For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Gliclazide & Metformin Hydrochloride Tablets
(Brand Name: K-GEM® Tablets)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Gliclazide IP ……. 80 mg.
Metformin Hydrochloride IP ……..…… 500 mg.
Excipients …… q.s.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Gliclazide 80 mg and metformin hydrochloride 500 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

K-GEM Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

4.2Posology and Method of Administration

For oral administration in adults.
Recommended dose is 1 tablet of K-GEM (gliclazide 80 mg + metformin 500 mg) to be administered twice daily with food. If glycemic control is not achieved within 2 to 4 weeks of therapy, increase the dose or consider a change to more appropriate treatment (higher doses of individual components may be given separately or addition of other anti-diabetic drugs should be considered). However, the dose should be adjusted according to the individual patient's response to therapy and tolerability. If higher doses are required, dosage of individual components should not exceed the maximum daily dose.
Maximum daily dose of individual agents:

- Gliclazide: 320 mg in divided doses.
- Metformin: 2000 mg in divided doses.

To avoid the risk of hypoglycemia, K-GEM Tablets should be strictly administered with food/meal. Swallow the tablet whole and never crush, cut or chew.
Or, as prescribed by the physician.

4.3Contraindications

K-GEM Tablets are contraindicated in the following

- Known hypersensitivity to gliclazide/other sulphonylureas or to metformin or to any component of the formulation.
- Type 1 diabetes.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Severe renal impairment (eGFR below 30 ml/min/1.73 m^2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock.
- Acute or chronic disease which may cause tissue hypoxia, such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, alcoholism, acute alcohol intoxication.
- Pregnancy.
- Lactation.
- Treatment with miconazole.
- Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials should temporarily discontinue taking metformin-containing preparation, because use may result in acute alteration of renal function.

4.4Special Warnings and Precautions for Use

Gliclazide

Hypoglycemia: All sulphonylurea drugs including gliclazide are capable of producing moderate or severe hypoglycemia, particularly in conditions such as accidental overdose, deficient glucose intake, and in patients with hepatic and/or renal impairment. Mild symptoms of hypoglycemia should be treated with oral glucose. Severe hypoglycemic reactions must be treated as a medical emergency, requiring immediate hospitalization. Careful selection of patients and of the dose used, as well as provision of adequate information to the patient is necessary to avoid hypoglycemic episodes. Hypoglycemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycemic agents is being used.

Renal and Hepatic Insufficiency: The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycemic episode occurring in these patients may be prolonged, so appropriate management should be initiated. A small starting dose should be used with careful patient monitoring.

Monitoring of Diabetic State: Patients treated with gliclazide should be closely observed to ensure optimal control of the diabetic state. Glycated hemoglobin (HbA1c) and/or fasting plasma glucose levels should be monitored at regular intervals. Blood glucose self-monitoring may also be useful. Particular care must be taken during the initial period of stabilization.

Poor Blood Glucose Control: Blood glucose control in treated patients may be affected by St. John's Wort (*Hypericum perforatum*) preparations, fever, trauma, infection or surgical

intervention. It may be necessary to discontinue treatment and to administer insulin in these cases. The efficacy of oral antidiabetic agents often decreases in the long term. This may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure and should be distinguished from primary failure, when the drug is ineffective as first-line treatment. However, before classifying the patient as a secondary failure, dose adjustment and reinforcement of dietary measures should be considered.

Dysglycemia: Disturbances in blood glucose, including hypoglycemia and hyperglycemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Indeed, careful monitoring of blood glucose is recommended in all patients receiving gliclazide and fluoroquinolone concomitantly.

Acute Complications Such As Severe Trauma, Fever, Infection or Surgery: These acute complications provoke additional metabolic stress which accentuates the predisposition to hyperglycemia and ketosis. Patients presenting with such conditions may require insulin to maintain control. It is not appropriate to increase the dosage of gliclazide.

Lactose Intolerance: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take gliclazide.

