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

Metformin Hydrochloride Sustained release 500mg, Voglibose 0.2mg and Glimepiride 1/2mg Tablets

(Brand Name: K-GLIM®-Trio 1 mg Tablets / K-GLIM®-Trio 2 mg Tablets)

2. Qualitative and Quantitative Composition

K-GLIM-Trio 1mg Tablets

Each uncoated bilayered tablet contains:
Metformin Hydrochloride IP ……..……. 500 mg.
(In sustained release form)
Voglibose IP …… 0.2 mg.
Glimepiride IP …….…….....…… 1 mg.
Excipients ……. q.s.
Colours: Lake of Brilliant Blue and Lake of Erythrosine.

K-GLIM-Trio 2mg Tablets

Each uncoated bilayered tablet contains:
Metformin Hydrochloride IP ……..……. 500 mg.
(In sustained release form)
Voglibose IP …… 0.2 mg.
Glimepiride IP …….…….....…… 2 mg.
Excipients …….…… q.s.
Colours: Ferric Oxide Red and Lake of Brilliant Blue.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Metformin hydrochloride (in sustained release – SR form) 500 mg / 500 mg, voglibose 0.2 mg / 0.2 mg and glimepiride 1 mg / 2 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

K-GLIM-Trio Tablets are indicated for the treatment of type 2 diabetes in adults when diet, exercise, and combination therapy with two drugs do not result in adequate glycemic control. This combination therapy decreases hyperglycemia including post-prandial hyperglycemia and reduces and/or delays complications associated with it.

4.2Posology and Method of Administration

For oral administration in adults.

The recommended dose is one tablet of K-GLIM-Trio 1 (metformin sustained release - SR 500mg/voglibose 0.2mg/glimepiride 1mg) to be administered once daily. After a 2 to 4 week interval, dosage requirement should be assessed based on glycemic control. If good glycemic control is achieved, continue the same dose as a maintenance therapy.

If glycemic control is not achieved with K-GLIM-Trio 1 Tablets, switch to higher dosage strength. In this case, 1 tablet of K-GLIM-Trio 2 (metformin SR 500mg/voglibose 0.2mg/glimepiride 2mg) to be administered once daily. If glycemic control is optimum, continue the dose as maintenance therapy.

Usually, therapy to be initiated with one tablet once daily and gradually, if required, dosage may be titrated to 1 tablet twice daily after assessment of therapeutic response.

If effect is not satisfactory, consider a change to more appropriate treatment (higher doses of individual components may be given separately or addition of other anti-diabetic drugs and/or insulin should be considered). Dosage should be individualized on the basis of both efficacy and tolerance. If higher doses are required, dosage of individual components should not exceed the maximum daily dose.

- Maximum recommended dose of metformin: 2000 mg/day in divided doses.
- Maximum recommended dose of voglibose: 1.8 mg/day in 3 divided doses.
- Maximum recommended dose of glimepiride: 8 mg/day.

Tablets should be strictly administered with breakfast or with the first main meal of the day to avoid the risk of hypoglycemia in diabetic patients. Swallow the tablets whole and never crush, cut or chew.

Or, as prescribed by the physician.

4.3Contraindications

K-GLIM-Trio Tablets are contraindicated in the following:

- In patients with known hypersensitivity to metformin or to voglibose or to glimepiride (sulfonamide derivatives) or to any component of the formulation.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Type 1 diabetes mellitus.
- Lactation.
- Severe renal impairment.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Gastrointestinal obstruction or patients predisposed to it.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, and shock.
- Acute conditions with the potential to alter renal function such as dehydration, trauma, surgery, severe infection, shock, intravascular administration of iodinated contrast agents.

4.4Special Warnings and Precautions for Use

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. Assess renal function more frequently in elderly 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. Warn patients against excessive alcohol intake while receiving 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 prerenal 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 by the kidney, creatinine clearance 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 anaesthesia. 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 B12 Deficiency: Long-term use of metformin may decrease absorption of vitamin B12 with resultant decrease in plasma B12 levels. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia, but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. It is recommended to measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on metformin therapy.

Other Precautions: The usual laboratory tests for diabetes monitoring should be performed regularly. Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetic drugs.

Voglibose

Glycemic Control: In patients who are being managed with lifestyle modifications (diet and/or exercise), voglibose must be given only when the 2-hour post-prandial blood glucose levels are > 200 mg/dl. During administration of voglibose, disease progression should be closely observed with monitoring of blood glucose levels at regular intervals. If the effect on post-prandial glucose levels is not satisfactory even after the administration of voglibose for 2 to 3 months (post-prandial glucose >200 mg/dl), consider a change to more appropriate treatment.

