1.3.1.1 Package Insert

SCHEDULING STATUS: S5

PROPRIETARY NAMES (AND DOSAGE FORM):

QUETOSER 25 (Film-coated tablets)

QUETOSER 100 (Film-coated tablets)

QUETOSER 200 (Film-coated tablets)

QUETOSER 300 (Film-coated tablets)

COMPOSITION:

Each **QUETOSER 25** film-coated tablet contains quetiapine fumarate, equivalent to 25 mg quetiapine free base.

Each **QUETOSER 100** film-coated tablet contains quetiapine fumarate, equivalent to 100 mg quetiapine free base.

Each **QUETOSER 200** film-coated tablet contains quetiapine fumarate, equivalent to 200 mg quetiapine free base.

Each **QUETOSER 300** film-coated tablet contains quetiapine fumarate, equivalent to 300 mg quetiapine free base.

QUETOSER 25, 100, 200 & 300 film-coated tablets contain lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Central nervous system depressants: Miscellaneous structures.

PHARMACOLOGICAL ACTION:

Quetiapine fumarate is a dibenzothiazepine atypical antipsychotic which interacts with a broad range of neurotransmitter receptors. In the brain quetiapine displays a higher affinity for serotonin 5-HT_2 receptors than it does for dopamine D_1 and D_2 receptors. It also shows a high affinity for histamine H_1, and adrenergic alpha$_1$ receptors, with a lower affinity for adrenergic alpha$_2$ receptors. It has no significant affinity for cholinergic muscarinic or benzodiazepine receptors.

Pharmacokinetics:

The pharmacokinetics of quetiapine are variable and are similar in both genders.

Absorption:

Quetiapine is rapidly and well absorbed after oral doses. Administration with food does not significantly affect bioavailability of quetiapine. Peak plasma concentrations are reached in about 1,5 hours.

Distribution:

Quetiapine is widely distributed throughout the body. It is about 83 % bound to plasma proteins. It is distributed into breast milk.

Metabolism:

Quetiapine is extensively metabolised in the liver by sulphoxidation mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and by oxidation. The major metabolites are inactive.

Quetiapine and several of its metabolites weakly inhibit human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities. Such inhibition occurs only at concentrations at least 10- to 50-fold higher than those seen in the usual effective dose range of 300 to 450 mg/day in humans.

Excretion:

Quetiapine is excreted mainly as inactive metabolites with about 73 % of a dose excreted in the urine and about 20 % in the faeces. The elimination half-life is reported to be about 6 to 7 hours.

Pharmacokinetics in special patient groups:

Geriatrics:

The mean clearance of quetiapine in the elderly, 65 years of age and over, is about 30 to 50 % less than in healthy younger adults, 18 to 65 years of age.

Renal and hepatic function impairment:

In subjects with severe renal impairment (creatinine clearance less than 30 ml/min per 1,73 m^2) or subjects with hepatic impairment (stable alcoholic cirrhosis), the mean plasma clearance of quetiapine is reduced by approximately 25 %; however, individual clearance values are within the range for normal subjects.

INDICATIONS:

QUETOSER is indicated for the treatment of schizophrenia and of mania associated with bipolar disorder.

CONTRA-INDICATIONS:

QUETOSER is contra-indicated in:

- Patients with a known hypersensitivity to quetiapine fumarate, or to any component of the product.
- Pregnancy and lactation (safety has not been established).
- Advanced renal and liver function impairment (safety has not been demonstrated).

- Children and adolescents below the age of 18 years (safety and efficacy have not been demonstrated).

Co-administration with cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin and clarithromycin, is contra-indicated (see **"INTERACTIONS"**).

WARNINGS:

Hyperglycaemia and diabetes mellitus:

There have been reports of hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, in patients treated with **QUETOSER**.