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD): Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to hemolytic anemia. Since gliclazide belongs to the class of sulphonylurea, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

Metformin

Lactic Acidosis: Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment) metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia. If metformin-associated lactic acidosis is suspected, immediately discontinue metformin therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients.

Excessive Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Acute alcohol intoxication is associated with an increased risk of lactic acidosis. Thus, it is advised that patients should strictly avoid consumption of excessive alcohol while on metformin therapy.

Radiologic Studies with Iodinated Contrast Media: Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock) of any kind, acute congestive heart failure,

acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

Cardiac Function: Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Renal Function: As metformin is excreted primarily by the kidney, creatinine clearance or eGFR should be determined before initiating treatment and regularly thereafter at least annually in patients with normal renal function and at least 2 to 4 times a year in patients with creatinine clearance levels at the upper limit of normal and in elderly subjects.

Loss of Blood Glucose Control: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold oral antidiabetic agents and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

Surgery: Metformin should be discontinued 48 hours before elective surgery with general spinal or peridural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or when normal renal function has been established.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of metformin in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Deficiency: Long-term use of metformin may decrease absorption of vitamin B_{12} with resultant decrease in plasma B_{12} levels. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia, but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. It is recommended to measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on metformin therapy.

Other Precautions: While on metformin therapy, disease progression should be closely observed with monitoring of blood glucose levels at regular intervals. Metformin alone does not cause hypoglycemia, but caution is advised when it is used in combination with insulin or other oral antidiabetic drugs.

4.5Drug Interactions

Gliclazide

1. Drug interactions likely to increase the risk of hypoglycemia.

Combination contraindicated.

Miconazole (systemic route, oromucosal gel): Increases the hypoglycemic effect with possible onset of hypoglycemic symptoms, or even coma.

Combinations which are not recommended.

- Phenylbutazone (systemic route): Increases the hypoglycemic effect of sulphonylureas (displaces their binding to plasma proteins and/or reduces their elimination). It is preferable to use a different anti-inflammatory agent. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.
- Alcohol: Increases the hypoglycemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycemic coma. Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use.

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur when one of the following drugs is taken: Other antidiabetic agents (insulin, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme (ACE) inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and non-steroidal anti-inflammatory agents.

2. Drug interactions which may cause an increase in blood glucose levels.

Combination which is not recommended.

- Danazol: If the use of danazol cannot be avoided, warn the patient and emphasize the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combinations requiring precautions during use.

- Chlorpromazine (neuroleptic agent): High doses (>100 mg/day) increase blood glucose levels (reduced insulin release). Warn the patient and emphasize the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic drug during and after treatment with the neuroleptic agent.
- Glucocorticoids (systemic and local route such as intra-articular, cutaneous and rectal preparations) and Tetracosactrin: Increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids). Warn the patient and emphasize the importance of blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.
- Ritodrine, Salbutamol, and Terbutaline (I.V.): Increased blood glucose levels due to β_2-agonist effects. Emphasize the importance of monitoring blood glucose levels. If necessary, switch to insulin.
- Saint John's Wort (*Hypericum perforatum*) Preparations: Gliclazide exposure is decreased by Saint John's Wort-Hypericum perforatum. Emphasize the importance of blood glucose levels monitoring.

3. Drug Interactions which may cause dysglycemia.

Combinations requiring precautions during use.

- Fluoroquinolones: In case of a concomitant use of gliclazide and a fluoroquinolone, the patient should be warned of the risk of dysglycemia, and the importance of blood glucose monitoring should be emphasized.

Combination which must be taken into account.

- Anticoagulant Therapy (warfarin): Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary.

Metformin

Carbonic Anhydrase Inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide): Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce hyperchloremic non-anion gap metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring of these patients is recommended.

Drugs that Reduce Metformin Clearance (e.g., ranolazine, vandetanib, dolutegravir, and cimetidine): Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Drugs Affecting Glycemic Control (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid): These drugs tend to produce hyperglycemia and may lead to loss of glycemic control. When these drugs are administered to a patient receiving metformin, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, observe the patient closely for hypoglycemia.

