PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

DIARAN MR 30 Modified Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains gliclazide 30 mg.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablets

White to off-white, biconvex, uncoated caplet with “G30” debossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of maturity onset diabetes mellitus (non-insulin dependant or Type II), where dietary management has been insufficient.

4.2 Posology and method of administration

Posology

For adult use only

The daily dose may vary from 1 to 4 tablets a day, i.e. 30 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 2nd 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 DIARAN MR 30

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

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

Replacement of another sulfonylurea with DIARAN MR 30

DIARAN MR 30 can replace another sulphonylurea treatment. For the transition to **DIARAN MR 30,** the dosage and the half-life of the previous oral hypoglycaemic agent must be taken into account. If the patient is changed from another 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 change over, it is recommended to follow the same procedure as for the initiation of the treatment with **DIARAN 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 evaluation of each patient.

Association with other oral antidiabetic agents

DIARAN MR 30 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 greater risk of cardiovascular mortality than with the use of gliclazide alone.

Special populations

Elderly patients and patients with renal failure

The dosage of **DIARAN MR 30** in subjects over 65 years and patients with mild to moderate renal failure (30-80 ml/min) will be identical to that recommended for adults under the age of 65 years, and for patients with normal renal function, with careful patient monitoring.

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.

Method of administration

DIARAN MR 30 must be taken in the morning with breakfast.

4.3 Contraindications

- Hypersensitivity to gliclazide other sulphonylureas, sulphonamides or to any of the excipients listed in section 6.1.
- Type 1 diabetes(Juvenile Insulin Dependent Diabetes Mellitus), diabetic keto-acidosis, and diabetic pre-coma and coma.
- Use in Type II diabetes mellitus is contra-indicated in patients with ketoacidosis and in those with severe infection, trauma, or other severe conditions where sulphonylurea is unlikely to control the hyperglycaemia. In such situations insulin should be administered.
- Children
- Severe renal or hepatic insufficiency.
- Treatment with miconazole.
- Pregnancy
- Lactation
- Safety in pregnant and breastfeeding mothers has not been established (see section 4.6) .

4.4 Special warnings and precautions for use

Should be avoided in patients with impairment of renal or hepatic function especially in the elderly, debilitated or malnourished patients, and those with adrenal pituitary insufficiency.

The administration of DIARAN MR 30 may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

Reduction in dose may be necessary in patients with mild to moderate renal dysfunction(see sections 4.3 and 4.2).

Hypoglycaemia may occur following administration of sulfonylureas including DIARAN MR 30 (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 favouring hypoglycaemia include:

- Patient refusing or (particularly in elderly subjects) being unable to co-operate.
- Malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes.
- Imbalance between physical exercise and carbohydrate intake.
• Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency.

These disorders should be controlled by appropriate therapy before introducing **DIARAN MR 30.**

- Concomitant administration of certain other medicines (see section 4.5).
- Deterioration in renal function

This treatment should only be prescribed if the patient is likely to have a regular food intake (including breakfast).

Hypoglycaemia is more likely to occur during periods of low-calorie diet, irregular carbohydrate intake, following prolonged or strenuous exercise, following alcohol intake or during the administration of a combination of hypoglycaemic agents.

Symptoms of hypoglycaemia usually disappear after absorption of carbohydrates (sugar). However, despite initial effective measures, hypoglycaemia may occur. Artificial sweeteners have no effect on hypoglycaemia. In the case of severe prolonged hypoglycaemia, immediate medical treatment and even hospitalisation is necessary.

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: 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 **DIARAN MR 30**, 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 **DIARAN MR 30** 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 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.

Porphyric patients:

Cases of acute porphyria have been described with some other sulfonylurea medicines, in patients who have porphyria.

4.5 Interaction with other medicines and other forms of interaction

The following products are likely to increase the risk of hypoglycaemia:

Contraindicated combinations:

- Miconazole, (systemic route, oral gel). Increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma (see section 4.3).

Combinations which are not recommended:

- Phenylbutazone (systemic route). Increases the hypoglycaemic effect of sulphonylureas.

- Alcohol. Avoid intake of alcohol or medication containing alcohol.

Combinations requiring precautions for use:

- Fluconazole, ketoconazole (systemic route, oral gel)
- Beta-blockers (may mask the symptoms of hypoglycaemia and may inhibit the normal physiological response to hypoglycaemia).
- Cimetidine, ranitidine.
- Other antidiabetic agents (insulin, acarbose, biguanides; metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists)

- ACE-inhibitors (captopril, enalapril)

- Sulphonamides
- NSAIDS
- Mono-amine-oxidase inhibitors.
- Chloramphenicol.

Potentiation of the hypoglycaemic action of the medicine may also occur with the concomitant administration of clofibrate or halofenate, cyclophosphamide and dicoumarol.

