

Diapro[®]

Gliclazide 80 mg Tablet

Description

Diapro[®] is a preparation of Gliclazide, a second generation sulphonylurea, that acts as a hypoglycemic (anti-diabetic) agent. It is used to treat maturity onset diabetes or non-insulin-dependent diabetes mellitus (NIDDM) that is not controlled by diet or exercise alone.

Mode of Action

Gliclazide belongs to the sulphonylurea class of insulin secretagogues, which act by stimulating β cells of the islet of Langerhans in the pancreas to release insulin.

Gliclazide selectively binds to sulphonylurea receptors (SUR-1) on the surface of the pancreatic beta-cells. This binding subsequently blocks the ATP sensitive potassium channels. This decreases the efflux of potassium ion from the cell which leads to the depolarization of the cell. This causes voltage dependent calcium channels to open increasing the influx of calcium ion. The calcium can then bind to and activate calmodulin which in turn leads to exocytosis of insulin vesicles leading to insulin release.

Gliclazide provides cardiovascular protection as it does not bind to sulphonylurea receptors (SUR-2A) in the heart.

Indications

As an adjunct to diet and exercise for the treatment of Non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes that is not controlled by diet or exercise alone.

Dosage and Administration

Diapro[®] (Gliclazide) should be taken by mouth with the breakfast. The dose should be adjusted according to the individual's response.

Usual Adult Dose

The total daily dose may vary from 40-320 mg. Starting dose is 40-80 mg daily and increasing until adequate control is achieved. The maximum single dose is 160 mg and the maximum daily dose is 320 mg. When higher doses are required, gliclazide should be taken twice daily with the main meals of the day.

In obese patients or those not showing adequate response to gliclazide alone, additional therapy may be required.

Elderly

No significant differences in efficacy and tolerance were observed between patients over 65 years of age and younger patients. However, care should be exercised when prescribing sulphonylureas in the elderly due to a possible age-related increased risk of hypoglycemia.

Pediatric use

Gliclazide, as with other sulphonylureas, is not indicated for the treatment of juvenile onset diabetes mellitus.

Renal Insufficiency

If necessary, gliclazide which is principally metabolized in the liver, can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.

Hepatic Insufficiency

Should be avoided in severe hepatic insufficiency. May cause jaundice.

Contraindications

Diapro[®] is contraindicated in patients with:

- known hypersensitivity to gliclazide or to any of the excipients of the medication, other sulfonylureas or sulfonamides
- type 1 diabetes mellitus, particularly juvenile diabetes
- diabetes complicated by ketosis or acidosis
- diabetics undergoing surgery, after severe trauma or during infections
- diabetic pre-coma and coma
- severe renal or hepatic insufficiency
- treatment with miconazole
- pregnancy and lactation

Diapro[®] should, where possible, be avoided in Acute porphyrias.

Special Warnings and Precautions

Hypoglycemia

This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycemic agents is being used.

Hypoglycemia may occur following administration of sulfonylureas. Some cases may be severe and prolonged. Hospitalization may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycemic episodes.

Factors which increase the risk of hypoglycemia:

- patient refuses or (particularly in elderly subjects) is unable to co-operate
- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes
- imbalance between physical exercise and carbohydrate intake
- renal insufficiency
- severe hepatic insufficiency
- overdose of Gliclazide
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency
- concomitant administration of alcohol or certain other medicines.

Renal and hepatic insufficiency

The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

Patient information

The risks of hypoglycemia, together with its symptoms, treatment and conditions that predispose to its development, should be explained to the patient and to family members. The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Poor blood glucose control

Blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients. This may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Laboratory tests

Measurement of glycated hemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.

Lactose intolerance

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

Drug Interactions

The following products are likely to increase the risk of hypoglycemia

Contraindicated combination

- *Miconazole (systemic route, oromucosal gel)*: increases the hypoglycemic effect with possible onset of hypoglycemic symptoms, or even coma.

Combinations which are not recommended

- *Phenylbutazone (systemic route)*: increases the hypoglycemic effect of sulfonylureas (displaces their binding to plasma proteins and/or reduces their elimination). It is preferable to use a different anti-inflammatory agent, or else to warn the patient and emphasize the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.

