DIAMICRONâMR Gliclazide

COMPOSITION

Gliclazide : 30 mg Excipient q.s.f for one modified release tablet.

PRESENTATION

Box of 30 modified release tablets
(3 strips @ 10 tablets)

PROPERTIES

SULPHONYLUREA-ORAL ANTI-DIABETIC
(Digestive tract and metabolism)

MODE OF ACTION OF THE DRUG

Pharmacodynamic properties

Gliclazide is a sulphonylurea, oral antidiabetic, containing an N-containing heterocyclic ring with an endocyclic bond which differentiates it from other sulfonamides.
Gliclazide reduces blood glucose levels by simulating insulin secretion from the beta cells of the islets of Langerhans.
In addition to these metabolic properties, gliclazide has haemovascular properties.

Effects on insulin release :

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

Haemovascular properties :

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

- a partial inhibition of platelet aggregation and adhesion, as well as a decrease in the markers of platelet activation (beta thromboglobulin thromboxane B2).
- an action on the vascular endothelium fibrinolytic activity with an increase in t-PA activity.

Pharmacokinetic properties

After oral administration, plasma levels increase progressively until the sixth hours, reaching a plateau between the sixth and the twelfth hour. 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 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 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 Diamicron MR 30 mg, maintains effective gliclazide plasma concentrations over 24 hours.

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 levels.

CONTRA-INDICATIONS
- known hypersensitivity to gliclazide or to one of the excipients, to 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 (refer to interactions with other drugs and other forms of interaction),
- pregnancy, breast-feeding (refer to Pregnancy and Breast-feeding).

WARNINGS & PRECAUTION :
Hypoglycaemia :
This treatment should only be prescribed if the patient is likely to eat regularly (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 eaten or if it is low in carbohydrate. Hypoglycaemia is more likely to occur during a low-calorie diet, following prolonged or strenous exercise, alcohol intake or if a combination of hypoglycaemic agents are being used.

Hypoglycaemia may occur following administration of sulphonylureas (refer to Adverse effects). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose infusion may need to be continued for several days.

Careful selection of patients, of the dose used, as well as sufficient patient information is necessary to reduce the risk of hypoglycaemic.

Hypoglycaemic is favored by the following factors :
- refusal or incapacity of the patient to co-operate (particularly in elderly subjects);
- malnutrition, irregular mealtimes, missed meals, periods of fasting or changed in diet;
- imbalance between physical exercise and carbohydrate intake;
- renal insufficiency;
- severe hepatic insufficiency;

- overdose of Diamicron MR 30 mg;
- certain endocrinal disorders : thyroidal disorders, hypophysial and adrenal insufficiency;
- concomitant administration of certain other medicines (see interactions with other drugs and other forms of interaction).

Renal and hepatic insufficiencies: the pharmacokinetics and/or pharmacodynamics of gliclazide may be modified in patients with hepatic insufficiency or severe renal failure. In these patients hypoglycaemia may be prolonged, appropriate management should be initiated.

Patient information:
The risks of hypoglycaemia, its symptoms, treatment, and any predisposing conditions, should be explained to the patient and to his/her family.
The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Glycaemic imbalance : the blood glucose levels in patients treated with an oral antidiabetic may be affected by any of the following : fever, trauma, infection or surgical intervention. In certain cases, it may be necessary to resort to insulin.

The hypoglycaemic efficacy of any oral antidiabetic, including gliclazide, may be attenuated over time in many patients : this may be linked to a progression 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 is ineffective from the very first administration. Adequate dose adjustment and supervision of dietary measures and physical exercise should be considered before classifying the patient as secondary failure.

Laboratory tests : measurement of glycated haemoglobin levels (or fasting glucose levels) is recommended for assessing blood glucose control. Self- monitoring of blood glucose may also be useful.

Pregnancy and lactation
Pregnancy
There is no clinical data on the use of glyclazide in pregnant women; little data exists with other sulfonylureas.
In animals, gliclazide is not teratogenic.

Control of diabetes must be achieved before conception in order to reduce the risk of congenital malformations caused by uncontrolled diabetes.
Oral antidiabetics are unsuitable during pregnancy, insulin therefore constitutes the choice of treatment of diabetes. Replacement of oral antidiabetics by insulin is recommended from the time that pregnancy is planned or as soon as pregnancy is discovered.
Lactation
There is no clinical data on the excretion of gliclazide or its metabolites into breast milk.
Given the risk of neonatal hypoglycaemia, gliclazide is contra-indicated in women breast-feeding.

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.

DOSAGE AND METHOD OF ADMINISTRATION

Oral route.

For adult use only.

The daily dose may vary from 1 to 4 tablets a day, i.e. 30 to 120 mg taken as a single daily dose.

It is recommended that the tablet(s) be taken at breakfast time.

If a dose is forgotten, the dose taken on the next day should not be increased. As with all hypoglycaemic agent, 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, and be careful. The interval between each dose increment must be minimal two weeks. The maximum recommended daily dose is 120 mg.
- Replacement of Diamicron 80 mg tablets by Diamicron 30 mg modified release tablets : 1 tablet of Diamicron 80 mg is comparable to 1 tablet of Diamicron MR 30 mg.

  Consequently replacement can be made provided that there is monitoring of blood glucose levels.
- Replacement of another oral antidiabetic by Diamicron MR 30 mg :

  Diamicron MR 30 mg can replace another oral antidiabetic treatment.

  In this case, the dosage and the half-life of the previous antidiabetic must be taken into account.

  The replacement will generally be carried out without any transitional period, preferably starting with a dose of 30 mg. The dosage should be adapted according to the blood glucose response of each patient, as described above.

