Approved Professional Information for DIARAN MR 30 & 60

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DIARAN MR 30 modified release tablets

DIARAN MR 60 modified release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIARAN MR 30:

Each modified release tablet contains gliclazide 30 mg.

Sugar free.

DIARAN MR 60:

Each modified release tablet contains gliclazide 60 mg.

Excipient with known effect:

Contains sugar (134,20 mg lactose monohydrate per tablet)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified Release Tablets

DIARAN MR 30:

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

DIARAN MR 60:

White to off white oval-shaped tablets, scored on both sides, engraved with ‘Z’ and ‘I’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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DIARAN MR is indicated for the treatment of 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 Posology and method of administration

Posology

For adult use only:

The daily dose may vary from 1 to 4 tablets for the DIARAN MR 30 and a half to 2 tablets a day for the DIARAN MR 60, i.e. 30 to 120 mg taken as a single daily dose. It is recommended that the tablets 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 (1 tablet for the DIARAN MR 30 and half a tablet for the DIARAN MR 60) 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.

One DIARAN MR 60 60 mg modified release tablet is equivalent to two DIARAN MR 30 30 mg modified release tablets. The breakability of the DIARAN MR 60 60 mg modified release tablet allows the use of a dose of 30 mg as a half tablet and of 90 mg as one and a half tablets.

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 sulphonylurea with DIARAN MR tablets:

DIARAN MR can replace other sulphonylurea treatment. For the transition to DIARAN MR, the dosage and the half-life at the previous oral hypoglycaemic agent must be taken into account. 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 DIARAN MR, 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 agents:

DIARAN 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 (see section 4.5)

Special populations:

Elderly patients and patients with renal failure:

The efficacy and tolerance of DIARAN MR, prescribed using the same therapeutic regimen in subjects over 65 years and patients with mild to moderate renal failure (30 - 80 mL/min) has been confirmed in clinical trials. The dosage will therefore 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

See section 4.4

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

Paediatric population

The safety and efficacy of DIARAN MR in children and adolescents have not been established.

No data are available.

Method of administration

DIARAN MR is for oral use.

The tablets are to be swallowed whole.

4.3 Contraindications

This medicine is contra-indicated in case of:

- Hypersensitivity to gliclazide or to any of the excipients listed in section 6.1, 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 4.5),
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

A reduction in dosage may be necessary in patients with renal dysfunction (see sections 4.3 and 4.2)

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.

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. In an exceptional stress situation e.g. trauma, fever, infection or surgical intervention, blood glucose regulation may deteriorate and a temporary change to insulin may be necessary to maintain good metabolic control.

Gastrointestinal side-effects can be avoided or minimised if DIARAN MR is taken with breakfast.

Hepato-biliary symptoms usually disappear after discontinuation of treatment. Discontinue treatment if cholestatic jaundice appears. Beta-blockers may decrease the efficacy of DIARAN MR (a sulphonyl urea) by impairing the release of insulin. Beta-lockers may mask the typical sympathomimetic warning signs and symptoms of hypoglycaemia and may inhibit the normal physiological response to hypoglycaemia.

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 gliclazide,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of certain other medicines (see section 4.5).

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.

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 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 DIARAN MR and a fluoroquinolone (**see section 4.5**).

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 (**see section 4.6**).

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.

For the DIARAN MR 60

Excipients: Lactose

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

4.5 Interaction with other medicines and other forms of interaction

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 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), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and non-steroidal anti-inflammatory agents (**see section 4.4**).

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.

The following products may cause dysglycaemia

Combinations requiring precautions during use

Fluoroquinolones: in case of a concomitant use of gliclazide modified release tablets 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 and INR should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established, as a precautionary measure, it is preferable to avoid the use of gliclazide during pregnancy (**see sections 4.3 and 4.4**).

Breastfeeding

It is unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the product is therefore contra-indicated in breast-feeding mothers. A risk to the newborns/infants cannot be excluded (**see section 4.3**).

Fertility

No data available.

4.7 Effects on the ability to drive and use machines

DIARAN MR may cause hypoglycaemia. 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

Summary of the safety profile

Class attribution effects: As for other sulfonylureas, the following adverse events have been observed: cases of erythrocytopoenia, agranulocytosis, haemolytic anaemia, pancytopoenia, allergic vasculitis, hyponatremia, 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 failure in isolated cases.

Table 1: Tabulated list of adverse reactions

System organ class	**Frequencies**	**Adverse reactions (Preferred terms)**
Gastro-intestinal disorders	Frequent	Abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
	Frequency not known	Angioedema, urticaria, erythema, maculopapular rashes and bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).
Endocrine disorders	Frequency not known	Hypoglycaemia (**see section 4.4**).
Blood and lymphatic system disorders	Frequency not known	Anaemia, leucopoenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.
Hepato-biliary disorders:	Frequency not known	Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis. Discontinue treatment if cholestatic jaundice appears.
Eye disorders	Frequency not known	Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Description of selected adverse reactions

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As for other sulfonylureas, treatment with DIARAN 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. Experience with other sulfonylureas reported 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the DIARAN MR is important. It allows continued monitoring of the benefit/risk balance of the DIARAN MR. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction 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 (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

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.

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 gliclazide modified release tablets 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 reported in elderly patients.

5.3 Preclinical safety data

No data available

6. Pharmaceutical particulars

6.1 List of excipients

DIARAN MR 30:

Povidone (PVP K30)

Calcium hydrogen phosphate dihydrate

Hypromellose

Colloidal anhydrous silica

Magnesium stearate

DIARAN MR 60:

Pregelatinised starch (Maize),

Lactose monohydrate,

Sodium citrate,

Purified water,

Hypromellose,

Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

DIARAN MR 30: 24 months

DIARAN MR 60: 36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

DIARAN MR 30:

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.

DIARAN MR 60:

Cold form blister pack

Cold form blister pack comprises of cold form blister laminate composed of oriented polyamide, aluminium foil and PVC with backing of aluminium foil coated with heat seal lacquer on the inner side in packs of 30’s.

Triplex blister pack

Triplex blister pack comprises of clear transparent PVC film laminated with polyethylene and coated with PVdC on inner side with the backing of hard tempered, aluminium foil coated with heat seal lacquer on inner side, in packs of 30’s.

HDPE bottle pack:

HDPE bottle pack comprises of white opaque HDPE bottle with child resistant closure with induction seal liner and absorbent cotton in packs of 30's and 100's.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

RANBAXY PHARMACEUTICALS (PTY) LTD

a Sun Pharma company

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

8. Marketing authorisation number(s)

DIARAN MR 30: 41/21.2/0698

DIARAN MR 60: 49/21.2/0926.927

9. Date of first authorisation/renewal of the authorisation

DIARAN MR 30: 19 March 2010

DIARAN MR 60: 27 July 2021

10. Date of revision of the text

To be advised

Namibia: NS2

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

Botswana: S2

Diaran MR 30: Reg.No.: BOT0701090