- *Alcohol*: increases the hypoglycemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycemic coma. Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use

Potential of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur when one of the following drugs is taken, for example:

Other antidiabetic agents (insulins, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, and nonsteroidal anti-inflammatory agents.

The following products may cause an increase in blood glucose levels

Combination which is not recommended

- *Danazol*: diabetogenic effect of danazol.

If the use of this active substance cannot be avoided, warn the patient and emphasize the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combinations requiring precautions during use

- *Chlorpromazine (neuroleptic agent)*: high doses (> 100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).

Warn the patient and emphasize the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.

- *Glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin*: increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids).

Warn the patient and emphasize the importance of blood glucose monitoring, particularly at the start of treatment. It may be

necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.

- *Ritodrine, salbutamol, terbutaline: I.V.*

Increased blood glucose levels due to beta-2 agonist effects.

Emphasize the importance of monitoring blood glucose levels. If necessary, switch to insulin.

Combination which must be taken into account

- *Anticoagulant therapy (e.g. warfarin):*

Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment.

Adjustment of the anticoagulant may be necessary.

The hypoglycemic effect of gliclazide may be potentiated by *salicylates, sulfonamides, octreotide, azapropazone, sulfinpyrazone, metabolism of gliclazide may be accelerated by aminoglutethimide, testosterone, tetracycline compounds, chloramphenicol, clofibrate, disopyramide, cimetidine. Co-trimoxazole* rarely enhances the effect of gliclazide.

Gliclazide may be diminished by *rifamycins, oral contraceptives, thiazide diuretics, diazoxide, phenothiazine derivatives, thyroid hormones, loop diuretics, and abuse of laxatives.*

Calcium channel blockers (nifedipine) may occasionally impair glucose tolerance as well as *Lithium* may occasionally impair glucose tolerance.

Pregnancy and lactation

Pregnancy

US FDA Pregnancy Category C

In animal studies embryo-toxicity and/or birth defects have been demonstrated with some sulfonylureas.

Gliclazide **should NOT be used** in pregnant women. Animal studies of gliclazide have not shown any teratogenic effect. From a clinical point of view, there are no adequate data to allow evaluation of the possible malformative or fetotoxic effects of gliclazide, when administered during pregnancy.

Oral hypoglycemic agents are not suitable and insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered. Control of diabetes should be achieved before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Lactation

It is not known whether gliclazide or its metabolites are excreted in breast milk. Other sulfonylureas have been found in milk. Given the risk of neonatal hypoglycemia, the product is **contra-indicated** in breast-feeding mothers.

Side Effects

Uncommon

Hypoglycemia.

Rare

Agranulocytosis, aplastic anemia, blood disorders, cholestatic jaundice, haemolytic anemia, hepatic failure, hepatitis, leucopenia, pancytopenia, thrombocytopenia.

Frequency not known

Allergic skin reactions (usually in the first 6–8 weeks of therapy), constipation, diarrhea, disturbance in liver function, erythema multiforme (usually in the first 6–8 weeks of therapy), exfoliative dermatitis (usually in the first 6–8 weeks of therapy), fever (usually in the first 6–8 weeks of therapy), gastrointestinal disturbances, hypersensitivity reactions (usually in the first 6–8 weeks of therapy), jaundice.

Overdose

Overdose of sulphonylureas may cause hypoglycemia.

Moderate symptoms of hypoglycemia (without loss of consciousness or neurological signs), should be corrected by carbohydrate intake, dose adjustment and/or modification of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycemic reactions are possible (with coma, convulsions or other neurological disorders) and should be treated as a medical emergency, requiring immediate hospitalization.

If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of 50 mL of concentrated glucose solution (20 to 30%). This should be followed by continuous infusion of a more dilute glucose solution (10%) at a rate necessary to maintain blood glucose levels above 5 mmol/L. It is recommended that patients should be monitored closely for a 48 hour period at least.

Plasma clearance of gliclazide may be prolonged in patients with hepatic disease. However, due to the strong binding of gliclazide to proteins, dialysis is not effective in these patients.

Pharmaceutical Precautions

Keep out of the reach of children. Store below 25°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

Commercial Pack

Diapro® Tablet: Box containing 50 tablets in 5 x 10's blister strips. Each tablet contains Gliclazide BP 80 mg.



Manufactured by

BEXIMCO PHARMACEUTICALS LTD.

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