When patients with diabetes are exposed to unusual stress(es) such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. In this case, it may be necessary to administer insulin therapy for certain period of time.

Voglibose should be administered with caution in the following category of patients:

- Patients with history of laparotomy or ileus.
- Patients with chronic intestinal disease accompanied by disturbance in digestion and absorption.
- Patients with aggravating symptoms due to increased generation of intestinal gas (e.g., Roemheld syndrome, severe hernia, stenosis, and ulcer of the large intestine).

Glimepiride

Hypoglycemia: All sulfonylureas, including glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing glimepiride doses in patients who may be predisposed to

hypoglycemia (e.g., the elderly, patients with renal impairment, and patients on other anti-diabetic medications). Debilitated or malnourished patients and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions: There have been post marketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson syndrome. If a hypersensitivity reaction is suspected, promptly discontinue the therapy, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia: Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Use with caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also post-marketing reports of hemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency.

Increased Risk of Cardiovascular Mortality with Sulfonylureas: The administration of oral hypoglycemic drugs (tolbutamide 1.5 grams per day) has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Monitoring of Glycemic Control: Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. In addition, determination of levels of glycosylated hemoglobin (HbA1c) is also recommended.

Others: Regular hepatic and hematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride.

Glimepiride should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

In stressful-situations (e.g., accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.

4.5Drug Interactions

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., sulfonylurea) 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.

Combinations Requiring Precautions for Use:

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, 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), beta 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.

<u>Voglibose</u>

Anti-Diabetic Drugs: When voglibose is used in combination with derivative(s) of sulfonylamide, sulfonylurea or biguanide, or with insulin, hypoglycemic symptoms may occur. Therefore, when used in combination with any of these drugs, care should be taken, such as to initiate therapy with lower dosage.

Drugs Affecting Glycemic Control: When voglibose is administered concomitantly with drugs that enhance or diminish the hypoglycemic action of antidiabetic drugs, caution should be taken as this might additionally delay the action of voglibose on the absorption of carbohydrates. Examples of drugs enhancing the hypoglycemic action of antidiabetic drugs include alpha-blockers, salicylic acid preparations, monoamine oxidase inhibitors, and fibrate

derivatives. Examples of drugs diminishing the hypoglycemic action of antidiabetic drugs include epinephrine, adrenocortical hormone, and thyroid hormone.

Warfarin: Voglibose does not affect the pharmacokinetics of warfarin; hence, it can be safely administered along with warfarin.

Glimepiride

Cytochrome P450 2C9 Interactions: Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9) enzyme. Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole). If glimepiride is given simultaneously with those drugs metabolized by cytochrome P4502C9, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. Results from an *in-vivo* interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Drugs Affecting Glucose Metabolism: A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

1. **Drugs which increases glucose-lowering effect of glimepiride:** The following are examples of drugs that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia:

   Oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase (MAO) inhibitors. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for hypoglycemia.
2. **Drugs which decreases glucose-lowering effect of glimepiride:** The following are examples of drugs that may reduce the glucose-lowering effect of sulfonylureas including glimepiride, leading to worsening glycemic control:

   Danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for worsening of glycemic control.
3. **Sympatholytic drugs:** Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glucose-lowering effects of glimepiride. The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

4. **Alcohol:** Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion.

Anticoagulants: Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
Miconazole: A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported.
Colesevelam: Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction has been observed when glimepiride administered at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.6Use in Special Populations

Pregnant Women

Metformin: Pregnancy Category B; Voglibose: Pregnancy Category B; Glimepiride: Pregnancy Category C. There are no adequate and well-controlled studies of this combination therapy in pregnant women. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. The safety of voglibose in pregnancy has not been established. Animal studies with voglibose do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or post-natal development. Voglibose and glimepiride can be given to pregnant women only when the potential benefits to the mother outweigh the possible hazards to the fetus. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers receiving a sulfonylurea at the time of delivery. Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality. Thus, when a 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 to reduce the risk of malformations of the fetus.

Lactating Women

Metformin is excreted into human breast milk. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Animal studies (e.g., rats) have revealed a suppressive action of voglibose on body weight increase in newborns probably due to suppression of milk production due to reduced carbohydrate absorption. Although the quantity of voglibose reached in human milk is exceedingly low, voglibose should not be administered to lactating women. It is not known whether glimepiride is excreted in human milk. However, glimepiride is excreted in rat milk. Other sulfonylureas are excreted in human milk and there is a risk of hypoglycaemia in nursing infants. Thus, breastfeeding is strictly avoided during treatment with this combination therapy. Accordingly, a decision should be made whether to discontinue nursing or discontinue therapy, taking into account the importance of these drugs to the mother.

