UNILAB

Gliclazide

Glubitor®

80 mg Tablet
oral hypoglycemic

Rx

FORMULATION
Each tablet contains 80 mg of gliclazide.

PHARMACEUTICAL FORM
White, round, flat, beveled-edged tablet, with a double score on one side and "SVP" imprint on the other side

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

DOSAGE AND ADMINISTRATION
Dosage
The daily adult dose may vary from 1 to 4 tablets per day, i.e. from 30 to 120 mg taken orally in a single intake at breakfast time.
It is recommended that the tablet(s) be swallowed whole.
If a dose is forgotten, there must be no increase in the dose taken the next day. As with any hypoglycemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbA_{1c}).

Initial dose
The recommended starting dose is 30 mg daily.

If blood glucose is effectively controlled, this dose may be used for maintenance treatment. If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between **each dose increment should be at least 1 month** except in patients whose blood glucose has not reduced after two weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment.

The maximum recommended daily dose is 120 mg.

Switching from tablets containing 80 mg of gliclazide to gliclazide modified-release tablet
1 tablet containing 80 mg of gliclazide is comparable to 1 modified-release tablet of gliclazide. Consequently, the switch can be performed provided a careful blood monitoring.

Switching from another oral antidiabetic agent to gliclazide
Gliclazide can be used to replace other oral antidiabetic agents. The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to gliclazide.

A transitional period is not generally necessary. A starting dose of 30 mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above.

When switching from a hypoglycemic sulfonylurea with prolonged half-life, a treatment-free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycemia. The procedure described for initiating treatment should also be used when switching to treatment with gliclazide, i.e. a starting dose of 30 mg/day, followed by a stepwise increase in dose, depending on the metabolic response.

Combination with other antidiabetic agents
Gliclazide can be given in combination with biguanides, alpha glucosidase inhibitors and insulin. In patients not adequately controlled with gliclazide, concomitant insulin therapy can be initiated under close medical supervision.

Special population
Elderly people
Gliclazide should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

Patients with renal impairment
In patients with mild to moderate renal insufficiency, the same dosing regimen can be used as in patients with normal renal function with careful patient monitoring. These data have been confirmed in clinical trials.

Patients at risk of hypoglycemia
- Undernourished or malnourished
- Severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotropic insufficiency)
- Withdrawal of prolonged and/or high dose corticosteroid therapy
- Severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease)

It is recommended that the minimum daily starting dose of 30 mg is used.

Pediatric population
The safety and efficacy of gliclazide in children and adolescents have not been established. No data are available.

CONTRAINDICATIONS
This medicinal product is contraindicated in case of
- hypersensitivity to gliclazide or to any of the excipients, other sulfonylureas, sulfonamides
- type 1 diabetes
- diabetic pre-coma and coma, diabetic ketoacidosis
- severe renal or hepatic insufficiency. In these cases the use of insulin is recommended.
- treatment with miconazole (see **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**)
- lactation (see **PREGNANCY AND LACTATION**)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
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 (see **UNDESIRABLE EFFECTS**). 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 cooperate
- Malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes
- Imbalance between physical exercise and carbohydrate intake
- Renal impairment
- Severe hepatic impairment
- Overdose of gliclazide
- Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency
- Concomitant administration of certain other medicines (see **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**)

Renal and hepatic insufficiency

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

Patient information

The risks of hypoglycemia, together with its symptoms (see **UNDESIRABLE EFFECTS**), 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: St. John's Wort (*Hypericum perforatum*) preparations (see **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**), 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.

Dysglycemia

Disturbances in blood glucose, including hypoglycemia and hyperglycemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Indeed, careful monitoring of blood glucose is recommended in all patients receiving at the same time gliclazide and a fluoroquinolone.

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. Since gliclazide belongs to the chemical class of sulfonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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. Alcohol or medicines containing alcohol should be avoided.

Combinations requiring precautions for use

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur when one of the following drugs is taken: other antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta blockers, fluconazole, angiotensin-converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and non-steroidal 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.

- ***St. John's Wort (Hypericum perforatum) preparations:*** Gliclazide exposure is decreased by St. John's Wort (*Hypericum perforatum*). Emphasize the importance of blood glucose levels monitoring.

The following products may cause dysglycemia

Combination requiring precautions during use

- ***Fluoroquinolones:*** In case of a concomitant use of gliclazide and a fluoroquinolone, the patient should be warned of the risk of dysglycemia, and the importance of blood glucose monitoring should be emphasized.

