PRODUCT INFORMATION
DIAMICRON
INN: Gliclazide

Composition

Gliclazide……...……80.00 mg

Excipient with known effect: lactose.

Excipients q.s.f. one tablet

Indications

Non-insulin-dependent diabetes, in association with an adapted diet, in cases where dietary measures alone provide inadequate control of blood glucose levels.

Dosage and method of administration

For adults only.

As with all hypoglycaemic agents, the dosage must be adapted to suit each individual case.

In the case of transient disturbance of glucose control, administration of the product for a short period of time may be sufficient in a patient in whom the glucose balance is normally well maintained by dietary measures.

***Subjects under the age of 65 years**

Initial dose

The recommended initial dose is 1 tablet per day.

Dosage increments

The dosage is usually adjusted in increments of 1 tablet depending on the glycemic response. Each dosage increment should be separated by at least 14 days.

Maintenance treatment

The dosage varies from 1 to 3 tablets per day, 4 in exceptional cases.

The standard dosage is 2 tablets per day, taken as 2 daily doses.

***High-risk subjects**

Subjects over the age of 65 years

- Begin the treatment with ½ tablet taken once a day.
- This dosage may be progressively increased until satisfactory glucose control is obtained in the patient, provided that an interval of at least 14 days is maintained after each dosage increase and blood sugar levels are monitored closely.

In other high-risk patients

In patients who are undernourished or with a marked change in their general state or whose calorie intake is irregular, and in patients with renal or hepatic insufficiency, treatment must be initiated at the lowest dose and the guidelines for dosage increases scrupulously respected, so as to avoid any hypoglycaemic reactions (cf. Warnings and special precautions for use).

Patients receiving other oral hypoglycaemic agents

As with all hypoglycaemic sulphonylureas, this drug may replace other anti-diabetic treatments without any transition period. On changing from a hypoglycaemic sulphonylurea with a longer half-life (e.g. chlorpropamide) to this drug, patients should be closely monitored (over several weeks) to avoid the occurrence of hypoglycaemia, due to the possibility of an overlap of the therapeutic effects.

Contra-indications

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;
- Type I diabetes, insulin-dependent diabetes, particularly juvenile diabetes;
- diabetic precoma and coma; diabetic ketoacidosis;
- severe hepatic or renal insufficiency: in these cases, the use of insulin is recommended;
- treatment with miconazole (see Drug interactions);
- pregnancy and lactation (see Pregnancy and Lactation).

In general, it is not advisable to combine this drug with phenylbutazone, danazol (see Drug interactions) or alcohol.

Warnings

Hypoglycaemia

This medication should be prescribed only to patients who are able to feed themselves regularly (including having breakfast).

It is important to consume carbohydrates regularly, in view of the increased risk of hypoglycaemia if meals are taken late, if food intake is inadequate or if there is an imbalance in carbohydrates. Hypoglycaemia is all the more likely to occur when the patient's diet is low in calories, following major or prolonged exercise, following ingestion of alcohol or when a combination of hypoglycaemic agents is being administered.
Hypoglycaemia may occur following administration of sulphonylureas. Some episodes may be severe and prolonged. Admission to hospital may then be necessary, and glucose administration may need to be carried out for several days.

To reduce the risk of hypoglycaemia, the patient must be carefully selected, the posology must be carefully matched to the patient, and the patient must be given appropriate information. Factors which increase the risk of hypoglycaemia:

- patient refuses or is unable to co-operate (particularly in elderly subjects);
- 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 Diamicron;
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency;
- concomitant administration of other medicinal products (see section 4.5).

Renal and hepatic insufficiency

The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. If hypoglycaemia occurs in such patients, it can be prolonged, and appropriate management must be initiated.
Information for the patient

The risks of hypoglycaemia, together with its symptoms (see section 4.8), treatment, and conditions that predispose to its development, should be explained to patients and to family members. They must be informed of the importance of keeping to an appropriate diet, undertaking regular physical exercise, and of regular monitoring of blood glucose levels.

Blood sugar imbalance

Blood glucose control in a patient receiving oral antidiabetic treatment may be affected by any of the following: St.John's Wort (*Hypericum perforatum*) preparations, fever, injury, infection or surgery. In these 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 Diamicron 80 mg 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 (glucose-6-phosphate dehydrogenase deficiency) with sulfonylurea 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 nonsulphonylurea alternative should be considered.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interactions with other medicaments

The following substances can increase hypoglycaemia

Combination contraindicated

- **Miconazole** (systemic route, oral gel): Increase in the hypoglycaemic effect with possible occurence of hypoglycaemia symptoms, or even coma.

Combinations which are not recommended

- **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 should preferably be used, otherwise 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**: Antabuse effect, particularly for chlorpropamide, glibenclamide, glipizide, tolbutamide. Increased hypoglycaemic reaction (inhibition of compensatory mechanism), which may increase the likelihood of hypoglycaemic coma.