The following products may cause an increase in blood glucose level:

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 for use

- Chlorpromazine: (neuroleptic agent): high doses (> 100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).
- Glucocorticoids: (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis.
- Salbutamol, terbutaline, ritodrine and other beta-adrenergic agonists: Increased blood glucose levels due to beta-2 agonist effects. Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.
- Ephedrine, pseudoephedrine and common cold products.
- 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 hypoglycaemic action of **DIARAN MR 30** may be reduced with the concomitant administration of thiazide diuretics, corticosteroids, oestrogen and adrenaline.

The following products may cause dysglycaemia:

Combinations requiring precautions during use:

- Fluoroquinolones: in case of concomitant use of **DIARAN MR 30** and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.
- Anticoagulant therapy (warfarin): sulphonylureas such as **DIARAN MR 30** may lead to potentiation of anticoagulation during concurrent treatment. Regular monitoring of the INR is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (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.

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.

Breastfeeding

Safety in breastfeeding has not been established (see section 4.3) .

It is unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, **DIARAN MR 30** is therefore contra-indicated in breastfeeding mothers. A risk to the newborns/infants cannot be excluded.

4.7 Effects on ability to drive and use machines

DIARAN MR 30 has no known influence on the ability to drive and use machines. Patients should be made aware of the symptoms of hypoglycaemia, and should be careful when driving, or operating machinery, especially at the beginning of treatment

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, granulocytopenia. These are in general reversible upon discontinuation of medication.
Immune system disorders	Less frequent	Hypersensitivity reactions
Eye disorders	Less frequent	Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.
Gastrointestinal disorders	Frequent	Abdominal pain, nausea, vomiting, heartburn, , diarrhoea, constipation . This is usually dose dependent. If these should occur, they can be avoided or minimised if DIARAN MR 30 is taken with breakfast.
Metabolism and nutrition disorders	Frequent	Anorexia
Hepatobiliary disorders	Less frequent	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.
Skin and subcutaneous tissue disorders	Frequent	Skin reactions and pruritus may occur and photosensitivity has been reported. Rashes may progress to more serious disorders.

	Less frequent	Urticaria, Erythema multiforme, maculopapular rashes and bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), exfoliative dermatitis, erythema nodosum, and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).
General disorders and administration site conditions	Frequent	Metallic taste may occur.

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.

The following side-effects have been reported and the frequencies are unknown:

Hypoglycaemia:

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As for other sulphonylureas, treatment with **DIARAN MR 30** 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. 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 is required.

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 DIARAN MR 30 may cause hypoglycaemia which could be severe and prolonged.

Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or modification of diet.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders should be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of 50 ml of concentrated glucose solution (20 – 30 %). This should be followed by continuous infusion of a more dilute solution (10 %), at a rate necessary to maintain blood glucose levels above 5,5 mmol/l.

Patients should be monitored closely, long enough to be sure that hypoglycaemia will not re-occur, and, depending on the patient's condition, the doctor will decide if further monitoring is necessary.

Dialysis is of no use in these patients due to the strong binding of gliclazide to proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral Hypoglycaemics.

Gliclazide is a second generation sulphonylurea. Gliclazide causes lowering of blood glucose by stimulating insulin release from pancreatic ß-cells. It further increases insulin levels by reducing hepatic clearance of the hormone.

The effect of gliclazide is initiated by binding to and blocking an ATP–sensitive K + channel.

5.2 Pharmacokinetic properties

Absorption

Gliclazide is absorbed from the gastro-intestinal tract. The elimination half-life of gliclazide varies between 12 to 20 hours.

Distribution

Plasma levels increase progressively until the sixth hour, resulting in a plateau-shaped curve from the sixth to twelfth hour after administration. The relationship between the dose administered and the area under concentration curve, as a function of time, is linear up to 120 mg. In plasma it is approximately 85–97% bound to plasma protein, especially albumin. The volume of distribution is 0,2 l/kg.

Biotransformation

Gliclazide is metabolized by the liver and all the metabolites are excreted in the urine.

Elimination

A single daily dose of **DIARAN MR 30** maintains glucose-lowering effects over 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (PVP K30)

Calcium hydrogen phosphate dihydrate

Hypromellose

Colloidal anhydrous silica

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from moisture.

6.5 Nature and contents of container

Cartons contain 30 or 60 tablets packed in cold form blister strips or PVdC coated PVC blister strips of 10 tablets each.

Cold form blister strips comprise of cold form blister laminate composed of aluminium foil (one side bright, soft tempered, plain; dull side lacquer laminated to oriented polyamide film; bright side lacquer laminated to PVC film), PVC and polyamide with a backing of aluminium foil coated with heat seal lacquer on the inner side.

PVdC coated PVC blister strips comprise of clear transparent PVC film coated uniformly with PVdC on the inner side with a backing of aluminium foil coated with heat seal lacquer on the inner side.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

a Sun Pharma company

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER:

41/21.2/0698

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 March 2010

10. DATE OF REVISION OF THE TEXT

30 November 2022

Namibia: NS2

Diaran MR 30: Reg.No.:10/21.2/0134

Botswana: S2

Diaran MR 30: Reg No.: BOT0701090