Insulin Secretagogues or Insulin: Co-administration of metformin with an insulin secretagogue (e.g., sulphonylurea) or insulin may increase the risk of hypoglycemia. Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Interactions with Other Drugs:

1. Some drugs may adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX)-2 inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
2. Glucocorticoids (systemic and local routes), β_2-agonists, and diuretics have intrinsic hyperglycemic activity. More frequent blood glucose monitoring, especially at the beginning of treatment is required. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.
3. ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.

4.6Use in Special Populations

Pregnant Women

Gliclazide: Pregnancy Category C; Metformin: Pregnancy Category B. No clinical data are available on use of gliclazide and metformin combination therapy during pregnancy. In general, oral antidiabetic drugs are not suitable during pregnancy; insulin is the drug of first choice in the treatment of diabetes during pregnancy.

There is no or limited data available for use of gliclazide in pregnant women. Studies of gliclazide in animals have shown reproductive toxicity. Thus, as a precautionary measure, gliclazide is best avoided during pregnancy.

With metformin, animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development. No adverse developmental effects were observed when metformin was administered to pregnant rats and rabbits. Also, a limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. However, these studies cannot definitely establish the absence of any metformin-associated risk to fetus or pregnant women. Thus, due to lack of safety data metformin use is not recommended during pregnancy.

Uncontrolled or poorly controlled diabetes during pregnancy (gestational or permanent) increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. It also increases the fetal risk for major birth defects, still birth, and macrosomia-related morbidity. Thus, when the patient plans to become pregnant and during pregnancy, it is recommended that insulin be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

Lactating Women

Metformin is excreted into human breast milk. However, no adverse effects were observed in breastfed newborns/infants. It is unknown whether gliclazide or its metabolites are excreted in human milk. As other sulphonylureas are excreted in human milk and because there is a risk of hypoglycemia in nursing infants, breastfeeding is not recommended. Thus, due to potential risk of neonatal hypoglycemia, K-GEM Tablets are contra-indicated in breastfeeding mothers.

Accordingly, a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the drug therapy to the mother.

Paediatric Patients

The safety and effectiveness of this combination therapy in paediatric patients have not been established. Thus, K-GEM Tablets are not recommended for use in children.

Geriatric Patients

With metformin therapy, elderly patients are at higher risk of having lactic acidosis. With gliclazide, risk of hypoglycemia may be more in the elderly population. In general, dose

selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Moreover, metformin is mainly excreted by renal route. Due to the potential for decreased renal function in elderly subjects, the metformin-containing preparations should be used with caution. Assess renal function more frequently in elderly patients.

Renal Impairment Patients

Caution should be exercised while administration of gliclazide with metformin combination therapy in patients with renal dysfunction. The metabolism and excretion of sulphonylureas including gliclazide may be decreased in patients with impaired renal function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted. In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased. Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Thus, K-GEM Tablets are contraindicated in severe renal impairment patients with an estimated glomerular filtration rate (eGFR) below 30 ml/minute/1.73 m^2. Drug therapy should be discontinued immediately if evidence of renal impairment is present. Before initiation of drug therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Hepatic Impairment Patients

K-GEM Tablets are not recommended in patients with hepatic impairment. The metabolism and excretion of sulphonylureas, including gliclazide, may be reduced in patients with impaired hepatic function. Use of metformin-containing preparations in patients with hepatic impairment has been associated with some cases of lactic acidosis. Thus, K-GEM Tablets are contraindicated in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

All sulphonylurea class of drugs, including gliclazide, can cause hypoglycemia as an adverse drug reaction. Severe hypoglycemia can lead to unconsciousness or convulsions and impairment of brain function. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycemia and visual impairment. These impairments may present a risk in situations where these abilities are especially important, such as driving a vehicle or operating machinery. Patients should be advised to take precautions to avoid hypoglycaemia while engaging in activities that require mental alertness. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. Further, if patients feel any symptoms of hypoglycemia, driving or operating machinery should be strictly avoided.

