PRODUCT MONOGRAPH

GLIZID-MV OD

Gliclazide SR 80mg + Metformin ER 500mg + Voglibose 0.2mg

Hypoglycemic sulfonylurea - Oral Anti-diabetic Agent

Manufactured By:

Panacea Biotec Limited.

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GLIZID MV

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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-MV contains Gliclazide 60 mg Metformin ER 500mg and Voglibose 0.2mg	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.

Known hypersensitivity to Metformin hydrochloride, voglibose or another component of this product; renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5mg/dL (males), ≥ 1.4 mg/dL (females) or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse, acute myocardial infarction and septicaemia; acute or chronic metabolic acidosis including diabetic ketoacidosis with or without coma. Metformin and Voglibose should be temporarily discontinued in patients undergoing radiologic studies. Not to be used in patients with severe ketosis or in a state of diabetic coma or precoma, severe infections before or after operation or with severe trauma.

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.

Lactic acidosis is a medical emergency that must be treated in hospital setting. Metformin and Voglibose must be discontinued immediately

and general supportive measures promptly instituted. For patients undergoing basic treatment for diabetes mellitus, voglibose should be given when 2-hr post prandial blood sugar is 200mg/dl or more. For patients on oral hypoglycemic drugs or insulin preparations, in addition to dietary treatment and/or exercise therapy, voglibose is to be given when the fasting blood sugar is about 140mg / dl or more. Closely monitor blood sugar at regular intervals.

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.

No clinical studies establishing conclusive evidence of macrovascular risk reduction with Metformin or any other anti-diabetic drug. Before initiation of Metformin and Voglibose therapy and annually while on Metformin and Voglibose therapy renal function should be assessed and verified as being within normal range. Concomitant medication that may affect renal function or result in significant hemodynamic change or may interfere with disposition of Metformin should be used with caution. Intravascular contrast studies with iodinated material can lead to acute alteration of renal function, hence Metformin should be temporarily discontinued in whom such studies are planned. Drug should be promptly discontinued in case of cardiovascular collapse, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia (may be associated with lactic acidosis). Metformin and Voglibose must be temporarily suspended before surgical intervention. Alcohol potentiates effect of Metformin on lactate metabolism therefore patients should be warned against excessive alcohol intake. Metformin and Voglibose is to be avoided in patients with clinical or laboratory evidence of hepatic disease. Measurement of serum vitamin B12 levels every two to three years is recommended. Patient with Type II diabetes, previously well controlled on Metformin, who develops laboratory abnormality or clinical illness should be promptly evaluated for lactic acidosis or ketoacidosis. Hypoglycemia could occur when caloric intake is deficient or strenuous exercise is not compensated. Withhold Metformin and Voglibose and temporarily

administer insulin in case of temporary loss of glycemic control due to fever, trauma, infection or surgery. Periodic measurements of fasting blood glucose and glycosylated haemoglobin levels are required. Initial and periodic monitoring of hematologic parameters and renal function should be performed on annual basis. Administer carefully in patients receiving other antidiabetic drugs or with a history of laparotomy or ileus or with chronic intestinal disease accompanied by a disturbance in digestion and absorption or with Roemheld's syndrome, severe hernia or stenosis or ulceration of the large intestine or with serious hepatic dysfunction or with serious renal dysfunction

Usage in pregnancy

Contraindicated

ADVERSE REACTIONS

Side Effects:

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

Dermatological effects: Rash, pruritus, 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.

Metformin: Commonly reported adverse events include diarrhoea, nausea, vomiting.

Voglibose: Gastrointestinal adverse effects like diarrhea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting and heartburn, abdominal swelling, increased flatus may occur. Serious hepatic dysfunction accompanied with jaundice, increased AST, ALT may occur. When administered to patients with serious liver cirrhosis, hyperammonemia may worsen with the development of constipation, etc, followed by disturbance of consciousness. Hypoglycemia may occur.

DRUG INTERACTIONS

Concomitant administration of angiotensin enzyme inhibitors (captopril, enalapril), other antidiabetic drugs (Insulin, Voglibose) 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.

When Voglibose is used in combination with derivative(s) of sulfonylamide, sulfonylurea or biguanide, or with insulin, hypoglycemic symptoms may occur. Therefore, when used in combination with any of these drugs, care should be taken, such as starting the administration at a low dose. When Voglibose is administered concomitantly with drugs that enhance or diminish the hypoglycemic action of antidiabetic drugs, caution should be taken as this might additionally delay the action of Voglibose on the absorption of carbohydrates. Examples of drugs enhancing the hypoglycemic action of antidiabetic drugs: ablockers, salicylic acid preparations, monoamine oxidase inhibitors, and fibrate derivatives. Examples of drugs diminishing the hypoglycemic action of antidiabetic drugs: epinephrine, adrenocortical hormone, and thyroid hormone. Voglibose does not affect the pharmacokinetics of warfarin; hence it can be safely administered along with warfarin.

Renal impairment:

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

Hepatic impairment:

The use of Gliclazide, Metformin and Voglibose 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, Metformin and Voglibose 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, Metformin and Voglibose 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, Metformin and Voglibose 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, Metformin and Voglibose

should be used only in patients with normal renal function. Because aging is associated with reduced renal function the use of Gliclazide, Metformin and Voglibose 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 MV can be taken, two tablets 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 MV 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.

