EvoKaLM®

(Quetiapine fumarate USP)

ایووکام

COMPOSITION:
Evokalm 25mg:
Each film coated tablet contains:
Quetiapine fumarate USP eq. to Quetiapine....25 mg
Evokalm 100mg:
Each film coated tablet contains:
Quetiapine fumarate USP eq. to Quetiapine....100 mg
Evokalm 200mg:
Each film coated tablet contains:
Quetiapine fumarate USP eq. to Quetiapine....200 mg
(USP Specs.)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

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. Quetiapine fumarate is not approved for the treatment of patients with dementia-related psychosis. See WARNINGS & PRECAUTIONS

Suicidal Thoughts and Behavior:
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. Quetiapine fumarate is not approved for use in pediatric patients less than ten years of age. See WARNINGS & PRECAUTIONS.

DESCRIPTION:
EVOKALM tablets contain quetiapine fumarate, a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [b, f] [1, 4] thiazepin-11-yl-1 piperazinyl-ethoxy)-ethanol fumarate (2:1) (salt). Its molecular formula is $C_{42}H_{30}N_6O_4S_2C_4H_4O_4$

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism of action of Quetiapine is unknown. The efficacy of Quetiapine in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonisms. Antagonism at receptors other than dopamine and 5HT2 with similar receptor affinities may explain some of the other effects of Quetiapine. Quetiapine's antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Quetiapine's antagonism of adrenergic α1 receptors may explain the orthostatic hypotension observed with this drug. Quetiapine's active metabolite nor-quetiapine has moderate to high affinity at several muscarinic receptors, which may explain its anti-cholinergic (muscarinic) effects. Inhibition of Norepinephrine transporter and partial agonist action at 5HT1A sites by nor-quetiapine may also contribute to Quetiapine's efficacy as an antidepressant.

Pharmacokinetics

Absorption
Quetiapine fumarate 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 Cmax and AUC values increased by 25% and 15%, respectively.

Distribution
Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations.

Metabolism
Quetiapine is highly metabolized by the liver via CYP3A4 isoenzyme. Major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to parent acid metabolite; both metabolites are inactive. Active metabolite is N-desalkyl quetiapine (nor-quetiapine)

Elimination
The elimination half-life of quetiapine and nor-quetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite nor-quetiapine is <5% excreted in the urine.

INDICATIONS

Quetiapine is an atypical antipsychotic indicated in adult patients for the treatment of:
• Schizophrenia
• Bipolar I disorder, acute treatment of manic episodes, both as monotherapy and as adjunct to lithium or divalproex
• Bipolar disorder I and II, acute treatment of depressive episodes, as monotherapy
• Bipolar I disorder, maintenance treatment, as an adjunct to lithium or divalproex

Pediatric Use
There is limited data to support the use of Quetiapine in pediatric patients less than 18 years of age. Based on the available evidence from place controlled clinical trials in pediatric population, Quetiapine can be used in the following indications:

• Schizophrenia (in patients 13-17 years of age)
• Bipolar I disorder, acute treatment of manic episodes, as monotherapy (in patients 10-17 years of age)

Pediatric schizophrenia and bipolar I disorder are serious mental disorders with a challenging diagnosis. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. Medication therapy should only be initiated after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment should be accompanied by psychological, educational and social interventions.
EVOKALM tablets should not be given to younger pediatric patients, if it is difficult for the patient to swallow the tablet.

