PACKAGE INSERT

SCHEDULING STATUS: **S5**

PROPRIETARY NAME (AND DOSAGE FORM)**:**

QUETIAPINE 25 VIATRIS (film-coated tablet)

QUETIAPINE 100 VIATRIS (film-coated tablet)

QUETIAPINE 150 VIATRIS (film-coated tablet)

QUETIAPINE 200 VIATRIS (film-coated tablet)

QUETIAPINE 300 VIATRIS (film-coated tablet)

COMPOSITION:

Each film-coated tablet contains:

Quetiapine fumarate corresponding to 25 mg, 100 mg, 150 mg, 200 mg and 300 mg quetiapine.

Lactose monohydrate (sugar) corresponding to 4,5 mg, 18 mg, 27 mg, 36 mg and 54 mg respectively.

The other ingredients are: microcrystalline cellulose, povidone, magnesium stearate, sodium starch glycolate, calcium hydrogen phosphate dehydrate and approved colourant; titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Central Nervous System Depressants: Tranquillisers - Miscellaneous structures

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Quetiapine is an atypical antipsychotic agent which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits affinity for brain serotonin ($5HT_2$) and

dopamine D_1 and D_2 receptors. Quetiapine also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

Quetiapine, when administered twice daily, maintains $5HT_2$ and D_2 receptor occupancy for up to 12 hours after dosing.

Pharmacokinetic properties:

After oral administration, quetiapine is absorbed and extensively metabolised. The principal human plasma metabolites do not have significant pharmacological activity. Food does not significantly affect the bioavailability of quetiapine. Elimination half-life is approximately 7 hours.

Quetiapine is approximately 65 %-83 % bound to plasma proteins.

Quetiapine pharmacokinetics are variable but do not differ significantly between men and women.

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

Quetiapine mean plasma clearance was reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2) and in subjects with hepatic impairment (stable alcoholic cirrhosis) but the individual clearance values are within the range for normal subjects.

Metabolism of quetiapine is extensive with parent compound accounting for less than 5 % of unchanged medicine-related material in the urine or faeces after the administration of radio-labelled quetiapine. Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

Investigations, *in vitro,* established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6, and 3A4 activities, but only at concentrations at

least 10 to 50 fold higher than those observed in the usual effective dose range of 300 to 450 mg/day in humans.

INDICATIONS:

QUETIAPINE VIATRIS is indicated for the treatment of schizophrenia.

QUETIAPINE VIATRIS is also indicated for the treatment of manic episodes associated with a bipolar disorder. Safety and efficacy beyond 12 weeks have not been demonstrated.

CONTRA-INDICATIONS:

QUETIAPINE VIATRIS is contra-indicated in patients hypersensitive to quetiapine or to any of the other ingredients in the product.

Pregnancy and lactation, as safety has not been demonstrated.

Children and adolescents, under the age of 18 years, as safety and efficacy have not been established.

Advanced liver and renal function impairment, as safety has not been demonstrated.

Quetiapine is not indicated for use in elderly patients with dementia exhibiting behavioural disturbance.

Co-administration with azole antifungals, macrolide antibiotics and HIV protease inhibitors.

WARNINGS:

Hyperglycaemia and Diabetes Mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with **QUETIAPINE VIATRIS.**

Patients with an established diagnosis of diabetes mellitus who are started on **QUETIAPINE VIATRIS** 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 **QUETIAPINE VIATRIS** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **QUETIAPINE VIATRIS** should undergo fasting blood glucose testing.

In some cases, hyperglycaemia has resolved when **QUETIAPINE VIATRIS** was discontinued, however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Where the use of **QUETIAPINE VIATRIS** in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, oversedation and complications associated with hyperglycaemia.

Before prescribing **QUETIAPINE VIATRIS** clinicians are advised to carefully assess the risks and benefits of the use of **QUETIAPINE VIATRIS** in elderly patients with dementia as there has been an increase in the cerebrovascular events (see **CONTRA-INDICATIONS**).
In these cases, the risk prediction for stroke in the individual patient (e.g. hypertension, diabetes, current smoking, atrial fibrillation and age > 80 years) must be taken into account.

QUETIAPINE VIATRIS must be used with caution in patients with known cardiovascular disease or other conditions predisposing to hypotension.

QUETIAPINE VIATRIS must be discontinued if signs and symptoms of tardive dyskinesia appear.

QUETIAPINE VIATRIS must be discontinued and appropriate medical treatment given in case of neuroleptic malignant syndrome (includes hyperthermia, altered mental status, muscular rigidity, autonomic instability and increased creatine phosphokinase).

INTERACTIONS:

QUETIAPINE VIATRIS must be used with caution in combination with alcohol and other centrally acting medicines.