Paediatric Patients
K-GLIM-Trio Tablets are not recommended for use in children as safety and efficacy of this formulation has not been established in this population.

Geriatric Patients
With metformin, elderly patients are at higher risk of having lactic acidosis. Both, glimepiride and metformin are known to be substantially excreted by the kidney. Thus, risk of serious adverse reactions to these drugs is greater in elderly patients with impaired renal function. Generally, elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the elderly. Thus, K-GLIM-Trio Tablets should only be used in elderly patients with normal renal and hepatic function. It is desirable to initiate therapy with lower dosage strength and assess the renal function more frequently. It is recommended to administer drug therapy under close observation, with careful attention to the blood sugar level and the onset of gastrointestinal symptoms.

Renal Impairment Patients
Both, glimepiride and metformin are significantly excreted by renal route. Thus, caution should be exercised during administration of this combination product in patients with renal dysfunction. K-GLIM-Trio Tablets are contraindicated in severe renal impairment patients with an estimated glomerular filtration rate (eGFR) below 30 ml/minute/1.73 m^2.
The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin-containing preparations. Before initiation of metformin-containing therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently. Voglibose is poorly absorbed after oral dose and renal excretion is negligible. Clinical studies have demonstrated that elimination of the two major metabolites of glimepiride is reduced in patients with renal impairment. The recommended starting dose of glimepiride is 1 mg daily in diabetic patients with renal impairment. K-GLIM-Trio Tablets should be discontinued, if evidence of renal impairment is present (eGFR < 30 ml/minute/1.73 m^2).

Hepatic Impairment Patients
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Also, hepatic impairment patients are particularly susceptible to the hypoglycemic action of glimepiride. Thus, K-GLIM-Trio Tablets are not recommended in patients with hepatic impairment. In patients with severe renal or hepatic impairment, insulin is indicated.

4.7Effect on Ability to Drive and Use Machines
Metformin and voglibose has no or negligible influence on the ability to drive and use machines. Sulfonylurea class of drugs, including glimepiride, 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

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.

Voglibose

Gastrointestinal: Gastrointestinal adverse events such as diarrhoea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting, or heartburn may occur with the use of voglibose. Also, abdominal distention, increased flatus, and intestinal obstruction like symptoms due to an increase in intestinal gas may occur with use of voglibose.
Hypersensitivity: Rash and pruritus may rarely occur. In such cases, voglibose should be discontinued immediately.
Hepatic: When voglibose is administered to patients with liver cirrhosis, hyperammonia may worsen with the development of constipation followed by disturbance of consciousness.
Laboratory Tests: Elevation of SGOT (serum glutamate oxaloacetate), SGPT (serum glutamate pyruvate transaminase), LDH (lactate dehydrogenase), alpha-GPT (alpha-glutamate pyruvate transaminase) or alkaline phosphatase may infrequently occur.
Hypoglycemia: When voglibose is used in combination with other antidiabetic drugs, hypoglycemia may occur (0.1% to <5%).
Psychoneurologic: Headache may rarely occur.
Hematologic: Anemia, thrombocytopenia, and leucopenia may rarely occur.
Others: Numbness, edema of face, blurred vision, hot flushes, malaise, weakness, hyperkalemia, increased serum amylase, decreased HDL-cholesterol, diaphoresis, or alopecia may occur rarely with the use of voglibose.

Glimepiride

Clinical Trials Experience

The most commonly reported adverse reactions of glimepiride include hypoglycemia, dizziness, asthenia, headache, nausea, accidental injury, and flu-like syndrome.

Hypoglycemia: In a randomized, double-blind, placebo-controlled, 14 week clinical trial, the overall incidence of possible hypoglycemia is 4% for glimepiride 1 mg and 17% for glimepiride 4 mg. The overall incidence of possible hypoglycemia for glimepiride vs. placebo is 19.7% vs. 3.2%.

Weight Gain: Glimepiride, like all sulfonylureas, can cause weight gain.

Allergic Reactions: Allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions have been reported rarely with glimepiride.

Laboratory Tests: Elevated levels of serum Alanine Aminotransferase (ALT) has been reported with glimepiride.

Post-Marketing Experience

The following adverse reactions have been reported during post-approval use of glimepiride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome.
- Hemolytic anemia in patients with and without G6PD deficiency.
- Impairment of liver function (e.g., with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.
- Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis.
- Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and pancytopenia.
- Hepatic porphyria reactions and disulfiram-like reactions.
- Hyponatremia and syndrome of inappropriate antidiuretic hormone (ADH) secretion, most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of ADH.
- Dysgeusia.
- Alopecia.

