PRODUCT MONOGRAPH

GLIZID-M

Gliclazide 80mg and Metformin 500mg

Hypoglycemic sulfonylurea - Oral Anti-diabetic Agent

Manufactured By:

Panacea Biotec Limited.

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Date of Preparation:

(24-07-2019)

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GLIZID-M / Semi GLIZID-M

Gliclazide 80mg and Metformin 500mg / Gliclazide 40mg and Metformin 500mg Tablets

Hypoglycemic Sulfonylurea - Oral Anti-Diabetic Agent

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Approved Indications**
Oral	One tablet Glizid-M contains Gliclazide 80 mg and Metformin 500mg	Non insulin Dependent diabetes (type2) in adults
Oral	One tablet Semi Glizid-M contains Gliclazide40 mg and Metformin 500mg	Non insulin Dependent diabetes (type2) in adults

INDICATIONS AND CLINICAL USE

Non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

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 AND PRECAUTIONS

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.

ADVERSE REACTIONS

Side Effects:

Gastrointestinal disturbances: Nausea, diarrhoea, gastric pain, constipation, vomiting, metallic taste in mouth. These reactions are generally dose related and disappear when the dose is reduced.

Dermatological effects: Rash, puritus, urticaria, erythema and flushing.

Miscellaneous: Headache and dizziness. Hypoglycaemia: Gliclazide appears to be associated with a low incidence of hypoglycaemia. Gliclazide may have the potiential to produce adverse cardiovascular effects; however Gliclazide has been established agent for the treatment of type 2 diabetes for a number of years without adverse cardiovascular effects.

DRUG INTERACTIONS

Concomitant administration of angiotensin enzyme inhibitors (captopril, enalapril), other antidiabetic drugs (Insulin, acarbose) beta-blockers, fluconozole, histamine (H) receptor antagonist, monoamine 2 oxidase inhibitors (MAOIs), sulphonamides and nonsteroidal anti-inflamatory agents increases sensitivity to Insulin and potentiation of blood glucose lowering effect and thus ,in some instances, hypoglycaemia may occur . Dosage of the oral antidiabetic agent may need to be reduced. Patients receiving estrogens or oral contraceptives, phenytoin, quinolones should be closely monitored for loss of diabetic control when therapy is instituted or discontinued.

Renal impairment:

The use of Gliclazide and Metformin is contraindicated in patients with renal impairment.

Hepatic impairment:

The use of Gliclazide and Metformin is not recommended in patients with hepatic impairment.

Pregnancy:

Abnormal blood glucose levels during pregnancy are associated with the higher incidence of congenital abnormalities. Most experts suggest Insulin be used to maintain the blood glucose levels as close to normal as possible. The use of Gliclazide and Metformin combination is not recommended for use in pregnancy.

Lactation:

Studies in lactating rats show that Metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted on nursing mothers. It is not known whether Gliclazide or its metabolites are excreted in breast milk. Hence, the use of Gliclazide and Metformin combination is not recommended for use in lactating mothers, and if the diet alone is inadequate for controlling blood glucose, Insulin therapy should be considered.

Paediatric use:

Safety and effectiveness of Gliclazide and Metformin combination in pediatric patients have not been established.

Geriatric use:

Metformin is known to be excreted by the kidneys and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, hence Gliclazide and Metformin should be used only in patients with normal renal function. Because aging is associated with reduced renal function the use of Gliclazide and Metformin combination should be with caution as age increases. Care should be taken in the dose selection and regular renal function be monitored.

DOSAGE AND ADMINISTRATION

Gliclazide and metformin can be taken, one tablet twice a day under medical supervision. One tablet is to be swallowed as a whole with a glass of water or milk, preferably just before meals or during meals. Do not take more Gliclazide and metformin than prescribed; in case you have missed a dose, do not take double the dose to make up for the one you have missed. Accidentally, if you have taken too many tablets and experience the symptoms of low blood sugar (hypoglycemia) e.g., dizziness, lightheadedness, hunger, nervousness, shaky-feeling, drowsiness, confusion, perspiration & palpitations; you should drink/eat something. Hypoglycemia may be potentiated during concomitant treatment with other drugs/other antidiabetic drugs/alcohol.

