24 mm

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Glycinorm-MR 60

Gliclazide Prolonged-Release Tablets 60 mg

DESCRIPTION

Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond. It is a second generation sulfonylurea drug that has hypoglycaemic properties. It has chemical formula N-[[Hexahydrocyclopenta[c] pyrrol- 2(IH) - yl)- amino] carbonyl]- 4 - methylbenzene sulfonamide. Its empirical formula is $C_{15}H_{21}N_3O_3S$.

PRODUCT DESCRIPTION

White to off white oval shaped tablet, debossed with "C" on one side and "55" on other side of breakline and breakline on other side.

Purpose of the breakline (scoreline): Scored and can be split for half dosing.

COMPOSITION

Each prolonged release tablet contains:
Gliclazide Ph. Eur. …. 60 mg

CLINICAL PHARMACOLOGY

Pharmacodynamics

The sulfonylureas, including gliclazide act mainly by augmenting insulin secretion from the β-cells of the islets of Langerhans and consequently are effective only when some residual pancreatic beta cell activity is present. During long term administration they also have an extrapancreatic action which restores peripheral insulin sensitivity, such as decreasing hepatic glucose production and increasing glucose clearance and skeletal muscle glycogen synthase activity.
In addition to these metabolic properties, gliclazide has haemovascular properties.

Effects on insulin release

In type 2 diabetes, 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.

Haemovascular properties

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

- A partial inhibition of platelet adhesiveness and aggregation, 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.
- There is no clinical evidence that the haemovascular effects of gliclazide are of therapeutic benefit in type 2 diabetes patients.

Pharmacokinetics

Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.
Plasma protein binding is approximately 95%.
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.
The elimination half life of gliclazide is approximately 16 hours.
No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.

INDICATIONS

Gliclazide prolonged release tablets are indicated in Type 2 diabetes mellitus in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

CONTRAINDICATIONS

Gliclazide prolonged release tablets are contraindicated in patients with:

- hypersensitivity to gliclazide, other sulfonylureas, sulphonamides, or to any of the excipients;
- type 1 diabetes;
- diabetic pre-coma and coma; diabetic keto-acidosis;
- severe renal or hepatic insufficiency: in these cases, the use of insulin is recommended;
- treatment with miconazole (refer to Drug interactions);
- pregnancy and lactation (refer to Usage in pregnancy and lactation).

WARNINGS AND PRECAUTIONS

Hypoglycaemia

This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.
Hypoglycaemia may occur following administration of sulphonylureas. Some cases may be severe and prolonged. Hospitalisation 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 needed to reduce the risk of hypoglycaemic episodes.
Factors which increases the risk of hypoglycaemia:

- 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 prolonged release tablets
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency
- concomitant administration of alcohol or certain other medicines

In order to reduce the risk of hypoglycaemia it is therefore recommended:

- To take into account the age of the patient: blood sugar levels not strictly controlled by diet alone might be acceptable in the elderly
- To adjust the dose of gliclazide according to the blood glucose response and to the 24 hour urinary glucose during the first days of treatment.
- Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Dosage adjustment may be necessary:

- On the occurrence of mild symptoms of hypoglycaemia (sweating, pallor, hunger pangs, tachycardia, sensation of malaise). Such findings should be treated with oral glucose and adjustment made in drug dosage and/or meal patterns.
- On the occurrence of severe hypoglycaemic reactions (coma or neurological impairment.
- On loss of control of blood glucose (hyperglycaemia). When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. At such time, it may be necessary to increase progressively the dosage of gliclazide and if this is insufficient, to discontinue treatment with gliclazide and to administer insulin. As with other sulphonylureas, hypoglycaemia will occur if the patients' dietary intake is reduced or if they are receiving a larger dose of gliclazide than required.

The risks of hypoglycaemia, 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.
Renal or 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.

Porphyric patients

Cases of acute porphyria have been described with some other sulfonylurea drugs, in patients who have porphyria.

Lactose intolerance

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

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, fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.
The hypoglycaemic 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.

Dysglycaemia

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia 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 prolonged-release tablets and a fluoroquinolone.

Laboratory tests

Measurement of glycated haemoglobin 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 sulphonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulphonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.
Effects on ability to drive and use machines - Gliclazide has no or negligible influence on the ability to drive and use machines. Patients should be made aware of the symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of the treatment.

Usage in pregnancy and lactation

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 sulphonylureas.
In animal studies, gliclazide is not teratogenic.
The use of gliclazide during pregnancy is contraindicated.
Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.
Oral hypoglycaemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycaemic therapy is changed to insulin before a pregnancy is attempted or as soon as pregnancy is discovered.
It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, the product is contra-indicated in breast feeding mothers. A risk to the newborns/infants cannot be excluded.

Usage in paediatrics

The safety and efficacy of gliclazide prolonged release tablets in children and adolescents have not been established. There are no data and clinical studies available in children.

Usage in geriatrics

Some elderly patients may be more sensitive to the drug, but the plasma clearance is not altered so that increased plasma levels are unlikely. All sulfonylureas should be used with caution in the elderly because of the greater likelihood of their missing meals and the more severe outcome of significant hypoglycemia.

