Quetiapine Tablets

1.GENERIC NAME: Quetiapine Fumarate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains:

Quetiapine Fumarate IP equivalent to Quetiapine ..... 25 mg

Colours: Yellow Oxide of Iron & Titanium Dioxide IP

Each film coated tablet contains:

Quetiapine Fumarate IP equivalent to Quetiapine..... 50 mg

Colours: Yellow Oxide of Iron & Titanium Dioxide IP

3. DOSAGE AND STRENGTH: Quetiapine 25 mg & Quetiapine 50 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indication: Indicated for the management of manifestation of psychotic disorders (Schizophrenia).

4.2 DOSAGE AND ADMINISTRATION

Posology: Quetiapine tablet should be administered twice a day or as directed by the Physician.

In Elderly population: 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 have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

In Children and adolescents: The safety and efficacy of quetiapine have not been evaluated in children and adolescents.

In Hepatic impairment: Quetiapine is extensively metabolized by the liver, and therefore 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 on 25mg/day. The dose should be increased daily, in increments of 25 to 50mg, to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 CONTRAINDICATIONS Contraindicated in patients with known hypersensitivity to Quetiapine or to any of the excipients. - Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. Contraindicated in Pregnant, lactating women & children below 18 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE 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.

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.

Cardiovascular disease: 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.

Tardive dyskinesia: If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

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 <O.5 * 109/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 histor y of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <O.1 * 109/L

Lipids: Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine. Lipid increases should be managed as clinically appropriate.

Extrapyramidal symptoms: In placebo controlled clinical trials quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder. Hypoglycemia: Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Venous Thromboembolism (VTE): Cases of VTE have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Quetiapine Tablets and preventive measures undertaken.

QT Prolongation: In clinical trials and use in accordance with the SPC, 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, hypokalemia or hypomagnesaemia.

Withdrawal: Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable.

Elderly patients with dementia-related psychosis: Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized placebo-controlled trials in the dementia population with some atypical antipsychotics. Quetiapine should be used with caution in patients with risk factors for stroke. Additional information: Quetiapine data in combination with divalproex or lithium in moderate to severe manic episodes is limited; however, combination therapy was well tolerated.

4.5 DRUG INTERACTION Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting agents and alcohol. Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450-mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) 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 take quetiapine together with grapefruit juice.

Carbamazepine: In a multiple-dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), Co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy.

Antiepileptic drugs: Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Antidepressants: The pharmacokinetics of quetiapine were not significantly altered by the co-administration of antidepressants, imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP2D6 inhibitor).

Antipsychotics: 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.

Formal interaction studies with commonly used cardiovascular agents have not been performed.

Caution should be exercised when quetiapine is used concomitantly with agents known to cause electrolyte imbalance or to increase QTc interval.

4.6 USE IN SPECIAL POPULATION

Liver patients: If you have liver problems your doctor may change your dose.

4.7 EFFECTS 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.

4.8 UNDESIRABLE EFFECTS

Urinary incontinence

Urinary incontinence as an adverse reaction to quetiapine reported

The most commonly reported Adverse Drug Reactions (ADRs) 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 edema, have been associated with quetiapine. Following adverse reactions reported with quetiapine, provided according to their occurrence.

Very common: Dizziness, somnolence, headache, extrapyramidal symptoms, Dry mouth, Withdrawal (discontinuation) symptoms, Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain,

decreased hemoglobin, increased appetite, Elevations in prolactin, increases in blood pressure, Vomiting.

Common: Leucopenia, Hyperprolactinemia, Increased appetite, Abnormal dreams and nightmares, Dysarthria, Tachycardia, palpitations, Vision blurred, Orthostatic hypotension, Dyspnea, Constipation, dyspepsia , vomiting, Mild asthenia, peripheral oedema, irritability, pyrexia, Elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels, decreased neutrophil count, eosinophils increased, blood glucose increased to hyperglycemic levels, QT prolongation, elevations in serum prolactin, decreases in Total T4, decreases in Free T4, decreases in Total T3 , increases in TSH, Syncope, Irritability, Rhinitis.

Uncommon: Thrombocytopenia, Hypersensitivity, Seizure, restless legs syndrome, tardive dyskinesia, syncope, Bradycardia, Urinary retention, Rhinitis, Dysphagia, Elevations in serum aspartate aminotransferase (AST), platelet count decreased, decreases in free T3.

Rare: Jaundice, Priapism, galactorrhea, Neuroleptic malignant syndrome, hypothermia, Elevations in blood creatine phosphokinase, agranulocytosis

Not known: Anaphylactic reaction, Diabetes mellitus, Somnambulism and other related reactions, Intestinal obstruction/Ileus, Neutropenia, Hepatitis, Angioedema, Stevens-Johnson syndrome, Neonatal withdrawal. 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.

4.9 OVERDOSE

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 post marketing 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines

Quetiapine is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives and is indicated for the treatment of schizophrenia. Quetiapine is a selective monoaminergic antagonist with high affinity for the serotonin Type 2 (5HT2), and dopamine type 2 (D2) receptors. Quetiapine is an antagonist at serotonin 5-HT1A and 5HT2, dopamine D1 and D2, histamine H1, and adrenergic alpha 1 and alpha 2 receptors. Quetiapine's antipsychotic activity is likely due to a combination of antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex. Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia. The antipsychotic effect of quetiapine is thought by some to be mediated through antagonist activity at dopamine and serotonin receptors. Specifically, the D1 and D2 dopamine, the alpha 1 adrenoreceptor and alpha 2 adrenoreceptor, and 5-HT1A and 5-HT2 serotonin receptor subtypes are antagonized. Quetiapine also has an antagonistic effect on the histamine H1 receptor.

5.2 Pharmacodynamic

Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5HT1A and 5HT2 (IC50s=717 & 148nM, respectively), dopamine D1 and D2 (IC50s=1268 & 329nM, respectively), histamine H1 (IC50=30nM), and adrenergic α1 and α2 receptors (IC50s=94 & 271nM, respectively). Quetiapine has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC50s>5000 nM).

5.3 Pharmacokinetic properties

Quetiapine is well absorbed and extensively metabolized following the 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 N-desalkyl quetiapine are 35% of that observed for quetiapine. Quetiapine is extensively metabolized by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or feces, following the administration of radiolabelled quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours, respectively. Elimination of quetiapine is mainly via hepatic metabolism. Following a single oral dose of 14C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly

metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

6. NON-CLINICAL PROPERTIES

6.1 Animal toxicology or Pharmacology: Not required

7. DESCRIPTION: Mentioned above

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITY: Not applicable.

8.2 SHELF LIFE: 24 months

8.3 PACKAGING INFORMATION: Film coated tablets, available in 10 tablets per strip.

8.4 STORAGE & HANDLING INFORMATION:

Store protected from light & moisture, at a temperature not exceeding 30 C.

Keep all medicines out of reach of children

9. Patient Counselling Information

9.1 Adverse reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.8

9.3 Dosage

Refer part 4.5

9.4 Storage

Refer part 8.4

9.5 Risk factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Details of manufacturer: Pure & Cure Healthcare Pvt Ltd.

11. Licence no. with date: 31/UA/2013

12. Date of revision: March 2023