diamicron®
gliclazide

COMPOSITION
Each tablet contains 80 mg of gliclazide

THERAPEUTIC INDICATIONS
Non-insulin-dependent diabetes, together with an appropriate diet, when that diet is not by itself sufficient to control the level of blood glucose.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
RESTRICTED TO ADULTS.
As with any hypoglycaemic agent,the dosages should be adjusted to the particular circumstances.
In the event of a transitory loss of blood glucose control in a patient where good control is usually achieved by diet, it may be sufficient to administer this product for a short period.

Patients under the age of 65

Initial dose:
The recommended initial dose is one tablet per day.

Dosage steps:
Adjustments in posology are usually made in steps of one tablet at a time, depending on the response in blood glucose. At least 14 days should separate successive steps in the dose.

Maintenance treatment:
The posology can vary from 1 to 3, or rarely 4, tablets per day.
The usual posology is 2 tablets a day, as 2 daily doses.

Patients at particular risk

Patients over the age of 65:
- Begin the treatment with a half-tablet once a day.
- The dose can be progressively increased until the patient's blood glucose is satisfactorily controlled, while keeping to steps of at least 14 days between successive levels, and with close monitoring of blood glucose.

Other patients at particular risk:
In patients who are malnourished or showing markedly poor general state of health, or whose calorie intake is irregular, or whose kidney or liver function is impaired, treatment should be begun at the lowest dose. The stepwise increases in dosage must be scrupulously as adhered to in order to avoid a hypoglycaemic reactions (see section "Special warnings and precautions for use").

Patients treated with other oral hypoglycaemic agents:
As with any sulfonylurea, this medicinal product can be used as follow-on from another antidiabetic drug, without any transitional period being needed. When patients change to this medication from a sulfonylurea with a longer half-life (such as chlorpropamide), they must be closely monitored (for several weeks). This is to avoid the possible occurrence of hypoglycaemia due to an overlapping of effects from the two treatments.

Paediatric population
The safety and efficacy of Diamicron 80 mg in children and adolescents have not been established. No data are available.

Method of administration
Oral route.

CONTRA-INDICATIONS
This medicinal product is contraindicated in cases of:
- Hypersensitivity to gliclazide or to any of the excipients, other sulfonylureas, sulfonamides,
- 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 section "Interaction with other medicinal products and other forms of interaction"),
- Lactation (see section "Fertility, pregnancy and lactation").

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 can occur following administration of sulfonylureas (see section "Undesirable effects").

Some episodes can 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 "Interaction with other medicinal products and other forms of interaction").

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 "Undesirable Effects"), 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 (see section "Interaction with other medicinal products and other forms of interaction"), fever, injury, infection or surgery.
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.

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 non-sulphonylurea alternative should be considered.

Porphyric patients:
Cases of acute porphyria have been described with some other sulfonylurea drugs, in patients who have porphyria

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The following substances can increase hypoglycaemia:

Combination contraindicated
- **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 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:**

"Antabuse effect", in particular with chlorpropamide, glibenclamide, glipizide and tolbutamine.
Increases hypoglycaemic reaction (due to inhibition of compensating reactions), that can lead to the onset of hypoglycaemic coma.
Consumption of alcoholic drinks and of medicinal products containing alcohol should be avoided.

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 antidiabetic agents (insulin, acarbose, metformin, thiazolidinediones, dipeptidylpeptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitor (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarythromycin and non-steroidal anti-inflammatory agents.

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 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 antidiabetic 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 antidiabetic active substance during and after treatment with the neuroleptic agent.

- **Glucocorticoids (systemic route and local route: intraarticular use, cutaneous or rectal preparations) and tetracosactide**

Increase in 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 antidiabetic active substance during and after treatment with glucocorticoids.

- **Ritodrine, salbutamol, terbutaline (I.V. route)**

Increased blood glucose levels due to beta-2 agonist effects.
Emphasise the importance of monitoring blood glucose levels.
If necessary, switch to insulin.

- **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.

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…)**

Sulfonylureas may lead to potentiation of anticoagulation during treatment.
Adjustment of the anticoagulant posology may be necessary.

FERTILITY, PREGNANCY AND LACTATION

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 (see section "Preclinical Safety Data").
As a precautionary measure, it is preferable to avoid the use of gliclazide during pregnancy.
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 (see section "Preclinical safety date").

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Diamicron 80 mg has no or negligible 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.

UNDESIRABLE EFFECTS

Based on the experience with gliclazide, the following undesirable effects have been reported:

Hypoglycaemia

The most frequent adverse reaction with gliclazide is hypoglycaemia.
As for other sulfonylureas, treatment with Diamicron can cause hypoglycaemia, in particular if mealtimes are irregular and 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.

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 autoimmune bullous disorders), 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via PUSAT FARMAKOVIGILANS-BPOM: Tlp. 021-4245459, 021-4244755 Ext. 111, Fax. 021-4243605, 021-42885404; Email: pv-center@pom.go.id and/or Indonesia-MESO-BadanPOM@hotmail.com.

OVERDOSE

An overdose of sulfonylurea drugs 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 hospitalisation.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: SULFONYLUREA – ORAL ANTIDIABETIC (A: Alimentary tract and metabolism), ATC code: A10BB09.

Mechanism of action

Gliclazide reduces blood glucose by stimulating insulin secretion from the βcells in the islets of Langerhans.

Pharmacodynamic effects

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.

Hemo-vascular 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.

Pharmacokinetic properties

Absorption

Gliclazide is rapidly absorbed from the gastrointestinal tract, and the concentration in the blood reaches a maximum 11-14 hours after administration.

Distribution

In humans, binding to proteins is 94.2%.

Elimination

As the apparent terminal elimination half-life for gliclazide is 20 hours in humans, the drug can be administered in two daily doses.
Elimination is mainly in the urine: less than 1% of the dose ingested is found unchanged in the 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 foetal 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

STORAGE

Store below 30ºC
Shelf life : 5 years

PRESENTATION

Box of 120 tablets in 12 strips of 10 tablets

Reg. No. : DKL1604524910A1

HARUS DENGAN RESEP DOKTER

Manufactured by :

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