patient on quetiapine, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.
Potential for Cognitive and Motor Impairment: Since quetiapine has the potential to impair judgment, thinking or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery until they are reasonably certain that quetiapine therapy does not affect them adversely**.** Somnolence may lead to falls.
Suicide: The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy**.** Prescriptions for quetiapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Seizures: As with other antipsychotic agents, caution is recommended when treating patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥ 65 years old.

Ophthalmologic Effects
Cataracts: Lens changes have been reported in patients during long-term quetiapine therapy**.** Examination of the lens by slit lamp exam is recommended at initiation of treatment or shortly thereafter, and at six month intervals during chronic treatment.

INTERACTIONS WITH OTHER MEDICAMENTS
Alcohol: Quetiapine potentiates the cognitive and motor effects of alcohol. Avoid alcohol during quetiapine therapy**.**

Anticholinergic Agents: Potential pharmacologic interaction (possible disruption of body temperature regulation). Use quetiapine with caution in patients concurrently receiving drugs with anticholinergic activity**.**

Grapefruit Juice: Concomitant use is not recommended. Drinking grapefruit juice during treatment with quetiapine may be expected to increase exposure to the drug owing to inactivation of intestinal CYP3A4.

Hepatic CYP3A4 Inducers *(e.g., phenytoin, carbamazepine, barbiturates, rifampicin, glucocorticoids, St. John's Wort, etc.)*: Quetiapine dose should be increased up to 5-fold of the original dose when used in combination with a chronic treatment (e.g., greater than 7 to 14 days) of a potent CYP3A4 inducer**.** The dose should be titrated based on the clinical response and tolerability of the patient. When the CYP3A4 inducer is discontinued, the dose of quetiapine should be reduced to the original level within 7 to 14 days**.** Caution should be exercised if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate).

Hepatic CYP3A4 Inhibitors *(e.g., ketoconazole, itraconazole, fluconazole, erythromycin, HIV-protease inhibitors)*: Quetiapine dose should be reduced to one sixth of the original dose when given concomitantly with a potent CYP3A4 inhibitor**.** When the CYP3A4 inhibitor is discontinued, the dose of quetiapine should be returned to its original dose.

Antihypertensive Agents: Quetiapine may add to the blood pressure lowering effects of these agents.

Drugs known to cause electrolyte imbalance or increase QT interval: Caution should be used when quetiapine is used concomitantly with these drugs.

Lorazepam: The mean oral clearance of lorazepam was reduced by 20% in the presence of quetiapine.

Thioridazine: Increased oral clearance of quetiapine by 65%.

Levodopa and dopamine agonists: Quetiapine may antagonize the effects of these drugs.

Divalproex: Coadministration of quetiapine and divalproex increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.
The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 20% when divalproex was administered with quetiapine. The mean oral clearance of total valproic acid was increased by 11% in the presence of quetiapine. The changes were not significant.

Cimetidine: Use of multiple daily doses of cimetidine (400 mg three times a day for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine. Dosage adjustment for quetiapine is not required.

Lithium: Concomitant use of quetiapine with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Fluoxetine, Imipramine, Haloperidol, or Risperidone: Concomitant use of these drugs with quetiapine did not alter the steady-state pharmacokinetics of quetiapine.

Antipyrine: Administration of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. Objects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites.

Laboratory Test Alterations: There have been reports of false positive urine drug screens for methadone or tricyclic antidepressants in patients taking quetiapine. Caution should be exercised in the interpretation of positive urine drug screen results for these drugs, and confirmation by alternative analytical technique (e.g., chromatographic methods) should be considered.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy and Lactation
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Therefore, quetiapine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms after 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 hospitalization.

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

Labor and delivery/Lactation: The effect of quetiapine on labor and delivery is unknown. Quetiapine is excreted into human milk and breastfeeding is not recommended during quetiapine therapy**.**

Pediatrics (< 18 years old)
The safety and efficacy of quetiapine has only been established for schizophrenia in adolescents 13 to 17 years old and for bipolar mania in children and adolescents 10 to 17 years old.

The safety and efficacy of quetiapine in the maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients. The safety and efficacy of quetiapine in the maintenance treatment of bipolar disorder has not been established in pediatric patients < 18 years old.

The safety and efficacy of quetiapine in pediatric patients < 10 years old with bipolar mania has not been established.

The safety and efficacy of quetiapine in pediatric patients < 18 years old with bipolar depression has not been established.

Adverse reactions observed in children and adolescents during clinical trials were generally similar to those in adults 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 compared to children and adolescents.