Drug interactions

The following products are likely to increase the risk of hypoglycaemia

Contraindicated combination

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

Combinations which are not recommended

Phenylbutazone (systemic route): increases the hypoglycaemic effect of sulphonylureas (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 emphasise the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.
Alcohol: increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Ingestion of alcohol may also cause a disulfiram-like reaction with characteristic flushing of the face, throbbing headache, giddiness, tachypnoea, tachycardia or angina pectoris. Chronic alcohol abuse may, as a result of liver enzyme induction, increase the metabolism of sulfonylurea drugs, shortening the plasma half life and duration of action. Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is

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taken, for example:
Other antidiabetic agents (insulins, acarbose, biguanides (e.g. metformin), thiazolidinediones, dipeptiyl peptidase-4 inhibitors, GLP-1 receptor agonists), clofibrate, salicylates (high doses), chloramphenicol, testosterone, anabolic steroids, beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, trimethoprim, sulphonamides, clarithromycin and nonsteroidal anti-inflammatory agents.
Warn the patient and emphasise the importance of self-monitoring of blood glucose levels. It may be necessary to adjust the dose of the antidiabetic agent during treatment with these substances.
The warning signs of hypoglycaemia (such as tremor) may also be masked by beta blockers.
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 emphasise 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
As with all hypoglycaemics, caution should be observed in administering thiazide diuretics, since these diuretics have been reported to aggravate the diabetic state.
Chlorpromazine (neuroleptic agent): high doses (>100mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).
Warn the patient and emphasise 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 emphasise 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.
Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.
Saint John's Wort (*Hypericum perforatum*) preparations:
Gliclazide exposure is decreased by Saint John's Wort-*Hypericum perforatum*. Emphasise the importance of blood glucose levels monitoring.
The following products may cause dysglycaemia.
Combinations requiring precautions during use of Gliclazide
Fluoroquinolones: in case of a concomitant use gliclazide prolonged-release tablets and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.
Combination which must be taken into account
Anticoagulant therapy (warfarin)
Sulfonlyureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary.

ADVERSE DRUG REACTIONS
Based on the experience with gliclazide, the following undesirable effects have been reported.
The most frequent adverse reaction with gliclazide is hypoglycaemia.
As for other sulfonylureas, treatment with gliclazide can cause hypoglycaemia, if mealtimes are irregular, and in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headaches, intense hunger, nausea, vomiting, lassitude, drowsiness, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerfulness, 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 carbohydrate (sugar). However, artificial sweeteners have no effect. Experience with other sulfonylureas shows that hypoglycaemia can recur even when measures prove effective initially.
If a hypoglycaemic episode is severe or prolonged and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.
Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, and constipation have been reported; if these should occur they can be avoided or minimised if gliclazide is taken with breakfast.
The following undesirable effects have been more rarely reported:

- **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), photosensitivity skin reactions. Allergic vasculitis has been reported in very rare cases for other sulphonylureas.
- **Blood and lymphatic system disorders**: Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. There are in general reversible upon discontinuation of medication.
  Rare cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia have been described for other sulphonylureas.
- **Hepatobiliary disorders**: Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases. Discontinue treatment if cholestatic jaundice appears.
  With other sulphonylureas rare cases were observed of elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases.
  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.
- **Hypersensitivity:** Hypersensitivity reactions can occur, usually in the first 6-8 weeks of therapy. They consist mainly of allergic skin reactions which progress rarely to erythema multiforme and exfoliative dermatitis, fever, and jaundice.
- **Metabolism and nutrition disorders**: Hyponatremia

OVERDOSAGE
An overdose of sulphonylureas may cause hypoglycaemia.
Moderate symptoms of hypoglycaemia, 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 hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as medical emergency, requiring immediate hospitalisation.
If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50ml 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.

DOSAGE AND ADMINISTRATION
Oral use – For adult use only
The daily dose may vary from 30 to 120mg taken orally in a single intake at breakfast time. It is recommended that the tablets be swallowed whole.
If a dose is forgotten, there must be no increase in the dose taken the next day.
As with any hypoglycaemic 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 30mg daily.
If blood glucose is effectively controlled, this dose maybe used for maintenance treatment.
If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120mg 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 120mg.
Switching from another oral antidiabetic agent to gliclazide prolonged release tablets
The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to gliclazide prolonged release tablets.
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.
When switching from a hypoglycaemic sulphonylurea with a 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 hypoglycaemia. The procedure described for initiating treatment should also be used when switching to treatment with prolonged release gliclazide, *i.e.* a starting dose of 30 mg/day, followed by a stepwise increase in dose, depending on the metabolic response.
Combination treatment with other antidiabetic agents
Gliclazide prolonged release tablets can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.
In patients not adequately controlled with gliclazide prolonged release tablets, concomitant insulin therapy can be initiated under close medical supervision.

Elderly
Gliclazide prolonged release tablets 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.

Patients at risk of hypoglycaemia
- undernourished or malnourished,
- severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic 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 30mg is used.

LIST OF EXCIPIENTS
Lactose Monohydrate, Maize Starch, Hypromellose 2208, (Methocel K4 MPremium CR), Hypromellose 2208(Methocel K 100Premium LV CR), Magnesium Stearate.

PRESENTATION
Alu-Alu blister strip of 10 tablets [Box of 30 (3x10) tablets]

STORAGE
Store below 30ºC
KEEP OUT OF REACH OF CHILDREN

Made in India by
ipca
Ipca Laboratories Ltd.
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