4.8Undesirable Effects

Gliclazide

Hypoglycemia: The most frequent adverse reaction with gliclazide is hypoglycemia. Possible symptoms of hypoglycemia are headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and/or death. In addition, signs of adrenergic counter-regulation may be observed such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia. Usually, symptoms disappear after intake of carbohydrate such as sugar. Experience with other sulphonylureas shows that hypoglycemia can recur even when these measures are initially effective. If a hypoglycemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalization is required.

Gastrointestinal Disturbances: Nausea, dyspepsia, diarrhoea, abdominal pain, vomiting and constipation.

The following adverse effects have been rarely reported:

Skin and Subcutaneous Tissue Disorders: Pruritus, urticaria, maculopapular rashes, rash, angioedema, erythema and bullous reactions such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).

Blood and Lymphatic System Disorders: Anemia, leucopenia, thrombocytopenia and agranulocytosis.

Hepatobiliary Disorders: Elevations of serum bilirubin and hepatic enzymes (AST, ALT, alkaline phosphatase) levels, and exceptionally, hepatitis (isolated reports). Treatment should be discontinued if cholestatic jaundice appears. These symptoms usually disappear after discontinuation of treatment.

Investigations: Occasional elevations of serum creatinine, blood urea nitrogen.

Eye Disorders: Transient visual disturbances may occur due to changes in blood glucose levels, particularly on initiation of treatment.

Adverse Effects of Sulphonylurea Drugs (Class Effect).

The following adverse events have been observed with sulphonylureas: Cases of erythrocytopenia, agranulocytosis, hemolytic anemia, pancytopenia and allergic vasculitis, hyponatremia, elevated liver enzyme levels and even impairment of liver function (e.g., with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases.

Metformin

The most common adverse reactions reported with metformin are nausea, vomiting, diarrhoea, indigestion, abdominal pain, abdominal discomfort, constipation,

dyspepsia/heartburn, flatulence, dizziness, taste disturbance, headache, upper respiratory infection, asthenia, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. Very rarely metformin may cause skin reactions such as erythema, pruritus, urticaria; abnormal liver function test or hepatitis; and lactic acidosis which generally resolve upon metformin discontinuation. Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with post-marketing use of metformin.

4.9Overdose

Gliclazide

An overdose of sulphonylureas may cause hypoglycemia. Moderate symptoms of hypoglycemia without any loss of consciousness or neurological signs, must be corrected by sugar intake, dose adjustment and/or change of diet. Strict monitoring should be continued until the patient is out of danger. Severe hypoglycemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50 ml of concentrated glucose solution (20 to 30 %). This should be followed by continuous infusion of a more dilute glucose solution (10 %). Patients should be monitored closely for blood sugar until the effect of the drug has ceased. Dialysis is of no benefit to patients due to the strong binding of gliclazide to protein.

Metformin

Overdose of metformin hydrochloride has been reported with ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Lactic acidosis is a medical emergency and must be treated in the hospital. Metformin is dialyzable, with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, in case of overdose, hemodialysis may be useful for the removal of metformin.

5. Pharmacological Properties

5.1 Mechanism of Action

Gliclazide

Gliclazide is a sulphonylurea class of oral hypoglycaemic agents. Gliclazide primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Gliclazide regulates insulin secretion by binding to the sulphonylurea receptor in the pancreatic beta cell plasma membrane, leading to closure of the ATP-sensitive potassium channel. Closing the potassium channel induces depolarisation of the beta cell and results in an increased influx of calcium (by opening of calcium channels) into the cell. This leads to insulin release through exocytosis.

Metformin

Metformin is a biguanide class of oral antidiabetic drugs. Metformin produces its antihyperglycemic effect via following 3 mechanisms:

1) Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2) In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3) Delay of intestinal glucose absorption.

