

PACKAGE INSERT TEMPLATE FOR GLICLAZIDE MODIFIED RELEASE TABLET

Brand or Product Name

[Product name] MR Tablet 30mg

[Product name] MR Tablet 60mg

Name and Strength of Active Substance(s)

Gliclazide 30mg

Gliclazide 60mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)

eg :Tablet - White, circular flat beveled edge tablets marked '100' on one side]

Pharmacodynamics

Gliclazide is a hypoglycaemic sulphonylurea 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 the secretion of insulin by the beta cells of the islets of Langerhans. In type 2 diabetics, gliclazide restores early peak insulin secretion in the presence of glucose, and increases the second phase of insulin secretion.

A significant increase in insulin response is observed following a meal or a glucose stimulus. In addition to these metabolic properties, gliclazide has haemovascular properties. Gliclazide reduces the process of microthrombosis by two mechanisms which may be involved in the complications of diabetes :

- partial inhibition of platelet adhesiveness and aggregation with a reduction in the markers of platelet activation (beta-thromboglobulin, thromboxane B₂),
- an effect on the fibrinolytic activity of the vascular endothelium (increase in tPA activity).

Pharmacokinetics

After oral administration, plasma levels increase progressively until 6 hours post-dose, reaching a plateau between 6 and 12 hours post-dose. Intra-individual variability is low. Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption. Up until 120 mg the relationship between the dose administered and the area under the concentration-time curve is linear (AUC). Plasma protein binding is approximately 95 %. Gliclazide is mainly metabolised in the liver. Excretion is essentially 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

Updated August 2011

half-life of gliclazide is between 12 and 20 hours. The volume of distribution is approximately 30 litres. In the elderly, no clinically significant modifications in the pharmacokinetic parameters have been observed. A single daily dose of gliclazide MR tablet maintains effective gliclazide plasma concentrations over 24 hours.

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 levels.

Recommended Dosage

For adult use only. The daily dose may vary from 30 to 120 mg taken as a single dose at breakfast time. It is recommended to swallow the whole tablet without crushing or chewing. If a dose is forgotten, the dose taken on the next day should not be increased. As with all hypoglycaemic agents, the dose should be adjusted according to the individual patient's metabolic response (glycaemia, HbA1c).

Initial dose

The initial recommended dose is 30 mg daily.

- if blood glucose levels are satisfactory, this dosage may be adopted as maintenance treatment,
- if blood glucose levels are not satisfactory, the dosage can be increased to 60, 90 or 120 mg per day, by successive increments, respecting an interval of at least one month between each increment, except in patients whose blood glucose levels do not decrease after two weeks of treatment. In this case, it is possible to propose a dosage increase at the end of the second week of treatment. The maximum recommended daily dose is 120 mg.

Replacement of Gliclazide 80 mg tablets by Gliclazide MR tablets

Replacement can be made provided that there is monitoring of blood glucose levels.

Replacement of another oral antidiabetic by Gliclazide MR tablets

Gliclazide MR tablets can replace another oral antidiabetic treatment. In this case, the dosage and half-life of the previous antidiabetic must be taken into account. Replacement should generally be carried out without any transitional period, preferably starting with a dose of 30 mg. The dosage should then be adapted according to the blood glucose response of each patient, as described above. If a patient is switched from a sulphonylurea with a prolonged half-life, a therapeutic window of a few days may prove necessary to avoid an additive effect of the two products which may cause hypoglycaemia. During this changeover, it is recommended that the same procedure be followed as for the initiation of treatment with Gliclazide MR tablets, i.e.

Updated August 2011

initiate treatment with a dose of 30 mg per day and then increase the dosage by increments, according to the metabolic response.

Combination with other oral antidiabetics

Gliclazide MR tablets can be given in combination with biguanides, alpha glucosidase inhibitors or insulin. In patients not adequately controlled with Gliclazide MR tablets concomitant insulin therapy can be initiated under close medical supervision.

In subjects over 65 years

Gliclazide MR tablets should be prescribed according to the same therapeutic regimen used in subjects under 65.

In patients with mild to moderate renal insufficiency

The therapeutic regimen used should be the same as for subjects with normal renal function but with careful monitoring.

In patients at risk of hypoglycaemia

For example states of undernourishment or malnutrition, severe or poorly compensated endocrine pathologies (hypopituitarism, hypothyroidism, adrenal insufficiency), withdrawal from prolonged and /or high dose corticosteroid therapy and severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease),
It is recommended that treatment be systematically initiated with a minimal dose of 30 mg / day.