UNDESIRABLE EFFECTS
Body as a Whole: *Very common* - Withdrawal symptoms, fatigue. *Common* - Asthenia, fever, flu syndrome, pain, back pain. *Uncommon* - Neck pain, pelvic pain, malaise, chills, face edema, moniliasis. *Rare* - Hypothermia. *Unknown* - Neonatal withdrawal

Cardiovascular: *Common* - Tachycardia, palpitations, postural hypotension. *Uncommon* - Bradycardia, syncope, vasodilation, cerebral ischemia, irregular pulse, cerebrovascular accident, deep thrombophlebitis, hypotension, prolonged QT interval T wave abnormality, bundle branch block, T-wave inversion. *Rare* - VTE, angina pectoris, atrial fibrillation, congestive heart failure, thrombophlebitis, AV block first degree, ST elevated, T-wave flattening, ST abnormality, increased QRS duration. *Unknown* - Cardiomyopathy, myocarditis

Central and Autonomic Nervous System: *Very Common* - Dizziness, somnolence, EPS (i.e., akathisia, tremor, hypokinesia, hypertonia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia), headache, agitation. *Common* - Irritability, dysarthria, abnormal dreams and nightmares, suicide attempt, sedation, lethargy, anxiety, paresthesia, hypersomnia. *Uncommon* - Seizures, restless leg syndrome, abnormal thinking, tardive dyskinesia, involuntary movements, confusion, amnesia, psychosis, hallucinations, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia. *Rare* - NMS, somnambulism (and other related events), aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, neuralgia, stuttering, subdural hematoma

Dermatologic and Sensitivity Reactions: *Common* - Rash. *Uncommon* - Hypersensitivity, photosensitivity reaction, pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer**.** *Very Rare* - Anaphylactic reaction, Stevens-Johnson syndrome. *Unknown* - Toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, psoriasis, skin discoloration

Endocrine and Metabolic: *Very Common* - Elevations in non-fasting serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain. *Common* - Peripheral edema, hyperglycemia, elevations in serum prolactin, hypothyroidism, hyperthyroidism, increased appetite. *Uncommon* - Angioedema, hyponatremia, diabetes mellitus, increased libido, weight loss, increased alkaline phosphatase, hyperlipemia, alcohol intolerance, dehydration, hypoglycemia. *Rare* - Increased creatinine, priapism, galactorrhea, metabolic syndrome, glycosuria, gout, hand edema, hypokalemia, water intoxication, decreased libido

Gastrointestinal: *Very common* - Dry mouth. *Common* - Constipation, dyspepsia, vomiting, abdominal pain, anorexia. *Uncommon* - Dysphagia, increased salivation, gingivitis, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema. *Rare* - Enlarged abdomen, pancreatitis, glossitis, hematemesis, intestinal obstruction, melena, esophageal dysmotility, aspiration

Genitourinary/Reproductive: *Uncommon* - Urinary retention, sexual dysfunction, dysmenorrhea, vaginitis, urinary incontinence, metrorrhagia, impotence, dysuria, vaginal moniliasis, abnormal ejaculation, cystitis, urinary frequency, amenorrhea, female lactation, leukorrhea, vaginal hemorrhage, vulvovaginitis, orchitis. *Rare* - Gynecomastia, nocturia, polyuria, acute kidney failure. *Very Rare* - Syndrome of inappropriate antidiuretic hormone secretion (SIADH), breast swelling, menstrual disorder**.**

Hematologic: *Very Common* - Decreased hemoglobin. *Common* - Leukopenia, eosinophilia, neutropenia. *Uncommon* - Thrombocytopenia, anemia, leukocytosis, ecchymosis, hypochromic anemia, lymphadenopathy, cyanosis. *Rare* - Agranulocytosis, hemolysis

Hepatic: *Common* - Elevations in serum transaminases such as alanine transaminase (ALT) and aspartate aminotransferase (AST), elevations in gamma-glutamyl transpeptidase (GGT) levels. *Rare* - Jaundice, hepatitis

Musculoskeletal: *Uncommon* - Pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. *Very Rare* - Rhabdomyolysis

Respiratory: *Common* - Increased cough, dyspnea, pharyngitis, nasal congestion. *Uncommon* - Rhinitis, pneumonia, epistaxis, asthma. *Rare* - Hiccup, hyperventilation

Special Senses: *Common* - Blurred vision, amblyopia, conjunctivitis, abnormal vision, dry eyes, blepharitis, eye pain, tinnitus, ear pain. *Uncommon* - Vertigo, abnormality of accommodation, glaucoma, deafness

OVERDOSE AND TREATMENT
Survival has been reported in acute overdosage of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported after an overdosage of 13.6 grams of quetiapine alone. Hypokalemia and first degree heart block were reported after an estimated overdose of 9.6 grams of quetiapine. In postmarketing experience, there have been very rare cases of overdose with quetiapine alone resulting in death, coma, or QT_c prolongation.

Reported signs and symptoms of quetiapine overdose were drowsiness, sedation, tachycardia, and hypotension. Patients with pre-existing severe cardiovascular disease may be at increased risk of the overdose effects. Cardiovascular monitoring should start immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is given, disopyramide, procainamide and quinidine may produce additive QT-prolonging effects when given in patients with acute quetiapine overdose.

There is no specific antidote to quetiapine overdose. In cases of severe intoxication, 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.

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

STORAGE CONDITIONS
Keep the product out of sight and reach of children.

Store at temperatures not exceeding 30°C.

AVAILABILITY
Quetiapine (Victus) 25 mg film-coated tablet **-** PVC film with PVDC coating (opaque white) blister foil X 10 tablets (box of 30's).
Quetiapine (Victus) 300 mg film-coated tablet **-** PVC film with PVDC coating (opaque white) blister foil X 10 tablets (box of 30's).

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

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Trusted Quality Healthcare

P30000013934 Date of revision: **July 2014**

*Reg. IPOPHIL