Combination which must be taken into account

- ***Anticoagulant therapy (warfarin):*** Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary.

PREGNANCY AND LACTATION

Pregnancy

There is no or limited amount of data (less than 300 pregnancy outcomes) from the use of gliclazide in pregnant women, even though there are few data with other sulfonylureas.

Studies in animals have shown reproductive toxicity (see **PRECLINICAL SAFETY DATA**).

As a precautionary measure, it is preferable to avoid the use of gliclazide during pregnancy.

Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Oral hypoglycemic agents are not suitable, 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 pregnancy is attempted, or as soon as pregnancy is discovered.

Breastfeeding

It is unknown whether gliclazide/metabolites are excreted in human milk. Given the risk of neonatal hypoglycemia, the product is therefore contraindicated in breastfeeding mothers. A risk to the newborn infant/children cannot be excluded.

Fertility

No effect on fertility or reproductive performance was noted in male and female rats (see **PRECLINICAL SAFETY DATA**).

Effects on ability to drive and use machines

Gliclazide has no or negligible influence on the ability to drive and use machines. However, patients should be informed that their concentration may be affected if their diabetes is not satisfactorily controlled, especially at the beginning of treatment (see S**PECIAL WARNINGS AND PRECAUTIONS FOR USE**).

UNDESIRABLE EFFECTS

Based on the experience with gliclazide, the following undesirable effects have been reported.

The most frequent adverse reaction with gliclazide is **hypoglycemia.**

As for other sulfonylureas, treatment with gliclazide can cause hypoglycemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycemia are: headache, intense hunger, nausea, vomiting, fatigue, sleep disorders, agitation, aggression, impaired concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and lethal outcome.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulfonylureas shows that hypoglycemia can recur even when measures prove effective initially.

If a hypoglycemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalization is required.

Gastrointestinal disorders

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhea, and constipation have been reported. If these should occur they can be avoided or minimized if gliclazide is taken with breakfast.

The following undesirable effects have been more rarely reported:

Blood and lymphatic system disorders

Changes in hematology are rare. They may include anemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.

Hepatobiliary disorders

Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears.

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens Johnson syndrome and toxic epidermal necrolysis), and exceptionally, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

These symptoms usually disappear after discontinuation of treatment:

Eye disorders

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Class attribution effects

As for other sulfonylureas, the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, hemolytic anemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzyme levels and even impairment of liver function (e.g., with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

OVERDOSE

An overdose of sulfonylureas may cause hypoglycemia.

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

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

If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid I.V. 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 that will maintain blood glucose levels above 1g/L. Patients should be monitored closely and, depending on the patient's condition after this time, the doctor will decide if further monitoring is necessary.

Dialysis is of no benefit to patients due to the strong binding of gliclazide to proteins.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, sulfonylureas
ATC code: A10BB09

Gliclazide is hypoglycemic sulfonylurea oral antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the ß-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.

In addition to these metabolic properties, gliclazide has hemovascular properties.

Effects on insulin release

In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.

Hemovascular properties

Gliclazide decreases microthrombosis by two mechanisms, which may be involved in complications of diabetes:

- a partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B_2)
- an action on the vascular endothelium fibrinolytic activity with an increase in tPA activity

Pharmacokinetic properties

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 liters. A single daily intake maintains effective gliclazide plasma concentrations over 24 hours.

Biotransformation

Gliclazide is mainly metabolized 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 populations

Elderly people

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

Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done. No teratogenic changes have been shown in animal studies, but lower foetal body weight was observed in animals receiving doses 25 fold higher than the maximum recommended dose in humans.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

STORE AT TEMPERATURES NOT EXCEEDING 30°C
DRUGS SHOULD BE KEPT OUT OF THE REACH OF CHILDREN

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY

Gliclazide (Glubitor®) 80 mg Tablet, in blister pack x 10s (box of 60s)

Manufactured by Interphil Laboratories, Inc.
Canlubang Industrial Estate, Bo. Pittland, Cabuyao, Laguna
For Sandoz Philippines Corporation
5th and 6th Floor Ayala North Exchange Tower 1 (HQ), Ayala Ave.
cor. Salcedo and Amorsolo Sts., Brgy. San Lorenzo, Makati, Metro Manila
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No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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Reg. IPOPHIL
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Trusted Quality Healthcare

UNILAB Consumer Care
8-UNILAB-1
8-864522-1
Provincial Toll Free: +1-800-10-864522-1
E-mail: info@unilab.com.ph
Website: www.unilab.com.ph