5.2Pharmacodynamic Properties

Gliclazide

Gliclazide is an oral antidiabetic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Gliclazide belongs to the sulphonylurea class of insulin secretagogues.

1) Pancreatic Effects

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans of pancreas. Gliclazide shows high affinity, strong selectivity and reversible binding to the β-cell K_{ATP} channels with a low affinity for cardiac and vascular K_{ATP} channels. In type 2 diabetes, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin release is seen in response to stimulation induced by a meal or glucose.

2) Extra-Pancreatic Effects

- Gliclazide has been shown to increase peripheral insulin sensitivity in muscles.
- Gliclazide potentiates insulin action on muscle glycogen synthase. These effects are consistent with a post-transcriptional action of gliclazide on GLUT4 (glucose transporters 4).
- Gliclazide decreases hepatic glucose production, leading to an improvement in fasting blood glucose levels.

3) Hemovascular Effects.

- Partial inhibition of platelet aggregation and adhesion with a decrease in markers of platelet activation (beta-thromboglobulin, thromboxane B2).
- Increased vascular endothelial fibrinolytic activity (increased tPA activity).
- Anti-oxidant properties, notably a reduction in plasma lipid peroxides and increased erythrocyte superoxide dismutase activity.
- Inhibition of the increased adhesiveness of type 2 diabetic patient's monocytes to endothelial cells *in vitro*.

The anti-oxidant, platelet inhibiting and fibrinolytic actions of gliclazide involve processes which have been implicated in the pathogenesis of vascular complications of type 2 diabetes. There is no clinical evidence that the hemovascular effects of gliclazide are of therapeutic benefit in type 2 diabetes patients.

Metformin

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In clinical studies, the major non-glycemic effect of metformin is either weight neutral or modest weight loss.

5.3Pharmacokinetic Properties

Gliclazide

Absorption: Gliclazide is absorbed in the gastrointestinal tract reaching peak serum concentrations within 4 to 6 hours. Single dose studies have demonstrated that maximal decrease in blood glucose levels (23% of an 80 mg dose; 30% of a 160 mg dose) occur approximately 5 hours after drug administration; nine hours after a dose of 160 mg, a reduction of 20% was still observed. The half-life of gliclazide is approximately 12 hours.

Distribution: Gliclazide is distributed to the extracellular fluid. The apparent volume of distribution of gliclazide is low (20 to 40%), which reflects the high degree of protein binding (94.2%).

Metabolism: Gliclazide is extensively metabolised in the liver. At least eight metabolites (three major) of gliclazide have been known and some of these are glucuronic acid conjugates. These metabolites are devoid of significant hypoglycemic activity.

Excretion: Approximately 70% of the administered dose appears to be excreted in the urine and 11% in the faeces. The urinary excretion of the drug is slow and the maximum rates do not occur until 7 to 10 hours after initial administration.

Metformin

Absorption: The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50 to 60%. Food decreases the extent of and slightly delays the absorption of metformin.

Distribution: The apparent volume of distribution of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 liters. Metformin is negligibly bound to plasma proteins.

At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 µg/ml.

Metabolism: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. No metabolites have been identified in humans.

Excretion: Renal clearance of metformin is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2

hours.

6. Nonclinical Properties

6.1 Animal Toxicology

Gliclazide

Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done. No teratogenic changes have been shown in animal studies, but lower foetal body weight was observed in animals receiving doses 9.4 fold higher than the maximum recommended dose in humans. Fertility and reproductive performance were unaffected after gliclazide administration in animal studies.

Metformin

Carcinogenesis: Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis: There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility: Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.

Teratogenicity: Metformin hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively.