DOSAGE AND ADMINISTRATION

Indication	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia-Adults	25 mg twice daily (Day 1)*	150-750 mg/day	750 mg/day
Schizophrenia-Adolescents (13-17) years	25 mg twice daily (Day 1)#	400-800 mg/day	800 mg/day
Bipolar-I Mania-Adults, Monotherapy or as an adjunct to lithium or divalproex	50 mg twice daily (Day 1)%^	400-800 mg/day	800 mg/day
Bipolar-I Mania -Children & Adolescents (10-17 years), Monotherapy	25 mg twice daily (Day 1)@	400-600 mg/day	600 mg/day
Bipolar I and II Depression-Adults	50 mg at bed time (Day 1)^	300 mg/day	300 mg/day
Bipolar I Disorder, Maintenance Therapy-Adults	Administer twice daily totaling 400-800 mg/day as adjunct to lithium or divalproex$	400-800 mg/day	800 mg/day

* Increase in increments of 25 mg-50 mg divided two or three times on Days 2 and 3 to range of 300-400 mg by Day 4. Further adjustments can be made in increments of 25–50 mg twice a day, in intervals of not less than 2 days.
\# Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.
% Day 2: Twice daily dosing totaling 200 mg. Day 3: Twice daily dosing totaling 300 mg. Day 4: Twice daily dosing totaling 400 mg. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.
@ Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-600 mg/day. Based on response and tolerability, may be administered three times daily.
^ Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg
$ Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized

Dosing considerations in special populations:

Elderly
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. This applies especially to debilitated patients or those pre-disposed to hypotensive reactions.

Hepatic Impairment
Lower starting dose (25 mg/day) and slower titration may be needed. The dose should be increased daily in increments of 25 mg/day - 50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient

Dose modification in patients taking CYP3A4 inhibitors
Quetiapine therapy is not recommended with concomitant CYP3A4 inhibitors. If this cannot be avoided, the dose of Quetiapine should be modified and reduced to one-sixth of the original dose. See DRUG INTERACTIONS

Dose modification in patients taking CYP3A4 inducers
Concomitant use of Quetiapine with CYP3A4 inducers is not recommended. If concomitant use cannot be avoided, increase quetiapine dose up to 5 fold when used in combination with a chronic treatment (more than 7-14 days) of potent CYP3A4 inducers. See DRUG INTERACTIONS

Re-initiation of treatment in patients who previously discontinued Quetiapine
When restarting therapy of patients who have been off Quetiapine for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off Quetiapine for less than one week, gradual dose escalation may not be required and the maintenance dose may be reinitiated.

Switching from 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 drugs should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate Quetiapine therapy in place of the next scheduled injection.

CONTRAINDICATIONS

Known hypersensitivity to Quetiapine

WARNINGS & PRECAUTIONS

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. The causes of the reported deaths were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Quetiapine is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse events including stroke in elderly patients with dementia related psychosis
Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) including fatalities has been seen in elderly patients with dementia -related psychosis treated with atypical antipsychotic drugs

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex called Neuroleptic Malignant Syndrome (NMS) has been reported with antipsychotic drugs. Only rare cases of NMS have been reported with Quetiapine. NMS may include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure may also occur. Other differential diagnoses (pneumonia, sepsis, untreated extrapyramidal signs/symptoms, central anticholinergic toxicity, heat stroke, drug fever and primary CNS pathology) should be ruled out. If NMS is confirmed, therapy with antipsychotic drug should be discontinued and intensive symptomatic treatment with medical monitoring is recommended. After resolution of NMS, therapy may be carefully started with close monitoring to prevent recurrence.

Metabolic Changes
Atypical antipsychotics including Quetiapine have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain

• **Hyperglycemia and Diabetes Mellitus:** Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes
• **Dyslipidemia:** Undesirable alterations in blood lipids have been observed in patients treated with atypical antipsychotics. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment
• **Weight Gain:** Gain in body weight has been observed; clinical monitoring of weight is recommended