There are no data or clinical studies in children.

Mode of Administration

Oral

Contraindications

The use of this medicine is contra-indicated in the following cases :

- hypersensitivity to gliclazide or other sulphonylureas or sulphonamides, or to any of the excipients used,
- insulin-dependent diabetes (type 1 diabetes), particularly juvenile diabetes
- diabetic pre-coma and coma, diabetic keto-acidosis,
- severe hepatic or renal insufficiency; in these cases the use of insulin recommended
- treatment with miconazole
- breast-feeding

Updated August 2011

In general, it is not advisable to combine this drug with phenylbutazone, danazol or alcohol.

Warnings and Precautions

Hypoglycaemia

Hypoglycaemia may occur during treatment with hypoglycaemic sulphonylureas. Some cases may be severe and prolonged. Hospitalisation may be required and blood sugar levels should be corrected for several days if necessary. Careful selection of the patient and the dosage, as well as keeping the patient adequately informed are necessary to avoid episodes of hypoglycaemia.

Patients who are elderly, undernourished or with a change in their general state, and patients with adrenal insufficiency or hypopituitarism are particularly sensitive to the hypoglycaemic effects of anti-diabetic agents. Hypoglycaemia may be difficult to diagnose in elderly subjects and patients treated with beta-blockers.

This treatment should only be prescribed if the patient is likely to eat regularly (including breakfast). A regular intake of carbohydrates is important due to the increased risk of hypoglycaemia if meals are taken late, in cases of inadequate diet or if the diet contains an inadequate balance of carbohydrates. Hypoglycaemia is more likely to occur in subjects following a low-calorie diet, after considerable or prolonged exertion, after the consumption of alcohol or during the administration of a combination of hypoglycaemic agents.

Renal or hepatic insufficiency may alter the distribution of gliclazide and hepatic insufficiency may also reduce the capacity for gluconeogenesis ; these two effects increase the risk of serious hypoglycaemic reactions.

Glycaemic imbalance

Control of blood glucose levels by anti-diabetic agents may be reduced in patients with fever, trauma or infection or in patients undergoing surgery. In these cases, it may be necessary to discontinue the treatment and administer insulin.

The efficacy of all oral hypoglycaemic agents, including gliclazide, in lowering blood sugar to the desired level decreases in the long term in many patients. This may be due to an increase in the severity of the diabetes or to a reduced response to the treatment. This phenomenon is known as secondary failure and should be distinguished from primary failure, in which the drug proves to be ineffective when prescribed as first-line treatment for a given patient. Adequate dosage adjustment and observation of the diet must be considered before classing the patient as a secondary failure.

Updated August 2011

Biological tests

Blood and urinary glucose levels should be monitored periodically. Measurements of glycosylated haemoglobin levels may prove to be useful.

Renal and hepatic insufficiency

The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with renal or hepatic insufficiency. If hypoglycaemia occurs in these patients and there is a risk that it will be prolonged, an appropriate treatment should be instituted.

Carriers of a G6PD (glucose-6-phosphate dehydrogenase) enzyme deficiency

Medicinal products of the sulphonylurea class can cause a haemolytic anaemia in patients who are carriers of a G6PD enzyme deficiency. As gliclazide belongs to this class, precautions must be taken in G6PD deficient patients and a treatment from another therapeutic class other than sulphonylureas must be envisaged.

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.

Effects on ability to drive and use machines

Patients should be made aware of the symptoms of hypoglycaemia and should be careful when driving and/or operating machinery, especially at the beginning of treatment.

Interactions with Other Medicaments

1) The following products are likely to increase hypoglycaemia

Contra-indicated association

Miconazole (systemic route, oral gel)

Increase in the hypoglycaemic effect with possible occurrence of hypoglycaemic symptoms, or even coma.

Inadvisable associations

Updated August 2011

Phenylbutazone (systemic route)

Increase in the hypoglycaemic effect of sulphonylureas (displacement of plasma protein binding and/or decrease in their elimination). An alternative anti-inflammatory agent with less potential for interaction should preferably be used, otherwise to warn the patient and emphasize the need for self-monitoring; if necessary, adjust the dosage of gliclazide during treatment with the anti-inflammatory agent and after it has been discontinued.

Alcohol

Increased hypoglycaemic reaction (inhibition of compensatory mechanisms), which may increase the likelihood of hypoglycaemic coma. Avoid the consumption of alcoholic drinks and medicines containing alcohol.

