SCHEDULING STATUS:

S3

1 NAME OF THE MEDICINE

DIAGEN MR 30 Modified release tablet

DIAGEN MR 60 Modified release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains 30 mg or 60 mg gliclazide.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release tablets.

DIAGEN MR 30: A white to off-white, oblong, biconvex tablet debossed with “M” on one side of the tablet and “GL30” on the other side.

DIAGEN MR 60: A white to off-white, oblong, biconvex tablet debossed with” M” on the left side of the breakline on one side and GL on the left side of the breakline and 60 on the right side of the breakline on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DIAGEN MR is indicated as in Type 2 diabetic patients, in association with dietary measures, life-style changes and exercise, when dietary measures, life-style and exercise alone are not sufficient to control blood glucose.

4.2 4.2 Posology and method of administration

Posology:

For adult use only:

The daily dose may vary from 30 mg to 120 mg taken as a single daily dose. It is recommended that the medication be taken with breakfast

If a dose is forgotten, the dose taken on the next day should not be increased. The dose should be adjusted according to the individual patient's metabolic response (blood glucose levels and/or glycosylated haemoglobin HbA_{1c}).

Initial dose:

The initial recommended dose is 30 mg once daily, taken with breakfast.

Dose adjustment:

If fasting blood glucose levels have not decreased satisfactorily, the dosage can be increased progressively 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 have not decreased after 15 days of treatment. In this case, it is possible to propose a dosage increase at the end of the second week of treatment. The daily dose should not exceed 120 mg. Previously untreated patients should commence with a dose of 30 mg.

Replacement of gliclazide 80 mg with DIAGEN MR 30:

In patients stabilised on gliclazide 80 mg, the replacement of gliclazide 80 mg by **DIAGEN MR 30** may initially be based on:

1 tablet gliclazide 80 mg = 1 tablet of **DIAGEN MR 30**.

Replacement of another sulphonylurea with DIAGEN MR 30:

DIAGEN MR 30 can replace another sulphonylurea treatment. For the transition to **DIAGEN MR 30**, the dosage and the half- life of the previous oral hypoglycaemic medicine must be considered. If a patient is changed from another oral sulphonylurea with a prolonged half-life, a therapeutic window of a few days may prove to be necessary to avoid the additive effect of the two products and the subsequent risk of hypoglycaemia. During such a changeover, it is recommended to follow the same procedure as for the initiation of the treatment with **DIAGEN MR 30,** i.e. to initiate treatment with a dose of 30 mg per day and then increase the dosage by increments, according to the metabolic evolution of each patient.

Association with other oral antidiabetic medicines:

DIAGEN MR, can be given in combination with alpha glucosidase inhibitors or insulin, but in that case, diabetic control should be checked with blood sugar readings, because of the possibility of hypoglycaemia. In combined therapy with biguanides, there may be a greater risk of cardiovascular mortality than with the use of gliclazide alone.

Special Populations

Elderly

DIAGEN MR should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

Renal impairment

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.

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.

Paediatric population

The safety and efficacy of **DIAGEN MR** in children and adolescents have not been established. No data are available in children.

4.3 Contraindications

- Known hypersensitivity to gliclazide, other sulphonylureas or sulphonamides or to any of the excipients (see section 6.1).
- Type 1 diabetes.
- Diabetic pre-coma and coma, diabetic keto-acidosis.
- Severe renal or hepatic insufficiency
- Treatment with miconazole (see section 4.5).
- Pregnancy and Lactation (see section 4.6).

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 sulfonylureas (see section 4.8). 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 **DIAGEN MR**,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of certain other medicines (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. 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 (see section 4.8), 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.
If 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.

Factors favoring hypoglycaemia include:

Poor blood glucose control: blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: St. John's Wort (*Hypericum perforatum*) preparations (see section 4.5), fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic medicine, 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. Careful monitoring of blood glucose is recommended in all patients receiving at the same time **DIAGEN MR** and a fluoroquinolone. (see section 4.5)

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 with sulfonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the chemical class of sulfonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered. (see section 4.5)

4.5 Interaction with other medicines and other forms of interaction

The following products are likely to increase the risk of hypoglycaemia

Contraindicated combination:

- Miconazole, fluconazole, ketoconazole (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 sulfonylureas (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: other anti-diabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulfonamides, clarithromycin 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 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.