When **QUETOSER** is started in patients with an established diagnosis of diabetes mellitus, they should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) require monitoring for symptoms of hyperglycaemia (including polydipsia, polyuria, polyphagia, and weakness) when they are started on **QUETOSER**.

If symptoms of hyperglycaemia should develop during treatment with **QUETOSER**, the patient should undergo fasting blood glucose testing. In some instances, hyperglycaemia resolved when **QUETOSER** was discontinued; however, some patients required on-going antidiabetic treatment despite discontinuation of the suspect medicine.

QUETOSER is not indicated for use in elderly patients with dementia exhibiting behavioural disturbances.

Before prescribing **QUETOSER**, clinicians are advised to carefully assess the risks and benefits of the use of **QUETOSER** in elderly patients, as there has been an increase in cerebrovascular events.

INTERACTIONS:

The central effects of other CNS depressants, including alcohol, may be enhanced by **QUETOSER**.

QUETOSER should be used with caution in patients also receiving antihypertensives or medication that prolongs the QT interval.

QUETOSER may antagonise the action of dopaminergics, such as levodopa.

CYP3A4 is the main isoenzyme responsible for the cytochrome P450-mediated metabolism of **QUETOSER**. **QUETOSER** should not be used with potent inhibitors of CYP3A4, such as HIV protease inhibitors, clarithromycin, erythromycin, fluconazole, itraconazole and ketoconazole. Plasma concentration of **QUETOSER** can be significantly increased and co-administration is not recommended (see **"CONTRA-INDICATIONS"**).

Conversely, enzyme inducers, such as carbamazepine, phenytoin, barbiturates and rifampicin, may decrease the plasma concentration of **QUETOSER**, and higher doses of **QUETOSER** may be necessary, depending on the individual clinical response of each patient. Withdrawing hepatic enzyme inducers, such as carbamazepine or phenytoin, and replacing them with non-inducer medicines (e.g. sodium valproate) may require a reduced dose of **QUETOSER**.

The pharmacokinetics of sodium valproate and **QUETOSER** were not altered to a clinically relevant extent following concurrent administration.

The pharmacokinetic properties of **QUETOSER** were not significantly altered following co-administration with the antipsychotics risperidone and haloperidol.

Thioridazine has been reported to increase the clearance of **QUETOSER**.

The pharmacokinetic properties of **QUETOSER** were not significantly altered following concurrent administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

Co-administration with cimetidine, a known P450 enzyme inhibitor, did not alter the pharmacokinetics of **QUETOSER**.

Mean oral clearance of lorazepam was decreased by 20 % when co-administered with **QUETOSER** 250 mg three times a day.

The pharmacokinetic properties of lithium were not altered following co-administration with **QUETOSER**.

PREGNANCY AND LACTATION:

QUETOSER is contra-indicated in pregnancy and lactation, as safety has not yet been established. It is distributed into breast milk.

DOSAGE AND DIRECTIONS FOR USE:

QUETOSER should be administered twice a day and can be taken with or without food.

Adults:

The total daily dose for the first 4 days of therapy in the treatment of schizophrenia is 50 mg **QUETOSER** on day one, 100 mg on day two, 200 mg on day three and 300 mg on day four. Daily doses must be given in two divided doses. From day 4 onwards, the dose should be titrated to the effective dose range of 300 to 450 mg per day. However, this dose may be adjusted, depending on the individual patient's clinical response and tolerability, within the range of 150 to 750 mg/day.

In the treatment of acute manic episodes associated with bipolar disorder, the initial dose is 50 mg twice daily on day one, 100 mg twice daily on day two, 150 mg twice daily on day three, and 200 mg twice daily on day four. The dose may then be adjusted according to response to a usual range of 400 to 800 mg daily, although, in some patients, 200 mg daily may be adequate. Increments in the dosage should be no greater than 200 mg daily.