Overdosage:

Overdosage of sulphonylureas, including Gliclazide, can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as medical emergency, requiring immediate hospitalization.

Lactic acidosis is a rare, but serious, metabolic complication that can occur if Metformin accumulates during treatment due to overdosing. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

ACTION AND CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

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, Ca^{2+} 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 anti hyperglycaemic 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_{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_{max} and delays T_{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.

STORAGE AND STABILITY

Keep out of reach or sight of children and pets.

GLIZID-M/ SEMI GLIZID-M should be stored at temperature below 30^0C, protect from light and moisture.

Medicines should not be disposed of down the drain or in household garbage. Ask your pharmacist how to dispose of medicines no longer

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS: Tablets Oral Administration

COMPOSITION:

GLIZID-M :	**Gliclazide IP**	**80mg**
	Metformin hydrochloride IP	**500mg**
Semi GLIZID-M :	**Gliclazide IP**	**40mg**
	Metformin hydrochloride IP	**500mg**

PACKAGING:

GLIZID-M :	**10 tablet per strip**
Semi GLIZID-M :	**10 tablet per strip**

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

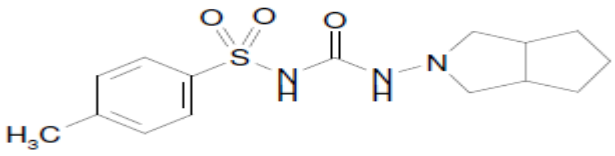
Proper name: Gliclazide

Chemical name: 1-(3-Azabicyclo [3.3.0]-oct-3-yl)-3-(p-tolylsulfonyl) urea

Molecular formula: C15H21N3O3S

Molecular mass: 323.42

Structural formula:



Physicochemical properties: Physical form: white, crystalline powder

Solubility: Practically insoluble in water; freely soluble in dichloromethane; sparingly soluble in acetone.

pKa: 5.8

Partition Coefficient:

pH %	gliclazide in organic phase(water/CHCl3)
0 to 7	almost 100%
8.6	80%
9.0	55%
10.0	12%

Melting Point: Approximately 168°C

PHARMACEUTICAL INFORMATION

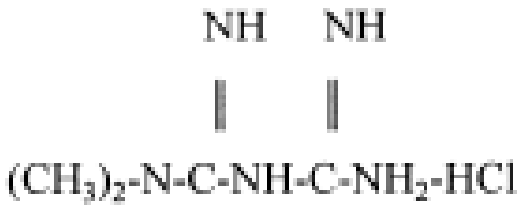
Drug Substance

Proper name: Metformin HCl

Chemical name: N, N-dimethyl biguanide hydrochloride

Molecular formula and molecular mass: 165.6

Structural formula:



Physicochemical properties:

Metformin HCl is a white crystalline powder.

Metformin HCl is soluble in water and in 95% ethyl alcohol.

It is practically insoluble in ether and in chloroform.

Melting Point: 218-220°C.

You should know that the usual signs of low blood sugar level (hypoglycemia) are: anxious feeling, drowsiness, chills, cold sweats, confusion, cool pale skin, difficulty in concentration, excessive hunger, fast heartbeat, headache, nausea, nervousness, shakiness, unsteady walk, unusual tiredness or weakness. If you recognize by some of these signs of the drop in blood sugar, immediately eat or drink something containing sugar and notify your doctor without delay. Good sources of sugar are: orange juice, corn syrup, honey, or sugar cubes or table sugar (dissolved in water).

This product monograph, prepared for health professionals can be found at:

(Panacea Biotec Web site)

or by contacting the Panacea Biotec Limited (INDIA)

(Address for correspondence)

Last revised: 09 September 2014