Voglibose competitively and reversibly inhibits the a-glucosidase enzymes (glucoamylase, sucrase, maltase, and isomaltase) in the brush

border of the small intestine, which delays the hydrolysis of complex carbohydrates. It is unlikely to produce hypoglycemia in overdose, but abdominal discomfort and diarrhoea may occur.

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.

Voglibose exerts its activity in the intestinal tract. In contrast to sulfonylureas, it has no stimulatory action on the pancreas. The action of Voglibose depends on an inhibition of intestinal enzymes (alpha-glucosidases) involved in the degradation of ingested disaccharides, oligosaccharides, and polysaccharides, but not monosaccharides. Maximal specific inhibitory activity is against sucrase. This leads to, dose dependently, to a delayed digestion of the above carbohydrates. The result is that absorbable monosaccharides (dextrose) originating from carbohydrates are released more slowly and hence more slowly taken

up into blood. Absorption of monosaccharides is not affected. In this way, Voglibose reduces the postprandial rise in blood glucose, the blood-glucose fluctuations in the course of the day become truncated, and the mean blood-glucose level is reduced. Voglibose lowers abnormally high levels of glycosylated haemoglobin.

RATIONALITY

Sulfonylureas, biguanides and Alpha Glucosidase Inhibitor act complementary to each other. All 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. Voglibose depends on an inhibition of intestinal enzymes (alpha-glucosidases) involved in the degradation of ingested disaccharides, oligosaccharides, and polysaccharides, but not monosaccharides.

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. As well as Voglibose delays the glucose absorption from the gut contributing to no 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. Voglibose help in maintaining the Postprandial Hyperglycemia.

Pharmacokinetically the three 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 and voglibose would help in treatment of NIDDM and probably prevention of its associated macrovascular and microvascular complications.

PHARMACOKINETICS

Gliclazide

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 daily intake of Gliclazide maintains effective 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, 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 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 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, Metformin did not accumulate in plasma. Within-subject variability in Cmax and AUC of Metformin from Metformin is comparable to that with METFORMIN. Although the extent of Metformin absorption (as measured by AUC) from the Metformin 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.

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.

Voglibose

Absorption:

Voglibose is poorly absorbed after oral doses. Plasma concentrations after oral doses have usually been undetectable. After an 80 mg dose (substantially higher than recommended dose), peak plasma levels of about 20 ng/mL were observed in 1 to 1.5 hours.

When Voglibose tablets were repeatedly administered to healthy male adults (6 subjects) in a single dose of 0.2 mg, 3 times a day, for 7 consecutive days, Voglibose was not detected in plasma or urine. Similarly, when Voglibose was administered to healthy male adults (10 subjects) as a single dose of 2 mg, Voglibose was not detected in plasma or urine.

Distribution:

After ingestion of Voglibose (and other glucosidase inhibitors), the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity.

Metabolism:

Voglibose is metabolized by intestinal enzymes and by the microbial flora.

Elimination:

Voglibose is excreted in the urine and feces.

STORAGE AND STABILITY

Keep out of reach or sight of children and pets.

GLIZID MV 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 MV:	**Gliclazide**	**80mg**
	Metformin hydrochloride ER	**500mg**
	Voglibose	**0.2mg**

PACKAGING:

GLIZID MV : **10 tablet per strip**

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

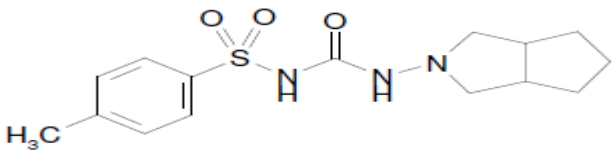
Proper name: Gliclazide

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

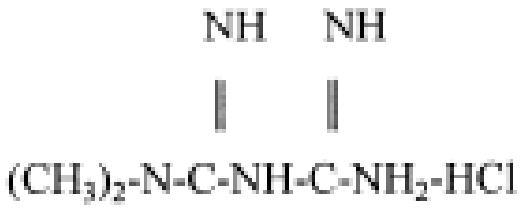
Drug Substance

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.

Drug Substance

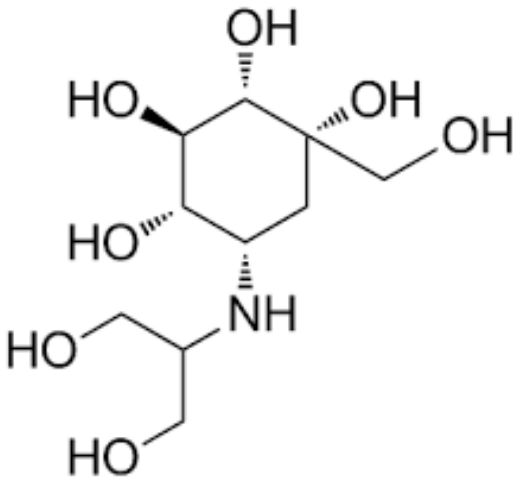
Proper name: Voglibose

Chemical name: 3,4-Dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epiinositol

Molecular formula: C10-H21-N-O7

Molecular mass: 267

Structural formula:



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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