GLIZID - M
Gliclazide and Metformin Hydrochloride Tablets

DESCRIPTION

Glizid-M contains Gliclazide and Metformin Hydrochloride. Gliclazide, chemically is 1-(3-azabicyclo [3.3.0.]Oct - 3-y1) -3-p-tolysulphonylurea. Metformin Hydrochloride is 1,1-dimethyl biguanide hydrochloride. Glizid -M is a white , oblong, biconvex tablet imprinted with "Glizid-M" on one side and scored on the other.

COMPOSITION

Each uncoated tablet contains:

Gliclazide BP 80 mg
Metformin Hydrochloride IP 500 mg

PHARMACOLOGY

Gliclazide reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. This occurs by closure of K+ channels in β -cells of pancreas. Subsequently, Ca2+ channel opens leading to increase in intracellular calcium and induction of insulin release. Gliclazide also increases the sensitivity of β -cells to glucose. Gliclazide restores peripheral insulin sensitivity such as decreasing hepatic glucose production and increasing glucose clearance. It has anti-platelet adhesive activity and reduces level of free radicals, thereby preventing vascular complications. Gliclazide has been reported to reduce plasma cholesterol and triglyceride levels after repeated administration.

Metformin acts as an antihyperglycaemic agent by improving hepatic and peripheral tissue sensitivity to insulin. It also appears to have beneficial effect on serum lipid levels and so on fibrinolytic activity. Metformin therapy is not associated with increase in body weight.

RATIONALITY

Sulfonylureas & biguanides act complementary to each other. Both compounds have an additive antihyperglycaemic effect without increasing the adverse effects of either pharmacological class. Gliclazide acts via stimulating β cells of pancreas to release insulin & also increases peripheral sensitivity of insulin. Metformin acts via enhanced peripheral glucose uptake & utilization. It also reduces hepatic glucose production, thereby metformin diminishes insulin resistance.

There are reports in which combination treatment of sulfonylurea with metformin has been reported to achieve satisfactory glycaemic control for several years. Such combination has been reported to be quite useful in comparative studies where secondary sulfonylurea failure had occured. The combination may therefore provide additional glycaemic control (blood glucose lowering effect by 20%) & thus obviate the need for insulin in some patients.
Gliclazide has less propensity to cause hypoglycaemia and increase in body weight as compared to other sulfonylurea. Since metformin is reported to have predominant peripheral mechanism of action, therefore it lacks the anabolic effects of sulfonylureas and does not cause weight gain. Gliclazide appears to be useful in both macro-vascular & micro-vascular complications, which occurs due to either hyperinsulinaemia, hypertension, hyperglycaemia, hyperlipidaemia, platelet aggregation.

Metformin is associated with a decrease in fasting & postprandial plasma insulin & triglyceride levels, increase in HDL-cholesterol, increase of tissue plasminogen activator, decrease in platelet aggregation.

Pharmacokinetically the two drugs appear to be compatible, as metformin is not plasma protein bound & does not get metabolized in liver. So interaction with gliclazide (having 80-90% plasma protein binding & metabolized via liver) does not appear to be possible. Hence the combination of gliclazide & metformin would help in treatment of NIDDM and probably prevention of its associated macrovascular and microvascular complications.

**PHARMACOKINETICS**

Single oral dose of gliclazide, 40 to 120 mg results in a $C_{\text{max}}$ of 2.2 to 8 mg/l within 2 to 8 hours. Steady state concentrations are achieved after 2 days of administration of 40-120 mg of gliclazide. Administration of gliclazide with food reduces $C_{\text{max}}$ and delays $T_{\text{max}}$. The volume of distribution is low due to extensive protein binding (85-97%). The half life of gliclazide varies from 8.1 - 20.5 hours after single dose administration. Gliclazide is extensively metabolised to 7 metabolites predominantly excreted in the urine, the most abundant being the carboxylic acid derivative; 60-70% of the dose is excreted in the urine and 10-20% in the faeces. Metformin has absolute oral bioavailability of 50-60%. GIT absorption is complete within 6 hrs of ingestion within metformin is rapidly distributed in body after absorption. The renal elimination of metformin is biphasic. 95% of the absorbed metformin is eliminated during primary elimination phase having half-life of 6 hours. Rest of the 5% is eliminated during slow terminal elimination phase with mean half-life of 20 hours. Metformin is not bound to plasma proteins, 40-60% of the dose is recovered as unchanged drug in urine with a further 30% recovered as unchanged drug in faeces.

**INDICATIONS**

Non-insulin dependent diabetes mellitus; diabetes with or without obesity in adults.

**CONTRAINDICATIONS**

Insulin-dependent diabetes mellitus, renal or hepatic failure, alcoholism, NIDDM complicated by severe ketosis and acidosis, diabetic precoma and coma, patients undergoing surgery, after severe trauma or during infections, chronic obstructive pulmonary disease, coronary heart disease, cardiac failure, peripheral vascular disease,pregnancy, known hypersensitivity to any of the ingredients.

**WARNINGS**

Hypoglycaemia may occur if the patient's dietary intake is reduced or after accidental or deliberate overdose or after severe exercise, trauma and stress. Hypoglycaemic symptoms can be reduced by prescribing a diabetic meal plan. Immediate intervention should be done if signs and symptoms of hypoglycaemia occur.

**PRECAUTIONS**

Adjust dose of combination according to blood and urinary glucose levels during the first few months. However, there have been few reports of lactic acidosis in patients of renal or liver disease.

**Usage in pregnancy**

Contraindicated.

**Pediatric use**
Safety and effectiveness in children have not been established.

**DRUG INTERACTIONS**
Diuretics, barbiturates, phenytoin, rifampicin, corticosteroids, estrogens, estroprogestogens and pure progestogens may reduce the glycaemic control. Its hypoglycaemic action may be potentiated by salicylates, phenylbutazone, sulphonamides, beta-blockers, clofibric acid, vitamin K antagonist, allopurinol, theophylline, caffeine and monoamine oxidase inhibitors. Concomitant administration of miconazole, perhexiline or cimetidine with gliclazide may result in hypoglycaemia. Concomitant administration of gliclazide with agents that increase blood glucose levels should not be considered without careful monitoring of blood glucose levels to avoid hyperglycaemia. Acarbose and guar gum has been shown to decrease the oral bioavailability of metformin significantly.

**ADVERSE REACTIONS**

**Gastrointestinal disturbances** - Nausea, diarrhoea, gastric pain, constipation, vomiting, metallic taste in mouth.

**Dermatological effects** - Rash, pruritus, urticaria, erythema and flushing.

**Miscellaneous** - Headache and dizziness.

Gliclazide appears to be associated with a low incidence of hypoglycaemia. Gliclazide may have the potential to produce adverse cardiovascular effects, however gliclazide has been an established agent for the treatment of NIDDM for a number of years without adverse cardiovascular effects. Impaired gastrointestinal absorption of vitamin B12 and folic acid has been associated with long term metformin therapy.

**OVERDOSAGE AND TREATMENT**
Hypoglycaemia may occur in case of an overdosage. In the event of an overdosage, gastric lavage should be performed and correction of hypoglycaemia should be attempted by intravenous administration of hypertonic glucose (10 or 30%) with continued monitoring of the patient's blood glucose levels.

**DOSAGE AND ADMINISTRATION**
1-2 tablets once or twice daily with meals to a maximum of 4 tablets/day.

**STORAGE INSTRUCTIONS**
Store in a cool, dry and dark place.