Tardive Dyskinesia (TD)
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs, including quetiapine. Risk appears to be highest in elderly especially elderly women. Risk also increases with increasing dose and duration of treatment and the same may also increase the risk of irreversibility of TD. However, it may occur (although much less commonly) after relatively brief treatment periods at low doses or even after discontinuation of treatment. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. However, there is no known treatment. Antipsychotic treatment, itself may possibly mask the signs and symptoms of TD. If signs and symptoms of tardive dyskinesia appear in a patient on Quetiapine, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Suicidality in adolescents and young adults
A meta-analysis of placebo controlled clinical trials of antidepressant drugs (particularly SSRIs and other drugs) showed an increased risk of suicidal behavior with antidepressants compared to placebo in adolescents and young adults less than 25 years old. This may be applicable to Quetiapine which is used in the treatment of bipolar depression. Depression in bipolar disorder is itself associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. Until remission patients should be closely monitored. Patients with a history of suicide related events, or those exhibiting suicidal ideation prior to starting treatment may be at greater risk of suicidal thoughts or suicide attempts, and should be carefully monitored during treatment. Patients being treated with Quetiapine for bipolar depression should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of drug therapy, or at times of dose increases or decreases. Families and caregivers should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately

Hypotension
Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and sometimes syncope, especially during the initial dose-titration period, probably reflecting its α 1-adrenergic antagonist properties. Orthostatic hypotension, dizziness, and syncope may lead to falls especially in elderly. Use quetiapine with caution in patients with known cardiovascular (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities) or cerebrovascular disease or conditions predisposing to hypotension (dehydration, hypovolemia and treatment with antihypertensives). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg twice daily. If hypotension occurs during titration to the target dose, a return to the previous dose may be considered.

Leukopenia, Neutropenia and Agranulocytosis
Events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including Quetiapine. Monitor complete blood count frequently during the first few months of treatment in patients with a pre-existing low white cell count or a history of leukopenia/neutropenia and discontinue Quetiapine at the first sign of a decline in WBC in absence of other causative factors. Patients with neutropenia should be monitored for fever or other symptoms/signs of infection and treated promptly, if they occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue Quetiapine and have their WBC followed until recovery.

QT Prolongation
In post marketing experience QT prolongation was reported in patients who overdosed on quetiapine, in patients with concomitant cardiac illness, and in patients taking medicines

known to cause electrolyte imbalance or increase QT interval. 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 either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia or hypomagnesaemia. See DRUG INTERACTIONS

Cataracts
Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination by methods adequate to detect cataract formation is recommended when starting treatment or shortly thereafter and at 6-month intervals during chronic treatment

Seizures
As with other antipsychotics, Quetiapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in elderly population

Hypothyroidism
Quetiapine may cause dose-related decreases in thyroid hormone levels. The reduction in total and free thyroxine (T4) is maximal at the higher end of the dose in the first six weeks of treatment and is maintained during chronic use. Cessation in quetiapine treatment results in reversal of these effects. Both TSH and free T4, in addition to clinical assessment, should be measured at baseline and at follow-up during Quetiapine therapy, especially in patients with existing hypothyroidism or prone to develop hypo-thyroidism.

Hyperprolactinemia
Like other drugs that antagonize dopamine D2 receptors, Quetiapine may cause prolactin elevation in some patients which may persist during chronic use. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. It is reasonable to monitor prolactin levels in some patients on Quetiapine therapy.

Extrapyramidal symptoms (EPS)
Quetiapine like other antipsychotics has been associated with increased incidence of extrapyramidal symptoms such as tremor, dystonia, dyskinesia, akathisia, tardive dyskinesia etc. However, the incidence is much lower as compared to typical antipsychotics. See ADVERSE REACTIONS. Akathisia is characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop EPS, increasing the dose may be detrimental. Extrapyramidal side effects may require appropriate management.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Antipsychotic drugs including quetiapine should be used cautiously in patients at risk for aspiration pneumonia.

Anticholinergic (muscarinic) effects
Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. Hence, anticholinergic (muscarinic) side effects may occur with quetiapine at normal or high doses and during concomitant use with other anticholinergic medications. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma.

Sleep apnea syndrome
Sleep apnea syndrome has been reported in patients using quetiapine. In patients receiving concomitant CNS depressants and who have a history of or are at risk for sleep apnea, such as those who are overweight/obese or are male, quetiapine should be used with caution.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine. Special care is needed in patients who are at higher risk of intestinal obstruction, including those who are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Discontinuation syndrome
Acute withdrawal symptoms, such as insomnia, nausea, vomiting, diarrhea, dizziness and irritability have been described after abrupt cessation of atypical antipsychotic drugs, including Quetiapine. Gradual withdrawal is advised.