4.9 Overdose

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 hospital. Metformin is dialyzable, with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of the accumulated drug from patients in whom metformin overdose is suspected.

Voglibose

Voglibose is unlikely to produce hypoglycemia in overdose, but abdominal discomfort and diarrhoea may occur. If overdose occurs, supportive and symptomatic treatment should be provided.

Glimepiride

An overdose of glimepiride can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

5. Pharmacological Properties

5.1 Mechanism of Action

Metformin

Metformin is a biguanide class of oral antidiabetic drugs. Metformin produces its antihyperglycemic effects 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.

Voglibose

Voglibose competitively and reversibly inhibits the alpha glucosidase enzymes (e.g., glucoamylase, sucrase, maltase, and isomaltase) in the brush border of the small intestine.

Alpha-glucosidase enzymes are essential for hydrolysis/decomposition of complex carbohydrates (starch, dextrin, polysaccharides, and disaccharides) into simpler carbohydrates (such as glucose/dextrose or fructose). Inhibition of these enzymes leads to delay in the absorption of glucose into the bloodstream resulting in improvement of post-prandial hyperglycemia.

Glimepiride

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Glimepiride regulates insulin secretion by binding to the sulfonylurea 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.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel, but which is different from the usual sulfonylurea binding site.

5.2Pharmacodynamic Properties

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.

Voglibose

Voglibose exerts its activity in the intestinal tract. Alpha glucosidase enzyme normally converts complex carbohydrates into simple monosaccharides (glucose) which can be absorbed through the intestine.

The action of voglibose depends on an inhibition of intestinal enzymes (alpha-glucosidase) involved in the degradation of ingested disaccharides, oligosaccharides, and polysaccharides into monosaccharides. Inhibition of these enzyme systems reduces/delays the rate of digestion of complex carbohydrates. As there is delay in digestion of complex carbohydrates, monosaccharides releases slowly and hence absorbed more slowly into the blood i.e., less glucose absorption from intestine into the blood circulation. Voglibose, thus dose dependently reduces the postprandial rise in blood glucose level.

Although voglibose reduces the impact of complex carbohydrates on blood sugar level, it does not affect/inhibit absorption of glucose from the intestine.

Alpha-glucosidase inhibitors such as voglibose do not stimulate insulin release and therefore do not result in hypoglycemia. Voglibose improves post-prandial hyperglycemia and thereby lowers abnormally high levels of glycosylated hemoglobin. Voglibose is highly useful in elderly patients or in patients with predominantly post-prandial hyperglycemia.

Glimepiride

Glimepiride is an orally active hypoglycemic agent which belongs to the sulphonylurea class. Glimepiride is used in the management of non-insulin dependent (type 2) diabetes mellitus. The effect of glimepiride is dose-dependent and reproducible. In diabetic patients, optimum glycemic control over 24 hours can be achieved with a single daily dose of glimepiride.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. This effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects.

Extrapancreatic Activity: The extrapancreatic effects are an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver. The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins (called GLUT) located in the cell membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride rapidly increases the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

5.3Pharmacokinetic Properties

Metformin Sustained Release

Absorption: After an oral dose of the sustained release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours). The AUC after a single oral administration of 2000 mg of metformin sustained release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets twice daily. The extent of absorption (as measured by AUC) of metformin (in sustained release form) increases when given with food. There was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin in sustained release form.

Distribution: Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ranged between 63 to 276 liters.

Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been detected in humans.

Excretion: Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus, the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Voglibose

Absorption: Voglibose is poorly absorbed after oral doses. Plasma concentrations after oral doses have usually been undetectable. Following repeated administration to healthy subjects (n=6) in a single dose of 0.2 mg, 3 times a day, for 7 consecutive days, voglibose was not detected in plasma or urine. Similarly, when voglibose was administered to healthy male adults (n=10) as a single dose of 2 mg, voglibose was not detected in plasma or urine.

Distribution: After ingestion of voglibose, the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity.

Metabolism: Voglibose is metabolized by intestinal enzymes and by the microbial flora.

Excretion: Voglibose is mainly excreted in the feces.

Glimepiride

Absorption: The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum plasma concentration (C_{max}) is reached approximately 2.5 hours after oral intake and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approximately 8.8 litres), high protein binding (>99%), and a low clearance (approximately 48 ml/min).

Metabolism: Glimepiride is completely metabolized by oxidative biotransformation after oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (CHMD) and the carboxyl derivative. Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to CHMD. CHMD is further metabolized to carboxyl derivative (inactive) by one or several cytosolic enzymes.