Avoid the consumption of alcoholic drinks and medicines containing alcohol.

Combinations requiring precautions

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 metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), clofibrate, salicylates (high doses), chloramphenicol, beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulphonamides, clarithromycin, and nonsteroidal anti-inflammatory drugs.

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 following products which may cause an increase in blood sugar levels

Combination which is not recommended

- **Danazol** (diabetogenic effect of danazol): If the combination is unavoidable, warn the patient of the potential risk and emphasize 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.

Combinations requiring precautions during use

- **Chlorpromazine** (neuroleptics): High doses (>100 mg per day of chlorpromazine) may increase blood sugar levels (reduced insulin release)
  Inform the patient and emphasize 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 route and local route: intraarticular use, cutaneous or rectal preparations) and tetracosactin**. Increase in blood glucose levels with possible ketosis (decrease in carbohydrate tolerance caused by corticosteroids).
  Inform the patient and emphasize the need for self-monitoring of blood glucose levels, particularly at the start of treatment. If necessary, adjust the dosage of the anti-diabetic agent during treatment with corticosteroids and after they have been discontinued.

- Ritodrine, salbutamol, terbutaline (I.V. route): Increased blood glucose levels due to beta-2 agonist effects. Emphasize the need for monitoring of blood glucose levels. If necessary, change to insulin treatment.

- **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.

- **Barbiturates, oestrogens and progestogens**

The following products may cause dysglycaemia:

Combinations requiring precautions during use

- Fluoroquinolones:
In case of concomitant use of Diamicron 80 mg and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.

Combinations which must be taken into account

- **Anticoagulant therapy (warfarin)**: Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment. It may be necessary to adjust the dose of the anticoagulant.

Pregnancy

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 sulfonylurea

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.

Breast-feeding

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 mother.

A risk to the newborns/infants cannot be excluded.

Fertility

No effect on fertility or reproductive performance was noted in male and female rats.

Effect on ability to drive and use machines

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 when driving and operating machines, especially at the beginning of treatment.

Undesirable effects

- Hypoglycaemia (see Special precautions for use and Overdosage).
  - As is the case with all sulphonylurea drugs, hypoglycaemic reactions have been reported following gliclazide administration. However, a number of studies have shown that hypoglycaemia is less common with gliclazide than with glibenclamide.
  - 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 selfcontrol, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and/or death.
  - 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 such as sugar (artificial sweeteners have no effect). Experience with other sulphonylureas shows that hypoglycaemia can recur even when these measures are initially effective.
  - 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.
  - In long-term comparative studies, the percentage of patients experiencing hypoglycaemic episodes was similar between patients treated with the modified release formulation of gliclazide (11.6%) and those treated with the immediate release formulation of gliclazide (11.1%). However, the number of hypoglycaemic episodes per 100 patient months was lower in the modified release group (3.5) than in the immediate release group (4.8).

- Analysis of elderly patients (over 65 years old) showed less hypoglycaemia than in the general population, with a prevalence of hypoglycaemic episodes lower in the modified release group (2.6 hypoglycaemic episodes for 100 patient months) than in the immediate release group (4.1).
- The percentage of patients experiencing hypoglycaemic episodes in the sub-population with renal failure, was similar to that observed in the general population.

Other undesirable effects

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 a meal or by splitting the doses.
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).
- **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.
- **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

As for other sulphonylureas, the following adverse events have been observed: cases of 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 sulfonylurea or led to life-threatening liver failure in isolated cases.

Overdosage

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 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.

Pharmacodynamic properties

HYPOGLYCAEMIC SULPHONYLUREA – ORAL ANTI-DIABETIC

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.

Other properties: 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 B_2),
- an effect on the fibrinolytic activity of the vascular endothelium (increase in tPA activity).

Pharmacokinetic properties

Gliclazide in rapidly absorbed from the gastrointestinal tract and maximum blood concentrations are attained between the 11th and the 14th hour. Protein binding is 94.2% in humans.
Since the apparent half-life of final elimination of gliclazide is twenty hours in humans, the treatment may be administered as two daily doses.
Elimination takes place mainly in urine: less than 1% of the ingested dose is found unchanged in urine.

Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done.
No teratogenic changes have been shown in animal studies, but lower fœtal body weight was observed in animals receiving doses 25-fold higher than the maximum recommended dose in humans. Fertility and reproductive performance were unaffected after gliclazide administration in animal studies

Presentation and storage conditions

Presentation

DIAMICRON Tablets 80 mg, gliclazide 80 mg tablets available in 100's and 300's.* The tablets are white and scored.

**Not all pack sizes may be available.*

Storage conditions

Store below 30°C.

Shelf-life

5 years.

Date of Last Revision of Package Insert: October 2017

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