BETAGLIM
Glimepiride Tablets

DESCRIPTION

BETAGLIM (Glimepiride Tablets) is an oral blood-glucose lowering drug of the sulfonylurea class. Chemically, Glimepiride is 1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4'-methylcyclohexyl)urea.

Betaglim - 1
Mosaic type light pink, oblong, uncoated tablets, scored on one side and plain on the other.

Betaglim - 2
Mosaic type bluish grey, oblong, uncoated tablets, scored on one side and plain on the other.

Betaglim - 3
Mosaic type light orange, oblong, uncoated tablets, scored on one side and plain on the other.

COMPOSITION

BETAGLIM - 1
Each uncoated tablet contains:
Glimepiride ................. 1 mg

BETAGLIM - 2
Each uncoated tablet contains:
Glimepiride ................. 2 mg

BETAGLIM - 3
Each uncoated tablet contains:
Glimepiride ................. 3 mg

CLINICAL PHARMACOLOGY
Glimepiride is a sulphonylurea antihyperglycemic agent that may be given in a single daily dose. It acts by stimulating insulin release from pancreatic beta-cells and possibly also via extrapancreatic mechanisms. The major site of activity of Glimepiride is thought to be membrane receptors on pancreatic beta-cells, where it acts via ATP-regulated potassium (\(K_{ATP}\)) channels, resulting in membrane depolarisation and release of insulin. Glimepiride is also internalised into pancreatic beta-cells, where it associates with secretory granules. This internalisation is thought to reflect insulinotropic mechanisms of Glimepiride other than at potassium channels. Glimepiride
decreases blood glucose and increases blood insulin levels, with maximum effects during the first 4 hours after the dose.¹

PHARMACOKINETICS
Glimepiride is rapidly and completely absorbed after oral administration. Oral bioavailability is approximately 100%. Peak serum concentrations occur 2 - 3 hours after oral administration, are proportional to dose and are similar in healthy volunteers and in patients with Type 2 diabetes. After multiple doses, there is no evidence of accumulation in serum. Meals have only modest effect on fasting pharmacokinetic data. When Glimepiride is administered with meals, the time to reach peak concentrations is delayed by approximately 10%; decrease in both peak concentration and AUC is also about 10%.²

After intravenous (i.v.) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg) and the total body clearance (CL) was 47.8 mL/min. More than 99% of Glimepiride was bound to plasma proteins.²

Glimepiride was completely biotransformed by hepatic oxidative metabolism. The CYP2C9 enzyme transformed Glimepiride to the cyclohexylhydroxymethyl derivative (M1), which is further metabolized to form carboxyl derivative (M2) by cytosolic enzymes. After a single dose, the elimination half-life of Glimepiride was 5 hours and increased to 9 hours after multiple doses. Urinary excretion of metabolites accounted for 60% of the dose; the remainder was found as metabolites in faeces. M1 was the predominant urinary metabolite and M2 was the predominant faecal metabolite.²

SPECIAL POPULATIONS
Comparison of Glimepiride pharmacokinetics in NIDDM patients < 65 years and those > 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in Glimepiride pharmacokinetics between the two age groups.³

No studies were performed in pediatric patients.³

There were no differences between males and females in the pharmacokinetics of Glimepiride when adjustment was made for differences in body weight.³

No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of Glimepiride in patients with NIDDM, the antihyperglycemic effect was comparable in whites (n=536), blacks (n = 63), and Hispanics (n = 63).³

A single-dose, open-label study was conducted in 15 patients with renal impairment. The results showed that Glimepiride serum levels decreased as renal function decreased. The apparent terminal half-life (T₁/₂) for Glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased.⁴ ⁵

No studies have been performed in patients with hepatic insufficiency

There were no important differences in Glimepiride metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine.

The pharmacokinetics of Glimepiride in morbidly obese patients were similar to those in the normal weight group, except for a lower Cmax and AUC.

DRUG INTERACTIONS
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, monoamine oxidase inhibitors, and beta adrenergic blocking agents. Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. Coadministration of aspirin and Glimepiride led to a 34% decrease in the mean Glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean Cmax had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported.
Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4-mg oral dose of Glimepiride did not significantly alter the absorption and disposition of Glimepiride.

Concomitant administration of propranolol (40 mg tid) and Glimepiride significantly increased Cmax, AUC, and t½ of Glimepiride by 23%, 22% and 15% respectively, and it decreased CL/f by 18%.

Concomitant administration of Glimepiride (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg Glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.

INDICATIONS AND USAGE
BETAGLIM is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. BETAGLIM may be used concomitantly with metformin when diet, exercise, and BETAGLIM or metformin alone do not result in adequate glycemic control.

BETAGLIM is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of BETAGLIM and insulin may increase the potential for hypoglycemia.

CONTRAINDICATIONS
Glimepiride is contraindicated in patients with

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

PRECAUTIONS
General
Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia: Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of BETAGLIM. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with BETAGLIM or even use insulin monotherapy.

Information for patients: Patients should be informed of the potential risks and advantages of BETAGLIM and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

ADVERSE REACTIONS
Vomiting, gastrointestinal pain and diarrhoea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas. Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients.

**Hemotologic reactions**

Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and pancytopenia have been reported with sulfonylureas. Hepatic porphyria reactions and disulfiram-like reaction have been reported with sulfonylureas; however, no cases have yet been reported with Glimepiride. Cases of hyponatremia have been reported with Glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone.

Change in accommodation and / or blurred vision may occur with the use of Glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated.

Overdosage of sulfonylureas, including Glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and / or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger.

Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

**DOSAGE AND ADMINISTRATION**

The usual starting dose of BETAGLIM as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully.

No exact dosage relationship exists between BETAGLIM and the other oral hypoglycemic agents. The maximum starting dose of BETAGLIM should not be more than 2 mg.

The usual maintenance dose of BETAGLIM is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dose increase should be made in increments of not more than 2 mg at 1 - 2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA1c levels, for example every 3 to 6 months.

**BETAGLIM - Metformin Combination Therapy**

Patients who do not respond adequately to the maximal dose of BETAGLIM monotherapy, addition of metformin may be considered. Published clinical information exists for the use of other sulfonylureas including glyburide, glipizide, chlorpropamide, and tolbutamide in combination with metformin.

**BETAGLIM - Insulin Combination Therapy**

Combination therapy with BETAGLIM and insulin may also be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of > 150 mg/dL in plasma or serum depending on the patient. The recommended BETAGLIM dose is 8 mg once daily administered with the first main meal. After starting with low dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose.

**Specific Patient Populations**

BETAGLIM is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

**Patients Receiving Other Oral Hypoglycemic Agents**

As with other sulfonylurea hypoglycemic agents, no transition period is necessary when transferring patients to BETAGLIM.

**STORAGE**
Store at a temperature below 30°C, protect from light and moisture.

REFERENCES

3. Campbell RK. Glimepiride: Role of a New Sulphonylurea in the treatment of Type 2 Diabetes Mellitus.