Excretion: Mean serum half-life of glimepiride is about 5 to 8 hours. After high doses, half-lives are slightly longer. After oral administration of glimepiride, about 58% is excreted in the urine and 35% in the faeces. No parent/unchanged drug has been detected in the urine or feces. Two metabolites are identified both in urine and faeces (i.e., CHMD and carboxyl derivative). The elimination half-lives of these metabolites are 3 to 6 and 5 to 6 hours, respectively.

6. Nonclinical Properties

6.1 Animal Toxicology

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.

Voglibose

No animal studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development have been conducted with voglibose.

Glimepiride

Carcinogenesis: Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface

area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation. No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.
Mutagenesis: Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).
Impairment of Fertility: There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (> 1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

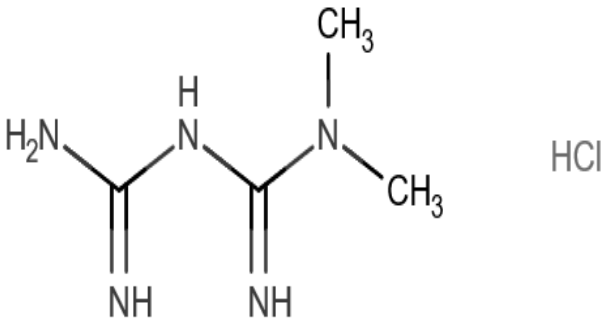
7. Description

K-GLIM-Trio 1mg Tablets are capsule shaped, uncoated bilayered, biconvex, bevelled edged Tablets plain on both the sides with one layer white to off-white (Metformin Hydrochloride SR layer) in colour and other is blue (Voglibose and Glimepiride layer) in colour.
K-GLIM-Trio 2mg Tablets are capsule shaped, uncoated bilayered, biconvex, bevelled edged Tablets plain on both the sides with one layer white to off-white (Metformin Hydrochloride SR layer) in colour and other is grey (Voglibose and Glimepiride layer) in colour.

Each tablet of K-GLIM-Trio 1 contains 500 mg of metformin hydrochloride (in a sustained release form), 0.2 mg of voglibose, and 1 mg of glimepiride for oral administration in adults.
Each tablet of K-GLIM-Trio 2 contains 500 mg of metformin hydrochloride (in a sustained release form), 0.2 mg of voglibose, and 2 mg of glimepiride for oral administration in adults.

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:



Voglibose

Voglibose is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in people with diabetes mellitus.

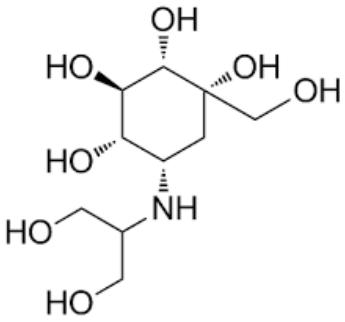
Voglibose is available in the form of white powder.

Molecular Weight: 267.28 g/mol.

Molecular Formula: C10H21NO7.

Chemical Name: (1S,2S,3R,4S,5S)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol.

Structural Formula:



Glimepiride

Glimepiride is a long-acting sulfonylurea class of oral antidiabetic agent.

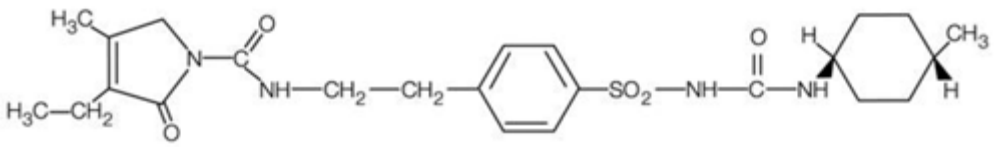
Glimepiride is a white to yellowish-white, crystalline, odorless powder.

Molecular Weight: 490.6 g/mol.

Molecular Formula: C24H34N4O5S.

Chemical Name: 4-ethyl-3-methyl-N-[2-[4-[(4-methylcyclohexyl) carbamoylsulfamoyl] phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide.

Structural Formula:



8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 25°C.
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.
- Patients should be instructed to avoid use of this medicine during severe infection, if they are seriously dehydrated, before and after surgery or in case of serious trauma.
- 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 glimepiride) 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

Inventia Healthcare Limited,
F1-F1-/1, Additional Ambernath M.I.D.C.
Ambernath (East) – 421 506, Dist. Thane.

11. Details of Permission or License Number with Date

Manufacturing License No.: KD/638. Date of Product Permission: 16/02/2016.

12. Date of Revision

April 2021.

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