Effects on ability to drive or use machines due to cognitive and motor impairment
Somnolence and sedation has been reported with Quetiapine. Excessive somnolence may lead to falls. 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 (including automobiles) or operating hazardous machinery.

ADVERSE REACTIONS

Blood and lymphatic system disorders
Very common: Decreased hemoglobin
Common: Leucopenia, decreased neutrophil count, eosinophils increased,
Uncommon: Neutropenia, Thrombocytopenia, Anaemia, platelet count decreased
Rare: Agranulocytosis
Immune system disorders
Uncommon: Hypersensitivity (including allergic skin reactions)
Very rare: Anaphylactic reaction
Endocrine disorders
Common: Hyperprolactinaemia, decreases in total T4, decreases in free T4, decreases in total T3, increases in TSH
Uncommon: decreases in free T3, Hypothyroidism
Very rare: Inappropriate ADH secretion
Metabolism and nutritional disorders
Very common: Elevations in serum triglyceride levels, Elevations in total cholesterol (predominantly LDL cholesterol), Decreases in HDL cholesterol, Weight gain
Common: Increased appetite, hyperglycemia
Uncommon: Hyponatremia, diabetes mellitus, exacerbation of pre-existing diabetes
Rare: Metabolic syndrome
Psychiatric disorders
Common: Abnormal dreams and nightmares, Suicidal ideation and suicidal behavior
Rare: Somnambulism and related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders
Very common: Dizziness, somnolence, headache, Extrapyramidal symptoms
Common: Dysarthria
Uncommon: Seizure, restless leg syndrome, tardive dyskinesia, syncope
Cardiac disorders
Common: Tachycardia, Palpitations
Uncommon: QT prolongation, bradycardia
Eye disorders
Common: Vision blurred
Vascular disorders
Common: orthostatic hypotension
Rare: Venous thromboembolism
Respiratory, thoracic and mediastinal disorders
Common: Dyspnea
Uncommon: Rhinitis
Gastrointestinal disorders
Very common: Dry mouth
Common: Constipation, dyspepsia, vomiting
Uncommon: Dysphagia
Rare: Pancreatitis, intestinal obstruction, ileus
Hepatobiliary disorders
Common: Elevations in serum alanine aminotransferase (ALT), Elevations in gamma-GT levels,
Uncommon: Elevations in serum aspartate aminotransferase (AST)
Rare: Jaundice, Hepatitis
Skin and sub-cutaneous tissue disorders
Very rare: Angioedema, Stevenson-Johnson syndrome
Unknown: Toxic Epidermal Necrolysis, Erythema Multiforme
Musculoskeletal and connective tissue disorders
Very rare: Rhabdomyolysis
Renal and urinary system disorders
Uncommon: Urinary retention
Pregnancy, puerperium and perinatal conditions
Unknown: neonatal drug withdrawal syndrome
Reproductive system and breast disorders
Uncommon: sexual dysfunction
Rare: priapism, galactorrhea, breast swelling, menstrual disorder
General disorders and administration site conditions
Very common: Withdrawal (discontinuation) symptoms
Common: Mild asthenia, peripheral oedema, irritability, pyrexia
Rare: Neuroleptic malignant syndrome, hypothermia
Investigations
Rare: Elevation in creatine phosphokinase

DRUG INTERACTIONS

CNS-acting agents
Given the primary CNS effects of Quetiapine, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

Concomitant use of strong CYP3A4 inhibitors
Quetiapine exposure is increased by the prototype CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone, etc) Concomitant use is not recommended. If this cannot be avoided, reduce quetiapine dose to one sixth when co -administered with strong CYP3A4 inhibitors. When the CYP3A4 inhibitor is discontinued, the dose of Quetiapine should be increased by 6 fold.

