IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1151/026/002
Case No: 2069197

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

DIAMICRON, 80 Milligram

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/08/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diamicron 80mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg gliclazide.
Excipients include: lactose monohydrate
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
Product imported from UK
White, circular, flat, bevel-edged, cross scored compressed tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of diabetes mellitus of the maturity onset type, which is not adequately controlled by dietary means, and does not require insulin therapy.

4.2 Posology and method of administration

Adults only:
The final dosage regimen depends upon the individual requirements of the patient and is at the discretion of the physician.
The dose will be generally between 80 and 320 mg daily.
Biguanide hypoglycaemic agents may be added to the regimen if required.

4.3 Contraindications

- known hypsersensitivity to gliclazide or to any of the excipients, 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 (see Section “Interactions with other medicinal products and other forms of interaction”),
- Pregnancy and lactation (see Section “Pregnancy and Lactation”).

4.4 Special warnings and precautions for use

HYPOGLYCAEMIA:
This treatment should be prescribed only if the patient is likely to have a regular food intake (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 consumed or if the food is low in carbohydrate.

Hypoglycaemia is more likely to occur during loc-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.
Hypoglycaemia may occur following administration of suphonylureas (see 4.8. Undesirable effects). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Factors which increase the risk of hypoglycaemia:
- patient refuses or (particularly in elderly subjects) is unable to co-operate,
- 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 80 mg Tablets,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of certain other medicines (see Interactions).

Renal and hepatic insufficiency: the pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

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.

Poor blood glucose control: blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. 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.

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.

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

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulfonylurea agents, cautions should be used in patients with G6PG-deficiency and a non-sulfonylurea alternative should be considered.

4.5 Interaction 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 (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use a different anti-inflammatory agent, or else to 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: increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma.

Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use

Potentation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken, for example:

Other antidiabetic agents (insulins, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, and nonsteroidal anti-inflammatory agents.

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 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 anitdiabetic agent during and after treatment with danazol.

Cominations 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 and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood clucose 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.)

Increase blood glucose levels due to beta-2 agonist effects. Emphasis the importanace of monitoring blood glucose levels. If necessary, switch to insulin.

3) Combination which must be taken into account

▪ Anticoagulant therapy (Warfarin …):

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

4.6 Pregnancy and lactation

Pregnancy

There is no experience with the use of gliclazide during pregnancy in humans, even though there are few data with other sufonylurea. In animal studies, gliclazide is not teratogenic.

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.

Lactation

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 mothers.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Based on the experience with gliclazide and with other sulphonylureas, the following undesirable effects have to be mentioned.

Hypoglycaemia

As for other sulfonylureas, treatment with Diamicron 80 mg 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 reaction, 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.

Gastro-intestinal 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.
- Hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, Alkaline phosphatise), 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 sulfonylureas 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 sulfonylurea or led to life-threatening liver failure in isolated cases.

4.9 Overdose

An overdose of sulphonylureas may cause hypoclycamia.
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 and other neruolocial 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

SULFONAMIDES,UREA DERIVATIVES, ATC code: A10BB09
Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic active substance differing from other related compounds y an N-containing heterocyclic ring with an endocylic bond.
Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. 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, 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.

Haemovascular properties:
Gliclazide decreases microthrombosis by two mechanisms which maybe 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 B_2).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

5.2 Pharmacokinetic properties

The drug's plasma level peaks at 4-6 hours, it is extensively metabolised and excreted through the kidney with a half life of about 10 hours. It is strongly protein bound.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carninogenicity 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
maize starch
pregelatinised maize starch
magnesium stearate
talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

No special precaution for storage.

6.5 Nature and contents of container

PVC/Aluminium blisters in a cardboard carton. Pack size 60 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/26/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th December 2007

10 DATE OF REVISION OF THE TEXT

August 2009