Combinations requiring precautions

Beta-blockers

All beta-blockers mask certain symptoms of hypoglycaemia : palpitations and tachycardia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia. Inform the patient and encourage self-monitoring of blood glucose levels, particularly at the start of treatment.

Fluconazole

Increase in the half-life of the sulphonylurea with the possible occurrence of hypoglycaemic symptoms. Inform the patient, emphasise the need for self-monitoring of blood glucose levels and, if necessary, adjust the dosage of the sulphonylurea during treatment with fluconazole.

Inhibitors of angiotensin converting enzyme (described for captopril, enalapril)

The use of angiotensin converting enzyme inhibitors may lead to an increase in the hypoglycaemic effect in diabetic patients treated with hypoglycaemic sulphonylureas. Symptoms of hypoglycaemia appear to be an exceptional occurrence. One theory put forward is that an improvement in glucose tolerance results in a reduction in insulin requirements. Emphasise the need for self-monitoring of blood glucose levels.

2) Products which may cause an increase in blood sugar levels

Inadvisable association

Danazol (diabetogenic effect of Danazol)

If the combination is unavoidable, warn the patient of the potential risk and emphasise the need for self-monitoring of blood and urinary glucose levels. If necessary, adjust the dosage of the anti-diabetic agent during treatment with Danazol and after it has been discontinued.

Updated August 2011

Combinations requiring special precautions

Chlorpromazine (neuroleptics)

At high doses (100 mg per day of chlorpromazine) blood sugar levels may be raised (decrease in the release of insulin). Inform the patient and emphasise the need for self-monitoring of blood glucose levels. If necessary, adjust the dosage of the anti-diabetic agent during treatment with the neuroleptic and after it has been discontinued.

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).

Beta-2 sympathomimetics (ritodrine, salbutamol, terbutaline)

Increased blood glucose levels by beta2-stimulants. Emphasise the need for monitoring of blood glucose levels. If necessary, switch to insulin treatment.

Statement on Usage During Pregnancy and Lactation

Pregnancy

Risk due to diabetes

When poorly controlled, diabetes (gestational or permanent) is responsible for an increase in congenital malformations and perinatal death. The best possible control must be achieved around the time of conception in order to reduce the risk of malformation.

Risk due to gliclazide

Hypoglycaemic sulphonylureas are teratogenic in animals at high doses.

Relevant clinical data is currently insufficient for an evaluation of the possible malformative or foetotoxic effects of gliclazide when it is administered during pregnancy.

Course of action

Maintaining diabetic control allows pregnancy to progress normally in this category of patients. Insulin treatment is essential, irrespective of the type of diabetes, I or II, gestational or permanent. In this last case, a change from oral treatment to insulin is recommended from the time that pregnancy is planned, or if a pregnancy is discovered accidentally in a patient exposed to gliclazide; in this case it is not automatically necessary to recommend a termination of the

Updated August 2011

pregnancy, but the pregnancy should be monitored with particular care with appropriate prenatal screening. Neonatal monitoring of blood glucose levels is recommended.

Lactation

In the absence of data concerning the passage into breast milk, and taking into account the risk of neonatal hypoglycaemia, breast-feeding is contraindicated during treatment with this drug.

Adverse Effects / Undesirable Effects

Hypoglycaemia

As for other sulphonylureas, treatment with gliclazide tablets can cause hypoglycaemia, if mealtimes 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 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, erythema, maculopapular rashes, bullous reactions.

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 medication.

Updated August 2011

Hepato-biliary disorders

Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), 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

Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas. With other sulphonylureas cases were also 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.

Overdose and Treatment

An overdose of sulphonylureas may lead to hypoglycaemia. Moderate symptoms of hypoglycaemia, with no loss of consciousness or neurological signs, should be completely corrected by the administration of carbohydrates and by adjusting the dosage and/or dietary measures. The patient should be closely monitored until the doctor is sure that he/she is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders, are possible and constitute a medical emergency requiring the immediate hospitalisation of the patient.

If a hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of a concentrated glucose solution (50 %). This should be followed by a continuous infusion of a more dilute glucose solution (10 %) at a rate necessary to maintain blood glucose levels above 100 mg/dl. The patient should be monitored closely for at least 48 hours. Depending on the state of the patient at this time, the doctor should decide whether additional monitoring is required.

Plasma clearance of gliclazide may be prolonged in patients suffering from a hepatic disorder. Dialysis is of no value as gliclazide is highly protein-bound.

Storage Conditions

Store below ...°C

Updated August 2011

Dosage Forms and Packaging Available

[Packaging type & pack size eg Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box etc]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]