- St John's Wort (*Hypericum perforatum*) preparations:

Gliclazide exposure is decreased by St John's Wort - *Hypericum perforatum*. Emphasise the importance of blood glucose levels monitoring.

Ephedrine, pseudoephedrine and common cold medicines.

The following products may cause dysglycaemia

Combinations requiring precautions during use:

- Fluoroquinolones: in case of a concomitant use of DIAGEN MR and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.

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 Fertility, pregnancy and lactation

Pregnancy

There is no or limited amount of data from the use of gliclazide in pregnant women, even though there are few data with other sulfonylureas. **DIAGEN MR** is contraindicated during pregnancy. (See section 4.3)

Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Insulin is the medicine 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 unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, **DIAGEN MR** is therefore contra-indicated in breast-feeding mothers. (See section 4.3)

Fertility

No effect on fertility or reproductive performance was noted in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

DIAGEN MR 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.

4.8 Undesirable effects

a) Summary of adverse effects

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

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As for other sulfonylureas, treatment with **DIAGEN MR** 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 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.

b) Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and the lymphatic system disorders	Less frequent	anaemia, leucopenia, thrombocytopenia, granulocytopenia
Metabolism and nutrition disorders	Frequent	hypoglycaemia (see section 4.4).
Nervous system disorders	Frequent	sweating, clammy skin, anxiety
Eye disorders	Less frequent	transient visual disturbances
Cardiac disorders	Frequent	tachycardia, palpitations, angina pectoris and cardiac arrhythmia
Vascular disorders	Frequent	hypertension

Gastrointestinal disorders	Less frequent	abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation
Hepato-biliary disorders	Less frequent	raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis, jaundice
Skin and subcutaneous tissue disorders	Less frequent	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)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

An overdose of sulfonylureas 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 (50 %). This should be followed by continuous infusion of a more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels above 5,5 mmol/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

Pharmacotherapeutic group: sulfonamides, urea derivative ATC code: A10BB09

Mechanism of action

Gliclazide is a hypoglycaemic sulfonylurea 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.

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.

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 B2).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

Plasma protein binding is approximately 95 %. The volume of distribution is around 30 litres. A single daily intake of **DIAGEN MR** maintains effective gliclazide plasma concentrations over 24 hours.

Biotransformation

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.

Elimination

The elimination half-life of gliclazide varies between 12 and 20 hours.

Linearity/non-linearity

The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear.

Special Populations:

Elderly

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

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. Fertility and reproductive performance were unaffected after gliclazide administration in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Magnesium stearate (E572)
Microcrystalline cellulose (E460I)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.
Store in original container.
Keep out of reach of children.

6.5 Nature and contents of container

DIAGEN MR 30:

PVC blister pack comprises of clear, transparent, PVC film on one side and hard tempered aluminium foil coated with heat seal lacquer on other side. Ten tablets per strip. 30/60/90 tablets per carton.

PVC/PVDC blister pack comprises of clear, transparent, PVC film coated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on other side. Ten tablets per strip. 30/60/90 tablets per carton.

HDPE bottle pack comprises of round wide mouth white high-density polyethylene bottle with white opaque polypropylene child resistant closure with wad containing aluminium induction sealing liner with absorbent cotton.

60 / 100 tablets per bottle.

DIAGEN MR 60:

HDPE bottle pack comprises of round wide mouth white high-density polyethylene (HDPE) bottle with white opaque polypropylene child resistant closure (CR) with wad containing aluminium induction sealing liner with desiccant (silica gel sachet/canister).60 / 100 tablets per bottle.

HDPE bottle pack (marketable pack) comprises of round wide mouth white high density polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminum induction sealing liner wad with desiccant (silica gel canister). 30 tablets per bottle.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD
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8 REGISTRATION NUMBERS

DIAGEN MR 30 mg: 52/21.2/1025

DIAGEN MR 60 mg: 52/21.2/1026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2021

10 DATE OF REVISION OF THE TEXT

07 September 2022