SUMMARY OF PRODUCT CHARACTERISTICS

DIAMICRON 30MG

Modified release tablet

INN : Gliclazide

1. NAME OF THE MEDICINAL PRODUCT

DIAMICRON 30MG, modified release tablet**.**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 30 mg of gliclazide.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablet.

White oblong tablet, engraved on both faces ("DIA 30" on one face and " " on the other face).

4. CLINICAL PARTICULARS

4.1 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 levels.

4.2 Posology and method of administration

Oral use.

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 dose at breakfast time.

It is recommended to swallow the whole tablet(s).

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, HbA_{1c}).

- 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 2nd week of treatment.

    The maximum recommended daily dose is 120 mg.

- Replacement of Diamicron 80 mg tablets by Diamicron 30MG, modified release tablets :

  1 tablet of Diamicron 80 mg is comparable to 1 tablet of Diamicron 30MG.

  Consequently, replacement can be made provided that there is monitoring of blood glucose levels.

- Replacement of another oral antidiabetic by Diamicron 30MG :

  Diamicron 30MG 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 Diamicron 30MG, i.e. 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:
  Diamicron 30MG can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.
  In patients not adequately controlled with Diamicron 30MG concomitant insulin therapy can be initiated under close medical supervision.

- In subjects over 65 years, Diamicron 30MG 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.
  These data have been confirmed in clinical trials.

- In patients at risk of hypoglycaemia:
  – states of undernourishment or malnutrition,
  – severe or poorly compensated endocrine pathologies (hypopituitarism, hypothyroidism, adrenal insufficiency),
  – withdrawal from prolonged and /or high dose corticosteroid therapy,
  – 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.

4.3 Contraindications
- known hypersensitivity to gliclazide or one of the excipients, other sulphonylureas, or 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),
- breast-feeding (refer to Pregnancy and lactation).

4.4 Special warnings and special precautions for use

HYPOGLYCAEMIA:

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

Hypoglycaemia may occur following administration of sulphonylureas (see section 4.8). Some episodes 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 hypoglycaemia.

Hypoglycaemia is favoured 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 change in diet;
- imbalance between physical exercise and carbohydrate intake;
- renal failure;
- severe hepatic failure;
- overdose of Diamicron 30 mg;
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency;
- concomitant administration of other medicines (see section 4.5).

Renal and hepatic failures: the pharmacokinetics and/or pharmacodynamics of gliclazide may be modified in patients with hepatic failure 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 particularly be informed of the importance of following dietary measures, taking regular exercise, and regularly monitoring blood glucose levels.

Blood glucose imbalanced: the blood glucose balance in patients treated with an oral antidiabetic may be affected by any of the following events: fever, trauma, infection or surgery.

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 reduction in the response to the treatment. This phenomenon is known as secondary failure and should be distinguished from primary failure, in which the medicine is ineffective from the very first administration. The possibility of dose adjustment and supervision of dietary measures should be considered before classifying the patient as a secondary failure.

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

Medicinal products of the sulphonylurea class can cause a haemolytic anaemia in patients who are carriers of a G6PD (glucose-6-phosphate dehydrogenase) 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.

4.5 Interactions with other medicinal products and other forms of interaction

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 (shifts their binding to plasma proteins and / or reduces their elimination).
It is preferable to use a different anti-inflammatory agent, otherwise, warn the patient and emphasise 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 during concomitant treatment with the following drugs: other antidiabetics (insulin, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulphonamides, and nonsteroidal anti-inflammatory drugs.

2) 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 emphasise 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 increases blood glucose levels (reduced insulin release).

Warn the patient and emphasise 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 corticosteroids).
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 during treatment with corticosteroids and after discontinuation.

Ritodrine, salbutamol, terbutaline: (I.V. route)
Increased blood glucose levels due to beta-2 agonists.
Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

3) Combinations 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 anticoagulant.

4.6 Pregnancy and lactation

Pregnancy

There are no clinical data on the use of gliclazide in pregnant women; few data exist concerning other sulphonylureas.
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 are no clinical data available concerning the excretion of gliclazide or its metabolites into breast milk. Given the risk of neonatal hypoglycaemia, gliclazide is contra-indicated in women who are breast-feeding.

4.7 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.

4.8 Undesirable effects
According to the clinical experience with gliclazide and other sulphonlylureas, the following undesirable effects must be mentioned.

Hypoglycaemia
As for other sulphonylureas, treatment with Diamicron 30MG 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 : headaches, intense hunger, nausea, vomiting, lassitude, sleep disturbances, agitation, aggressiveness, diminished concentration and attentiveness, slowed reactions, depression, confusion, visual disturbances and speech disturbances, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of 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 shows that despite initially effective measures, hypoglycaemia may recur.

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

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

The following **undesirable effects** have been more rarely reported:
- skin and subcutaneous reactions: rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.
- haematological disorders: they are rare and include anaemia, leukopaenia, thrombocytopaenia, granulocytopaenia. The anomalies are generally reversible upon discontinuation of treatment.

- hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated cases). Discontinue treatment if cholestatic jaundice appears.

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.

Class effect :

- Rare cases of erythrocytopaenia, agranulocytosis, haemolytic anaemia, pancytopaenia and allergic vasculitis have been described with other sulphonylureas.
- Rare cases of elevated hepatic enzyme levels, hepatic insufficiency (cholestasis and jaundice) and even hepatitis have been observed with other sulphonylureas and regressed when treatment was withdrawn: only a few cases resulted in life-threatening hepatic failure.

4.9 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 adjustment 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 the 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 the rate necessary to maintain blood glucose levels above 1 g/L.
Strict monitoring of the patient must be introduced by the doctor and intensified if necessary, depending on the patient's condition.
Dialysis is unnecessary in these patients due to the strong binding of gliclazide to proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

SULPHONYLUREA – ORAL ANTIDIABETIC
(A10BB09: Gastrointestinal tract and metabolism)
Gliclazide is a sulphonylurea, an oral antidiabetic, with an N-containing heterocyclic ring with an endocyclic bond which differentiates it from other sulphonamides.
Gliclazide reduces blood glucose levels by stimulating insulin secretion by beta cells in the islets of Langerhans. The 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, 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 an intake of glucose.

Haemovascular properties:
Gliclazide decreases microthrombosis by two mechanisms which could be involved in the 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.

5.2 Pharmacokinetic properties

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 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 maintains effective gliclazide plasma concentrations over 24 hours.

5.3 Preclinical safety data

Preclinical data, based on repeated dose toxicity and genotoxicity, have not revealed any risks for humans. No long term carcinogenicity studies have been carried out.
No teratogenic effects have been reported in animals; only lower foetal body weight has been observed in animals having received doses 25 times higher than the maximum recommended dose in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate, maltodextrin, hypromellose, magnesium stearate, anhydrous colloidal silica.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Store in the original packaging.
Store below 30°C.

DATE OF REVISION OF THE TEXT:

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