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

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

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Glimepiride IP …… 1 mg.
Excipients …… q.s.

Each uncoated tablet contains:
Glimepiride IP …… 2 mg.
Excipients …… q.s.
Colours: Yellow Oxide of Iron.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Glimepiride 1 mg and 2 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

K-GLIM Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
K-GLIM Tablets may be used alone, or in combination with other antidiabetic drugs.

4.2Posology and Method of Administration

For oral administration.
Adults: The recommended starting dose of glimepiride is 1 or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should start with dose of 1 mg once daily. If good glycemic control is achieved with this dose, continue the dose as a maintenance therapy.
If glycemic control is unsatisfactory, the dose should be increased in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3 or 4 mg of glimepiride per day.
Maximum recommended dose of glimepiride is 8 mg per day.

K-GLIM Tablets should be strictly administered with breakfast or the first main meal of the day to avoid the risk of hypoglycemia in diabetic patients.
Or, as prescribed by the physician.

4.3Contraindications

K-GLIM Tablets are contraindicated in patients with the following conditions:

- Hypersensitivity to glimepiride/other sulfonylureas or to sulfonamide derivatives or to any component of the formulation.
- Insulin dependent (type 1) diabetes mellitus, diabetic coma, ketoacidosis.
- Severe renal or hepatic disorders (in case of severe renal or hepatic function disorders, a changeover to insulin is required).

4.4Special Warnings and Precautions for Use

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 the proportion of glycosylated hemoglobin (HbA1c) is 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 stress-situations (e.g., accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.

4.5Drug Interactions

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.

I. **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.

II. **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.

III. **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.

IV. **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

Pregnancy Category C. There are no adequate and well-controlled studies of glimepiride in pregnant women. Glimepiride should be used during pregnancy only if the potential benefit justifies the potential risk 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. 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 avoid the teratogenic risk.

Lactating Women

It is not known whether glimepiride is excreted in human milk. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breastfeeding is not recommended during treatment with glimepiride.

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

Paediatric Patients

There are no data available on the use of glimepiride in patients below 8 years of age. For children aged between 8 to 17 years, available data on safety and efficacy are insufficient. Glimepiride is not recommended in paediatric patients because of its adverse effects on body weight and hypoglycemia. K-GLIM Tablets are not recommended for use in children.

Geriatric Patients

No overall differences in safety or effectiveness have been observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No adjustment of dosage is generally required in elderly people with normal renal function. Glimepiride is substantially excreted by the kidney. Elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the elderly. Thus, caution should be exercised while initiating and increasing the dose of glimepiride in elderly population.

Renal Impairment Patients

Glimepiride is significantly excreted by renal route. Clinical studies have demonstrated that elimination of the two major metabolites of glimepiride is reduced in patients with renal impairment. To minimize the risk of hypoglycemia, the recommended starting dose of glimepiride is 1 mg daily for all type 2 diabetes patients with renal impairment.

4.7Effect on Ability to Drive and Use Machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycemia and visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia.

4.8Undesirable Effects

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.

4.9Overdose
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
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

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

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

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 1 mg Tablets are off-white, round, flat beveled, uncoated tablets with breakline on one side and plain on the other side.

K-GLIM 2 mg Tablets are light yellow coloured, round, flat beveled, uncoated tablets with breakline on one side and plain on the other side.

Each tablet of K-GLIM 1 mg contains 1 mg of glimepiride while each tablet of K-GLIM 2 mg contains 2 mg of glimepiride for oral administration in adults.

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

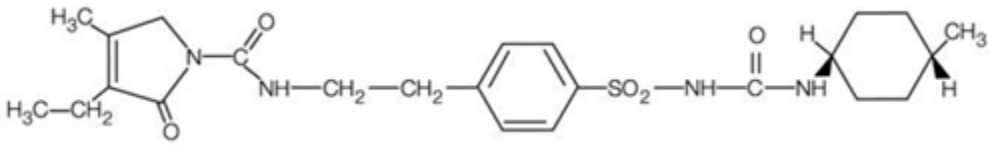
Glimepiride is a white to yellowish-white, crystalline, odorless powder.

Molecular Weight: 490.6 g/mol.

Molecular Formula: $C_{24}H_{34}N_4O_5S$.

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

Structural Formula:



Inactive ingredients (excipients) of K-GLIM 1 mg Tablet contain Lactose, Polyvinyl Pyrrolidone K 30, Microcrystalline Cellulose DC, Isopropyl Alcohol, Methylene Chloride, Sodium Starch Glycollate, and Magnesium Stearate.

Inactive ingredients (excipients) of K-GLIM 2 mg Tablet contain Lactose, Polyvinyl Pyrrolidone K 30, Colour Iron Oxide Yellow, Microcrystalline Cellulose DC, Isopropyl Alcohol, Methylene Chloride, Sodium Starch Glycollate, and Magnesium Stearate.

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 30^{o}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 not take this medicine unless advised by their physician.
- Instruct patients not to take this medicine if they have severe liver and/or kidney dysfunction.
- 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 to take this medicine strictly with breakfast or the first main meal of the day to avoid the risk of hypoglycemia.
- Inform patients about the potential side effects of this medicine 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

BLUE CROSS LABORATORIES PVT LTD.
A-12, MIDC, Ambad, Nashik – 422 010. Maharashtra, India.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : BD/25; Date of FDA Product Permission: 12/05/2004.

12. Date of Revision

April 2021.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.