

APO-GLICLAZIDE MR 60MG TABLETS

Gliclazide Modified Release Tablets

Gliclazide 60mg

Hypoglycemic sulphonylurea - Oral antidiabetic agent

PRODUCT DESCRIPTION

APO-GLICLAZIDE MR 60 mg tablets: White to off-white, oval shaped biconvex tablets. Engraved "GL" bisect "60" on one side, "APO" bisect "APO" on the other side.

PHARMACOLOGY

Pharmacodynamics

Gliclazide is a hypoglycaemic sulphonylurea 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 β -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 haemovascular 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.

Haemovascular 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 B₂).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

Pharmacokinetics

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 Bilxona 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 populations

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

INDICATION

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

RECOMMENDED DOSE

Posology and method of administration: Oral use.

The daily dose of APO-GLICLAZIDE MR 60 mg may vary from one half to 2 tablets per day, i.e. from 30 to 120 mg taken orally in a single intake at breakfast time.

It is recommended to swallow the dose without crushing or chewing.

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, HbA1c).

- Initial dose:

The recommended starting dose is 30 mg daily (half a tablet of APO-GLICLAZIDE MR 60 mg). 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.

One APO-GLICLAZIDE MR 60 mg modified release tablet is equivalent to two APO-GLICLAZIDE 30 mg modified release tablets. The breakability of the APO-GLICLAZIDE MR 60 mg modified release tablet enables flexibility of dosing to be achieved.

- Switching from GLICLAZIDE 80 mg tablets to APO-GLICLAZIDE MR 60 mg modified release tablets: One tablet of GLICLAZIDE 80 mg is comparable to 30 mg of the modified release formulation (i.e. half a tablet of APO-GLICLAZIDE MR 60 mg.) Consequently the switch can be performed with careful blood monitoring.

- Switching from another oral antidiabetic agent to APO-GLICLAZIDE MR 60 mg: APO-GLICLAZIDE MR 60 mg 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 APO-GLICLAZIDE MR 60 mg.

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 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 APO-GLICLAZIDE MR 60 mg, 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: APO-GLICLAZIDE MR 60 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

In patients not adequately controlled with APO-GLICLAZIDE MR 60 mg, concomitant insulin therapy can be initiated under close medical supervision.

Special Populations

Elderly: APO-GLICLAZIDE MR 60 mg 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 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 30 mg is used.

Pediatric population: The safety and efficacy of APO-GLICLAZIDE MR 60 mg in children and adolescents have not been established. No data are available.

MODE OF ADMINISTRATION

Oral

CONTRAINDICATION

- Known hypersensitivity to gliclazide or to any of the excipients, other sulphonylureas, sulphonamides
- 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 (see "Drug Interactions")
- Lactation (see "Use in Pregnancy and Lactation")

PRECAUTIONS/WARNINGS

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 a 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 (see "Adverse Effects"). 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 necessary to reduce the risk of hypoglycaemic episodes.

Factors which increase the risk of hypoglycaemia:

- 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 insufficiency,
- Severe hepatic insufficiency,
- Overdose of APO-GLICLAZIDE MR 30 mg Tablets,
- Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- Concomitant administration of certain other medicines (see Interactions).

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 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.

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 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.

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 chemical class of sulphonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

DRUG INTERACTIONS

1) The following products are likely to increase the risk of hypoglycaemia

Contra-indicated 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. 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 taken: Other anti-diabetic agents (insulins, acarbose, biguanides (e.g. metformin), thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1

receptor agonists); beta-blockers; fluconazole; angiotensin converting enzyme inhibitors (captopril, enalapril); H₂-receptor antagonists; monoamine oxidase inhibitors (MAOIs); sulphonamides; clarithromycin; and non-steroidal anti-inflammatory agents.

2) The following products may cause an increase in blood glucose levels

Combination which is not recommended

- *Danazol*: has a diabetogenic effect. 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 anti-diabetic 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 emphasise the importance of blood glucose monitoring. It may be necessary to adjust the dose of the anti-diabetic active substance during and after treatment with the neuroleptic agent.

- *Glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin*: increase 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 anti-diabetic active substance during and after treatment with glucocorticoids.

- *Ritodrine, salbutamol and terbutaline (I.V. administration)*: increased blood glucose levels due to beta-2 agonist effects. Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

3) Combination which must be taken into account

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

USE IN PREGNANCY AND LACTATION:

Pregnancy

There is no experience with the use of gliclazide during pregnancy in humans, even though there are few data with other sulphonylureas.

In animal studies, gliclazide is not teratogenic.

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.

Lactation

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.

ADVERSE EFFECTS

Based on the experience with gliclazide and with other sulphonylureas, the following undesirable effects have to be mentioned.

Hypoglycaemia

As for other sulphonylureas, treatment with gliclazide can cause hypoglycaemia, if meal times are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, 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 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 sulphonylureas 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 is required.

Other undesirable effects

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhoea and constipation have been reported. These can be avoided or minimised if gliclazide is taken with a meal.

The following undesirable effects have been more rarely reported.

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, and bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis)

Blood and lymphatic system disorders

Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of gliclazide.

Hepato-biliary disorders

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

The following adverse events have been described for other sulphonylureas: Erythrocytopenia; agranulocytosis; haemolytic anaemia; pancytopenia; allergic vasculitis; hyponatraemia; 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.

Effects on Ability to Drive and Use Machine

APO-GLICLAZIDE has no known influence on the ability to drive and use machines. However, patients should be made aware of the symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

SYMPTOMS AND TREATMENT OF OVERDOSE

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 a medical emergency, requiring immediate hospitalization.

If hypoglycaemic 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 1 g/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.

STORAGE CONDITIONS

Store below 30°C.

Dosage Forms and Packaging Available

APO-GLICLAZIDE MR 60 mg: Available in HDPE bottles of 30 tablets.

Name and Address of Manufacturer

Apotex Inc.

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Name and Address of Product Registration Holder

Pharmaforte (M) Sdn Bhd

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DATE OF REVISION

31 Jan 2024