Special patient groups:

Caution is advised when **QUETOSER** is given to the elderly, especially during the initial dosing period. **QUETOSER** should be given in reduced doses to the elderly. The recommended starting dose is 25 mg daily, which may be increased every day in increments of 25 to 50 mg to an effective dose. The effective dose range is likely to be lower than in younger adults.

Renal and hepatic impairment:

Quetiapine is extensively metabolised in the liver and the oral clearance of **QUETOSER** may be reduced by approximately 25 % in patients with hepatic or renal impairment and caution is therefore advised.

Reduced doses are recommended in patients with hepatic or renal impairment. A recommended starting dose is 25 mg daily, increased to an effective dose in increments of 25 to 50 mg daily.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The following undesirable effects have been observed during treatment with **QUETOSER**:

Blood and lymphatic system disorders:

Frequent:	Leucopenia (fever, chills or sore throat).
Less frequent:	Neutropenia, eosinophilia, thrombocytopenia.

Immune system disorders:

Less frequent:	Hypersensitivity reactions, including angio-oedema, Stevens-Johnson syndrome.

Metabolism and nutritional disorders:

Less frequent: Hypothyroidism (decreases in total and free thyroxine [T4]), hyperglycaemia and exacerbation of pre-existing diabetes.

Psychiatric disorders:

Frequent: Abnormal dreams, nightmares.

Nervous system disorders:

Frequent: Dizziness, drowsiness, somnolence.

Less frequent: Extrapyramidal symptoms, parkinsonian symptoms, neuroleptic malignant syndrome (NMS), seizures, anxiety.

Frequency unknown: Tardive dyskinesia.

Eye disorders:

Less frequent: Changes in lenses of eyes, blurred/abnormal vision, dry eyes.

Ear and labyrinth disorders:

Less frequent: Ear pain.

Cardiac disorders:

Frequent: Tachycardia.

Less frequent: Palpitations, prolongation of the QTc interval (See **"Special Precautions"**).

Vascular disorders:

Frequent:	Orthostatic hypotension (associated with dizziness, light headedness or fainting, tachycardia and syncope in some patients, especially when getting up from a lying or sitting position).
Less frequent:	Hypertension, hypotension, venous thromboembolism.

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Dyspnoea, pharyngitis, rhinitis.

Gastrointestinal disorders:

Frequent:	Constipation, dyspepsia, dry mouth.
Less frequent:	Abdominal pain, anorexia, diarrhoea.

Hepatobiliary disorders:

Frequent:	Raised liver enzyme values.
Less frequent:	Jaundice, hepatitis.

Skin and subcutaneous tissue disorders:

Less frequent:	Skin rash.

Musculoskeletal and connective tissue disorders:

Less frequent:	Hypertonia, myalgia.

Renal and urinary disorders:

Less frequent: Urinary tract infection.

Reproductive system and breast disorders:

Less frequent: Galactorrhoea, menstrual changes, priapism.

General disorders:

Frequent: Increased weight, peripheral oedema, asthenia.

Less frequent: Dysarthria, flu-like symptoms (fever, chills, muscle aches), increased sweating, headache, back pain, chest pain, fever.

Investigations:

Frequent: Elevations of serum transaminase (AST/ALT).

Less frequent: Rises in plasma triglyceride and cholesterol concentrations, reduced plasma thyroid hormone concentrations, elevations in gamma GT levels.

Special Precautions:

Alzheimer's dementia:

Caution is advised when prescribing **QUETOSER** to patients with Alzheimer's dementia, as they may suffer from dysphagia associated with the use of antipsychotic medications which may increase the risk of aspiration pneumonia. The risk of seizures is possibly also increased due to the lowered seizure threshold with Alzheimer's dementia.

Cardiovascular disease:

QUETOSER should be used with caution in patients with known cardiovascular disease, including conduction abnormalities, heart failure, myocardial infarction or ischemia, or cerebrovascular disease or history thereof, or conditions that would predispose to hypotension, including dehydration or hypovolaemia.