Lithium pharmacokinetics were not altered when used with **QUETIAPINE VIATRIS.**
The pharmacokinetics of sodium valproate and **QUETIAPINE VIATRIS** are not altered to a clinically relevant extent when co-administered.

QUETIAPINE VIATRIS should be used with caution in patients also receiving antihypertensives or medicines that prolong the QT interval.

QUETIAPINE VIATRIS may antagonise the actions of dopaminergics, such as levodopa.

QUETIAPINE VIATRIS did not induce the hepatic enzyme systems involved in the metabolism of antipyrine.

The co-administration of carbamazepine (a known hepatic enzyme inducer) and **QUETIAPINE VIATRIS** significantly increased the clearance of quetiapine.

This increase in clearance significantly reduced systemic **QUETIAPINE VIATRIS** exposure. Because of this interaction, lower plasma concentrations can occur, and hence in each patient, consideration for a higher dose of **QUETIAPINE VIATRIS**, depending on clinical response, should be considered.

It should be noted that the recommended maximum daily dose of **QUETIAPINE VIATRIS** is 750 mg/day, for the treatment of schizophrenia and 800 mg/day for the treatment of manic episodes associated with bipolar disorder.
Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit-risk assessment for an individual patient.

The co-administration of **QUETIAPINE VIATRIS** with another microsomal enzyme inducer, phenytoin, caused increases in clearance of **QUETIAPINE VIATRIS**. Increased doses of **QUETIAPINE VIATRIS** may be required to maintain control of psychotic symptoms in patients co-administered with **QUETIAPINE VIATRIS** and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc). The **QUETIAPINE VIATRIS** dose may have to be reduced when phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

The pharmacokinetics of **QUETIAPINE VIATRIS** were not significantly altered after co-administration with antipsychotics such as risperidone or haloperidol.

But co-administration of **QUETIAPINE VIATRIS** and thioridazine caused an increase in clearance of **QUETIAPINE VIATRIS.**

The pharmacokinetics of **QUETIAPINE VIATRIS** 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.

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of **QUETIAPINE VIATRIS**. The pharmacokinetics of **QUETIAPINE VIATRIS** were not altered after co-administration with cimetidine a known P450 enzyme inhibitor[s].

The co-administration of ketoconazole and **QUETIAPINE VIATRIS** may result in a significant (5-fold) increase in the AUC of **QUETIAPINE VIATRIS.** On the basis of this, concomitant use of **QUETIAPINE VIATRIS** and potent CYP3A4 inhibitors, such as HIV protease inhibitors, azole antifungals and macrolide antibiotics, is contra-indicated. (see **CONTRA-INDICATIONS**).

PREGNANCY AND LACTATION:

Safety and efficacy in pregnancy and lactation have not been established and use is not recommended. (See **CONTRA-INDICATIONS**)

DOSAGE AND DIRECTIONS FOR USE:

QUETIAPINE VIATRIS should be administered twice daily, with or without food.

Adults: For the treatment of schizophrenia the total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards the dose should be titrated to the effective dose range of 300-450 mg/day. This may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range 150-750 mg/day.

For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on the clinical response and tolerability of the individual patient, within the range of 200-800 mg/day. The usual effective dose is in the range of 400-800 mg/day.

Elderly:

QUETIAPINE VIATRIS should be used with caution in the elderly, especially during the initial dosing period. Elderly should be started on 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients. (See **CONTRA-INDICATIONS**)

Renal and Hepatic impairment:

The [~~oral~~] clearance of **QUETIAPINE VIATRIS** is reduced by approximately 25 % in patients with renal or hepatic impairment. **QUETIAPINE VIATRIS** is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment. Patients with renal or hepatic impairment should be started on **QUETIAPINE VIATRIS** 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The following side effects have been reported:

Blood and lymphatic system disorders:

Frequent: Leucopenia.

Less frequent: Eosinophilia, neutropenia, thrombocytopenia.

Reported but frequency unknown: Agranulocytosis.

Immune system disorders:

Less frequent: Hypersensitivity (angioedema, anaphylaxis, urticaria/rash), Stevens-Johnson syndrome.

Metabolism and nutritional disorders:

Less frequent: Hyperglycaemia, diabetes mellitus (or exacerbation of pre-existing diabetes).

Psychiatric disorders:

Frequent: Abnormal dreams, nightmares.

Nervous system disorders:

Frequent: Dizziness, somnolence, headache, anxiety, syncope, extrapyramidal symptoms.

Less frequent: Seizures, neuroleptic malignant syndrome (see **Special precautions**)**,** tardive dyskinesia.

Eye disorders:

Reported but frequency unknown: Dry eyes, asymptomatic changes in the lens of the eye with long-term treatment, blurred vision.

Ear and labyrinth disorders:

Reported but frequency unknown: Ear pain.