7. Description

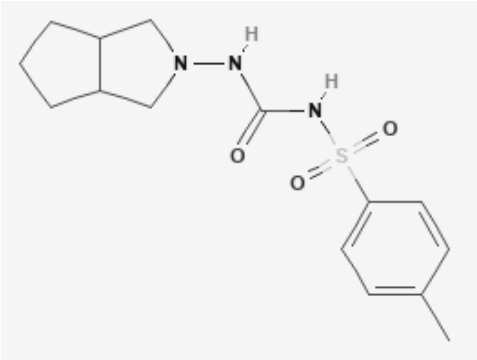
K-GEM Tablets are White coloured capsules shaped uncoated tablet with breakline on one side & plain on other sides.

Each tablet of K-GEM contains 80 mg of gliclazide and 500 mg of metformin hydrochloride for oral administration in adults.

Gliclazide

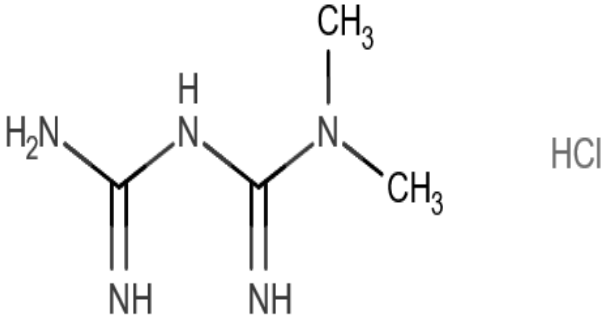
Gliclazide is a sulphonylurea class of oral hypoglycemic agent.

Gliclazide is a crystalline white or almost white powder which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and slightly soluble in ethanol.
Molecular Weight: 323.4 g/mol.
Molecular Formula: C15H21N3O3S.
Chemical Name: 1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-(4-methylphenyl) sulphonylurea .
Structural Formula:



Metformin Hydrochloride

Metformin hydrochloride is the hydrochloride salt of the biguanide metformin with antihyperglycemic effect.
Metformin hydrochloride is white powder which is freely soluble in water and slightly soluble in alcohol.
Molecular Weight: 165.62 g/mol.
Molecular Formula: C4H12ClN5.
Chemical Name: 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of K-GEM Tablet contain : Lactose Maize Starch, Dibasic Calcium Phosphate, Gelatin, Methyl Paraben, Propyl Paraben, Croscarmellose Sodium, Isopropyl Alcohol, Polyvinyl Pyrrolidone K-30, Talcum, Magnesium Stearate Colloidal Silicon Dioxide, Sodium Starch Glycolate & Microcrystalline Cellulose.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

Blister of 15 tablets.

8.4Storage and Handling Instructions

Store protected from light and moisture.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Pregnant women and breastfeeding mothers should strictly avoid use of this medicine.
- Instruct patients not to take this medicine if they have liver and/or kidney dysfunction.
- Advise patients not to take this medicine if they have a severe infection or if they are seriously dehydrated.
- Patients are advised not to take this medicine for type 1 diabetes or for the treatment of diabetic ketoacidosis.
- This medicine is not advisable for use in children.
- Instruct patients not to take this medicine if they are going to have a contrast x-ray.
- Advise patients not to drink alcohol excessively while on this drug therapy.
- Inform patients about the potential side effects of this medicine (as it contains gliclazide) including hypoglycemia (low blood sugar level) and weight gain. Explain the symptoms of hypoglycemia (dizziness, sweating, hunger, fast heartbeat, inability to concentrate, confusion, anxiety or nervousness, headache) and treatment (sugar, glucose biscuits, corn syrup, honey, fruit juice, candies/chocolates) as well as conditions that predispose to hypoglycemia.
- Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. Thus, patients are advised not to drive or operate machinery if they feel any hypoglycemic symptoms.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A Subsidary of Akums Drugs & Pharmaceuticals Ltd.) Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur, Haridwar – 249403, Uttarakhand, India.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 31/UA/2013, Date of FDA Product Permission: 03/06/2020

12. Date of Revision

May 2021.

Marketed by:

EXCEL BLUE CROSS || EXCEL

Division of

BLUE CROSS LABORATORIES PVT LTD.

A-12, M.I.D.C., NASHIK-422 010.

Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.