IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA0465/045/002A
Case No: 2083314

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Diamicron MR 30mg Modified Release Tablets

the particulars of which are set out in 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 **02/07/2010**.

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 MR 30mg Modified Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains gliclazide 30 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release tablet.

Product imported from the UK, Greece and Belgium:

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

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.

4.2 Posology and method of administration

Oral use.

For adult use only.

The daily dose may vary between 1 and 4 tablets per day, i.e. from 30 to 120 mg taken orally, once daily.
It is recommended that the tablet(s) be taken at breakfast time.
It is recommended that the tablet(s) be swallowed whole.
If a dose is forgotten, there must be no increase in the dose taken the next day. As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbAlc).

Initial dose
The recommended starting dose is 30 mg daily.
If blood glucose is effectively controlled, this dose may be used for maintenance treatment.

If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month except in patients whose blood glucose has not reduced after two weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment.

The maximum recommended daily dose is 120 mg.

Switching from Diamicron 80mg tablets to Diamicron MR 30mg:
1 tablet of Diamicron 80 mg is comparable to 1 tablet of Diamicron MR 30 mg. Consequently the switch can be

performed provided there is careful blood monitoring.

Switching from another oral antidiabetic agent to Diamicron MR 30mg:
Diamicron MR 30mg can be used to replace other oral antidiabetic agents.
The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to Diamicron MR 30mg.

A transitional period is not generally necessary. A starting dose of 30mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above.
When switching from a hypoglycaemic sulphonylurea with a prolonged half-life, a treatment free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycaemia. The procedure described for initiating treatment should also be used when switching to treatment with Diamicron MR 30mg, i.e. a starting dose of 30 mg/day, followed by a stepwise increase in dose, depending on the metabolic response.

Combination treatment with other antidiabetic agents:
Diamicron MR 30 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.
In patients not adequately controlled with Diamicron MR 30mg, concomitant insulin therapy can be initiated under close medical supervision.

In the elderly (over 65)
Diamicron MR 30 mg should be prescribed using the same dosing regimen recommended for patients under 65 years of age. In patients with mild to moderate renal insufficiency the same dosing regimen can be used as in patients with normal renal function with careful patient monitoring. These data have been confirmed in clinical trials.

In patients at risk of hypoglycaemia:
- Undernourished or malnourished
- Severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency)
- Withdrawal of prolonged and/or high dose corticosteroid therapy
- Severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease);

It is recommended that the minimum daily starting dose of 30 mg is used.

There are no data and clinical studies available in children.

4.3 Contraindications

- Known hypersensitivity 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")
- 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 low-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 sulphonylureas *(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 cooperate
- 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 MR 30mg
- 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 bv 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 gliciazide, 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 assessingblood glucose control. Blood glucose self-monitoring may also be useful.

Treatment of patients with G6PD-deficiency with sulfonylurea can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-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

Potentiation 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, sulphonamides, 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 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 and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: 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.)**

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

3. Combination which must be taken into account

- **Anticoagulant therapy** (Warfarin)**:**

Sulphonylureas 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 sulphonylureas.

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 breastfeeding 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 sulphonylureas, treatment with Diamicron MR 30mg 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, drowsiness, 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.

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, and constipation have been reported: if these should occur it is recommended to take the tablets after breakfast.

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

- Skin and subcutaneous tissue disorders: rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions. Allergic vasculitis has been reported in very rare cases for other sulphonylureas.

- 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.

Rare cases of erythrocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia have been described for other sulphonylureas.

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

With other sulphonylureas rare cases were 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 sulphonylurea or led to life-threatening liver failure in isolated cases.

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 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 50ml 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 1g/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

HYPOGLYCAEMIC SULPHONYLUREA - ORAL BLOOD GLUCOSE LOWERING DRUG
(A10BB09: Alimentary tract and metabolism)

Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic 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 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 B_2).

- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

5.2 Pharmacokinetic properties

Plasma levels increase progressively during the first 6 hours, reaching a plateau which is maintained from the sixth to the twelfth hour after administration.
Intra-individual variability is low.

Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption. The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear.

Plasma protein binding is approximately 95%.

Gliclazide is mainly metabolised in the liver and excreted 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 varies between 12 and 20 hours.

The volume of distribution is around 30 litres.

No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.

A single daily dose of Diamicron MR 30mg maintains effective gliclazide plasma concentrations over 24 hours.

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 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.

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

The shelf-life expriy date of this product is 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

Store in the original package.

6.5 Nature and contents of container

Blister packs containing 56 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

PCO Manufacturing Ltd.,
Unit 10, Ashbourne Business Park
Rath
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/045/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 August 2002

Date of last renewal: 01 August 2007

10 DATE OF REVISION OF THE TEXT

May 2009