Concomitant use of strong CYP3A4 inducers
Quetiapine exposure is decreased by the prototype CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, avasimibe, St. John's wort etc.). This could result in loss of efficacy of quetiapine. Concomitant use of Quetiapine with CYP3A4 inducers is not recommended. If concomitant use cannot be avoided, increase quetiapine dose up to 5 fold when used in combination with a chronic treatment (more than 7-14 days) of potent CYP3A4 inducers. When the CYP3A4 inducer is discontinued, the dose of Quetiapine should be reduced to the original level within 7-14 days

Antihypertensives
Because of its potential for inducing hypotension, Quetiapine may enhance the effects of certain antihypertensive agents.

Antagonism of dopaminergic drugs
Quetiapine may antagonize the effects of levodopa and dopamine agonists.

Drugs known to prolong QT interval
Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval. The use of quetiapine should be avoided in combination with drugs known to prolong QT interval including Class 1A antiarrythmics (e.g., quinidine, procainamide) or Class III antiarrythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QT interval (e.g., pentamidine, levomethadyl acetate, methadone). If used concomitantly, close cardiac, ECG and electrolyte monitoring is recommended.

Grapefruit juice
Grapefruit juice should not be consumed while Quetiapine therapy

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Pregnancy category C. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonates exposed to antipsychotic drugs including Quetiapine, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limiting, in other cases neonates have required intensive care and prolonged hospitalization.

Nursing Mothers
Quetiapine fumarate is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Quetiapine a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother's health.

Pediatric Use
Limited evidence exists to support the use of Quetiapine in pediatric patients less than 18 years of age. Based on the available data from place controlled clinical trials in pediatric population, Quetiapine can be used in accordance with the recommendations outlined in INDICATIONS section. In comparison to the known safety profile in adults, certain adverse events occurred at a higher frequency in children and adolescents (increased appetite, elevations in serum prolactin, vomiting, rhinitis, syncope, extrapyramidal symptoms and irritability) and one was identified that has not been described in adults (increases in systolic and diastolic blood pressure). The long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long term implications for cognitive and behavioural development are not known.

Geriatric Use
In general, there was no indication of any different tolerability of quetiapine fumarate in the elderly compared to younger adults. The mean plasma clearance of quetiapine fumarate was reduced by 30% to 50% in elderly patients as compared to young patients. A lower starting dose, slower titration, and careful monitoring during the initial dosing period should be considered in the elderly

Renal Insufficiency
Patients with severe renal impairment had a 25% lower mean renal clearance than normal subjects but plasma quetiapine concentrations even in these subjects with severe renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in patients with renal impairment

Hepatic Insufficiency
Hepatic impaired patients had a 30% lower mean renal clearance of quetiapine than normal subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatic impaired population and dosage adjustment may be needed. A low starting dose of 25 mg/day is recommended and the dose should be increased slowly in increments of 25 mg/day - 50 mg/day

OVERDOSAGE
In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, QT interval prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

In case of acute over dosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is used, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when given to patients with acute over dosage. There is no specific antidote to Quetiapine. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PRESENTATION
EVOKALM 25mg, 100mg & 200mg: Each is available in the pack of 10 film coated tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C. For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔
دوا کے ناقابل تلافی ری ایکشن کے متعلق reports@pharmevo.biz پر مطلع کریں۔
ہماری ادویات کی مزید معلومات کے لئے فارماسسٹ کی ہیلپ لائن نمبر 0800-82222 پر کال کریں۔
یا ہمیں ہفتہ صبح 9:00 بجے تا شام 6:00 بجے
یا ہمیں pharmassist@pharmevo.biz پر ای میل کریں

Manufactured by:
PharmEvo (Pvt.) Ltd.
Plot # A-29, North Western Industrial Zone, Port Qasim, Karachi-75020 Pakistan
www.pharmevo.biz
PharmEvo® Our dream, a healthier society

DI:EVOM 02 08/2019 1200001804