  If a patient is changed from a sulphonylurea with a prolonged half-life, a therapeutic window of a few days may prove to be necessary to avoid the additive effect of the two products, which may cause hypoglycaemia. During this changeover it is recommended to follow the same procedure as for the initiation of treatment by Diamicron 30 mg, that is to say, to initiated treatment with a dose of 30 mg per day and then increase the dosage by increments, according to the metabolic response.
- Association with other oral antidiabetics :

  Diamicron MR 30 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

  In patients not adequately controlled with Diamicron MR 30 mg, concomitant insulin therapy can be initiated under closed medical supervision.
- In subject over 65 years Diamicron MR 30 mg will be prescribed according to the same therapeutic regimen used in subjects under the age of 65 years.

- In patients with mild to moderate renal insufficiency, the therapeutic regimen used will be the same as for subjects with normal renal function but with careful monitoring. These data have been confirmed in clinical trials.

- In patients with a risk of hypoglycaemia:
  - state of undernourished or malnutrition,
  - severe or badly compensated endocrine pathologies (prehypophysial insufficiency, hypothyrosis, adrenal insufficiency),
  - withdrawal from a prolonged and/or high dose corticotherapy,
  - severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease);

  It is recommended to systematically initiate treatment with the minimal dose of 30 mg/day.
- There are no data or clinical studies in children.

SIDE EFFECTS

Hypoglycaemia

As for other sulphonylurea, treatment with Diamicron 30 mg may lead to the onset of hypoglycaemia, in particular, if meals are taken at irregular intervals or in the case of missed meals.

Possible symptoms are : cephalagia, intense hunger, nausea, vomiting, lassitude, drowsiness, sleep disturbance, agitation, aggressiveness, diminished concentration and attentiveness, slowed reaction, depression, confusion, visual disturbances and speech powerlessness, loss of self control, delirium, convulsions, shallow breathing, bradycardia, drowsiness, loss of consciousness, even coma, possibly with a lethal outcome.

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

These symptoms usually disappear after an intake of carbohydrates (glucose). However, artificial sweeteners have no effect. Experience with other sulphonylureas show despite initially effective measures, hypoglycaemia may recur.

In the case of severe of prolonged hypoglycaemia, even if it is temporarily controlled by an absorption of sugar, immediate treatment or even hospitalisation may be necessary.

Gastrointestinal disturbances, such as abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, constipation have been reported : these can be avoided or reduced if the treatment is taken at breakfast.

The following **undesirable effects** have been more rarely reported :

- Skin and subcutaneous reactions: rash, pruritus, urticaria, erythema, maculopapular rashes, bulbus reactions. Rare cases of allergic vasculitis have been reported with other sulphonylureas.

- Haematological disorders, they are rare and include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These anomalies are in generally reversible upon discontinuation of treatment. Rare cases of erythrocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia have been described with other sulphonylureas.
- Hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated cases). Discontinue treatment if cholestatic jaundice appears.
  Rare cases of elevated hepatic enzyme levels, hepatic insufficiency (cholestasis and jaundice) and even hepatitis have been observed with other sulphonylurea and which regressed upon treatment withdrawal; only a few cases resulted in life- threatening hepatic failure;
  As a general rule, these symptoms disappear after discontinuation of treatment.
- Visual disorders: transitory visual disorders due to changes in blood glucose levels may occur, especially on initiation of treatment.

OVERDOSE

An overdose of sulphonylureas may cause hypoglycaemia.

Moderate symptoms of hypoglycaemia, without loss of consciousness or neurological signs, must absolutely be corrected by carbohydrate intake, dose adjusment and/or change of diet.
Strict monitoring should be continued by the doctor until the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and should be treated as a medical emergency, requiring immediate hospitalisation of patient.

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%), followed by a continuous infusion of a more dilute glucose solution (10%) at a rate necessary to maintain blood glucose levels about 1 g/l.
Strict monitoring of the patient will be introduced by the doctor and intensified if necessary, depending on the patient's condition.
Dialysis is of no use in these patients due to the strong binding of gliclazide to proteins.

DRUG INTERACTIONS

The following products are likely to increase the risk of hypoglycaemia

Contra-indicated combinations :

- **Miconazole** (systemic route, oral 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-inflammatotory agent, otherwise, warn the patient and emphasize the importance of self-monitoring: if necessary, adjust the dose during and after treatment with the anti-inflammatory.
- **Alcohol**: increases the hypoglycaemic reaction (by inhibiting compensatory reactions) and may potentiate 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 in concomitant treatment with the following drugs: other antidiabetics (insulin, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonist, MAOIs, sulfonamides, and nonsteroidal anti-inflammatories

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 drug cannot be avoided, warn the patient and emphasize the importance of urine and blood glucose self monitoring. It may be necessary to adjust the dose of the antidiabetic during and after treatment with danazol.

Combinations requiring precautions during use
- **Chlorpromazine** (neuroleptics): at high doses (>100 mg per day of chlorpromazine) this increase blood glucose levels (reduced insulin release)
  Warn the patient and emphasize the importance of blood glucose self-monitoring. It may be necessary to adjust the dose of the antidiabetic agent during treatment with the neuroleptic agent and after its discontinuation.
- **Glucocorticoids** (systemic route and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose with possible ketosis (reduced tolerance to carbohydrates by corticoids).
  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 during treatment with corticoids and after discontinuation.
- **Ritodrine, salbutamol, terbutaline**: (I.V. route) increased blood glucose levels due to beta-2 agonists.
  Emphasize the importance of monitoring blood glucose levels. If necessary, switch to insulin.

Combination which should be taken into account
- **Anticoagulants** (Warfarin)
  Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment.
  It may be necessary to adjust the dose of the anticogulant.

STORAGE OF DRUGS

Storage under 30^0C.
Shelf life of 3 years.

ON MEDICAL PRESCRIPTION ONLY

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