# PRODUCT MONOGRAPH

**GLIZID-M OD**

Gliclazide SR 60mg and Metformin SR 500mg

**GLIZID-M OD**

Gliclazide SR 30mg and Metformin SR 500mg

**Hypoglycemic sulfonylurea - Oral Anti-diabetic Agent**

**Manufactured By:**

Panacea Biotec Limited.

Malpur, Baddi, Tehshil Nalagarh,

Distt. Solan(H.P) – 173205, India

**Date of Preparation:**

((24-07-2019)

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Gliclazide SR 60mg and Metformin SR 500mg / Gliclazide SR 30mg and Metformin SR 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 OD contains Gliclazide SR 60 mg and Metformin SR 500mg | Non insulin Dependent diabetes (type2) in adults |
| Oral | One tablet Glizid-M OD contains Gliclazide SR 30 mg and Metformin SR 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

Glizid-M OD can be taken, one tablet 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 Glizid-M OD 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**

Gliclazide SR

Absorption

Plasma levels increase progressively during the first 6 hours, reaching a plateau which is maintained from the sixth to the twelfth hour after administration.

Intra-individual variability is low.

Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.

Distribution

Plasma protein binding is approximately 95%. The volume of distribution is around 30 litres. A single daily intake of GLICLAZIDE MR 30 mg maintains effective gliclazide plasma concentrations over 24 hours.

Biotransformation

Gliclazide is mainly metabolised in the liver and excreted in the urine: less than 1% of the unchanged form is found in the urine. No active metabolites have been detected in plasma.

Elimination

The elimination half-life of gliclazide varies between 12 and 20 hours.

Linearity/non-linearity

The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear.

Special popluations

Elderly

No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.

**Metformin**

**Absorption and Bioavailability**

The absolute bioavailability of a Metformin 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin 500 to 1500 mg, and 850 to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 500 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of Metformin SR, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of Metformin, however, the extent of absorption (as measured by AUC) is similar to Metformin.

At steady state, the AUC and Cmax are less than dose proportional for Metformin SR within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from Metformin SR at a 2000 mg once-daily dose is similar to the same total daily dose administered as Metformin tablets 1000 mg twice daily. After repeated administration Of METFORMIN SR, metformin did not accumulate in plasma. Within-subject variability in Cmax and AUC of metformin from Metformin SR is comparable to that with Metformin. Although the extent of metformin absorption (as measured by AUC) from the Metformin SR tablet increased by approximately 50% when given with food, there was no effect of food on Cmax and Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of Metformin SR.

**Distribution**

The apparent volume of distribution (V/F) of metformin following single oral doses of Metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1

μg/mL. During controlled clinical trials of Metformin, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

**Metabolism and Elimination**

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

## STORAGE AND STABILITY

Keep out of reach or sight of children and pets.

GLIZID-M OD should be stored at temperature below $30^0$C, 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 OD:** | **Gliclazide SR** | **60mg** |
| | **Metformin hydrochloride SR** | **500mg** |
| **GLIZID-M OD:** | **Gliclazide SR** | **30mg** |
| | **Metformin hydrochloride SR** | **500mg** |

## PACKAGING:

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

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

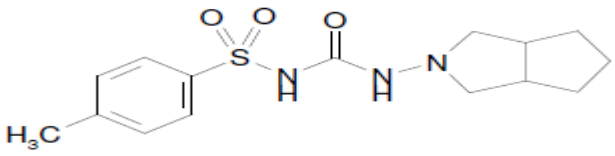
Proper name: Gliclazide

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

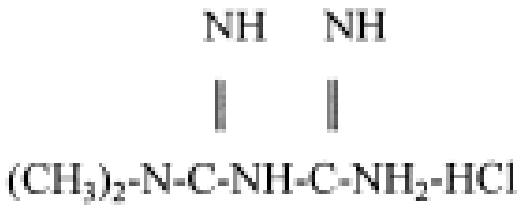
### Drug Substance

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)

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