Orthostatic hypotension may be exacerbated by **QUETOSER**, and hypotension may be exacerbated by pre-existing cardiovascular or cerebrovascular conditions, predisposing to hypotension. This is more common in elderly than in younger patients.

Caution is required when **QUETOSER** is prescribed with medicines known to prolong the QTc interval, especially in the elderly.

Seizures or history of seizures:

Seizures occurred rarely in premarketing studies of quetiapine. It is recommended that quetiapine be used with caution in patients with a history of seizures or a decreased seizure threshold.

Hepatic function impairment or abnormal hepatic function or renal function impairment:

Higher blood concentrations of quetiapine may occur, dosage adjustment may be necessary, especially during the initial dosing period (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Transaminase values should be measured prior to **QUETOSER** use in patients with known or suspected hepatic function impairment. Periodic reassessment should occur in these patients, as well as in patients who develop signs or symptoms suggestive of new onset liver disorders.

Tardive dyskinesia:

QUETOSER could potentially cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia develop, discontinuation of **QUETOSER** therapy should be considered.

Suicidal tendencies:

Careful supervision is recommended in high-risk patients, since the possibility of suicide attempt is inherent in schizophrenia. Prescribing the smallest quantity of medication necessary for good patient management is recommended to prevent overdosing.

Ophthalmologic examinations:

Examination of the lens of the eye by methods adequate to detect cataract formation, such as slit lamp examination, is recommended at baseline and every 6 months during treatment with **QUETOSER**. Lens changes have been observed in patients during long-term quetiapine therapy and cataracts developed in dogs during chronic quetiapine dosing.

Withdrawal:

Gradual withdrawal of **QUETOSER** is recommended because of the risk of acute withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses, with abrupt cessation.

Neuroleptic malignant syndrome (NMS):

NMS has been associated with **QUETOSER** therapy. NMS may clinically manifest as altered mental status, hyperthermia, muscular rigidity, autonomic instability and increased creatine phosphokinase. In such an event, therapy with **QUETOSER** should be stopped and appropriate medical treatment administered.

Lactose:

QUETOSER tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines:

QUETOSER may cause somnolence. Patients should be cautioned not to drive, operate hazardous machinery or perform hazardous tasks, while using **QUETOSER**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

Effects of overdose may be similar to side-effects experienced at therapeutic doses, but may be more severe or several effects may occur together.

Treatment:

Treatment is symptomatic and supportive.

IDENTIFICATION:

QUETOSER 25: Peach, round, biconvex, film-coated tablet, debossed with "25" on one side and a "P" logo on the other side.

QUETOSER 100: Yellow, round, biconvex, film-coated tablet, debossed with "100" on one side and a "P" logo on the other side.

QUETOSER 200: White, round, biconvex, film-coated tablet, debossed with "200" on one side and a "P" logo on the other side.

QUETOSER 300: White, capsule-shaped, biconvex, film-coated tablet, debossed with "300" on one side and a "P" logo on the other side.

PRESENTATION:

QUETOSER is packed in:

- Clear PVC/PCTFE and aluminium blister strips in a cardboard carton; or
- White opaque HDPE bottle with white opaque polypropylene ribbed cap with induction seal and silica gel sachet as desiccant in the following pack sizes:
    - **QUETOSER 25:** 60's, 100's and 500's
    - **QUETOSER 100:** 90's, 100's and 500's
    - **QUETOSER 200:** 60's, 90's, 100's and 500's
    - **QUETOSER 300:** 60's, 90's, 100's and 500's

STORAGE INSTRUCTIONS:

Store in the original packaging at or below 25 °C. Keep the blisters in the carton until required for use. The bottles must be tightly closed.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

QUETOSER 25: 43/2.6.5/0800

QUETOSER 100: 43/2.6.5/0801

QUETOSER 200: 43/2.6.5/0802

QUETOSER 300: 43/2.6.5/0803

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

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