Cardiac disorders:

Frequent: Tachycardia.

Less frequent: QTc prolongation.

Vascular disorders:

Frequent: Orthostatic hypotension, hypertension (associated with dizziness, tachycardia and syncope in some patients).

Less frequent: Venous thromboembolism.

Respiratory, thoracic and mediastinal disorders:

Frequent: Rhinitis.

Gastrointestinal disorders:

Frequent: Dry mouth, constipation, dyspepsia, abdominal pain, diarrhoea.

Hepatobiliary disorders:

Less frequent: Jaundice, hepatitis.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Myalgia, back pain.

Renal and urinary disorders:

Reported but frequency unknown: Urinary tract infection.

Reproductive system and breast disorders:

Less frequent: Priapism, galactorrhoea.

General disorders and administration site conditions:

Frequent: Asthenia, peripheral oedema, withdrawal symptoms (see **Special precautions).**

Less frequent: Fever.

Reported but frequency unknown: Chest pain.

Investigations:

Frequent: Weight gain, elevations in serum transaminases (ALT, AST).

Less frequent: Elevations in gamma-GT levels, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol.

QUETIAPINE VIATRIS was associated with dose-related decreases in thyroid hormone levels, particularly total T4 and free T4. The reduction in total T4 and free T4 was maximally within the first 2 to 4 weeks of **QUETIAPINE VIATRIS** treatment **with no further reduction during long term treatment. There was no evidence of clinical significant changes in TSH concentration over time. In nearly all cases, cessation of QUETIAPINE VIATRIS treatment has been associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. Smaller decreases in total T3 and reverse T3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with any indication that QUETIAPINE VIATRIS causes clinically relevant hypothyroidism.**

Special precautions:

Cardiovascular: Use **QUETIAPINE VIATRIS** with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. **QUETIAPINE VIATRIS** 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; this is more common in elderly patients than in younger patients.

Caution should be exercised when **QUETIAPINE VIATRIS** is prescribed with medicines known to prolong the QT[~~s~~]c interval, especially in the elderly.

Seizures: Caution is recommended when treating patients with a history of seizures.

Tardive Dyskinesia: There is a potential for **QUETIAPINE VIATRIS** to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of **QUETIAPINE VIATRIS** should be considered.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome has been associated with **QUETIAPINE VIATRIS** treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, **QUETIAPINE VIATRIS** should be discontinued and appropriate medical treatment given.

Lactose: QUETIAPINE VIATRIS contains lactose. Patients with hereditary galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **QUETIAPINE VIATRIS**.

Effect on ability to drive and use machines: QUETIAPINE VIATRIS may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to operate hazardous machines, or drive vehicles, until individual susceptibility is known.

Withdrawal recommendation: It is recommended that **QUETIAPINE VIATRIS** be gradually withdrawn because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses with abrupt cessation.

Recurrence of psychotic symptoms may also occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesias) have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See **SIDE EFFECTS AND SPECIAL PRECAUTIONS**)

In general, reported signs and symptoms of overdosage were those resulting from an exaggeration of the pharmacological effects, namely drowsiness, sedation, tachycardia and hypotension. There is no specific antidote to **QUETIAPINE VIATRIS**. Treatment is symptomatic and supportive.

IDENTIFICATION:

QUETIAPINE 25 VIATRIS: Peach coloured, round, biconvex, film-coated tablet engraved 'Q' on one side.

QUETIAPINE 100 VIATRIS: Yellow, round, biconvex, film-coated tablet engraved 'Q' over '100' on one side.

QUETIAPINE 150 VIATRIS: Pale yellow, round, biconvex, film-coated tablet engraved 'Q' over '150' on one side.

QUETIAPINE 200 VIATRIS: White, round, biconvex, film-coated tablet engraved 'Q' over '200' on one side.

QUETIAPINE 300 VIATRIS: White, capsule-shaped, biconvex, film-coated tablet engraved 'Q' breakline '300' on one side.

PRESENTATION:

Packs of 1, 3, 6, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 250, 500, 1000 * tablets in PVC/PVDC aluminium foil blister strips in an outer carton and/or white HDPE bottles with white polyethylene caps.

*Not all pack sizes will be marketed.

STORAGE INSTRUCTIONS:

Store at or below 25 ^{O}C. Keep containers dry and tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

QUETIAPINE 25 VIATRIS: 41/2.6.5/0951

QUETIAPINE 100 VIATRIS: 41/2.6.5/0952

QUETIAPINE 150 VIATRIS: 41/2.6.5/0953

QUETIAPINE 200 VIATRIS: 41/2.6.5/0954

QUETIAPINE 300 VIATRIS: 41/2.6.5/0955

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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4 Brewery Street,

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1609

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