PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

GLICLAZIDE MR 30 mg ZYDUS, 30 mg modified-release tablets

GLICLAZIDE MR 60 mg ZYDUS, 60 mg modified-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GLICLAZIDE MR 30 mg ZYDUS: Each modified-release tablet contains 30 mg gliclazide.

GLICLAZIDE MR 60 mg ZYDUS: Each modified-release tablet contains 60 mg gliclazide.

Excipients with known effect:

Contains sugar: lactose monohydrate.

GLICLAZIDE MR 30 mg ZYDUS: Each modified-release tablet contains 59,4 mg lactose monohydrate.

GLICLAZIDE MR 60 mg ZYDUS: Each modified-release tablet contains 118,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablets.

GLICLAZIDE MR 30 mg ZYDUS: White to cream white, oblong, uncoated tablets, engraved with “30” on one side and plain on the other side.

GLICLAZIDE MR 60 mg ZYDUS: White to cream white, oblong, uncoated tablets, engraved with “60” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In Type 2 diabetic patients, in association with dietary measures, life-style changes and exercise, when dietary measures, lifestyle and exercise alone are not sufficient to control blood glucose.

4.2 Posology and method of administration

For adult use only

The daily dose may vary from 1 to 4 tablets a day, i.e. 30 mg to 120 mg taken as a single daily dose. It is recommended that GLICLAZIDE MR ZYDUS 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 mg, 90 mg 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 GLICLAZIDE MR 30 mg ZYDUS

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

1 tablet gliclazide 80 mg = 1 tablet of GLICLAZIDE MR 30 mg ZYDUS.

Replacement of another sulphonylurea with GLICLAZIDE MR ZYDUS

GLICLAZIDE MR ZYDUS can replace other sulphonylurea treatment. For the transition to GLICLAZIDE MR ZYDUS, the dosage and the half-life of the previous oral hypoglycaemic medicine 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 GLICLAZIDE MR ZYDUS, 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

GLICLAZIDE MR ZYDUS 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 MR ZYDUS alone.

Special populations

Elderly patients and patients with renal failure

The efficacy and tolerance of gliclazide, as in GLICLAZIDE MR ZYDUS, prescribed using the same therapeutic regimen in subjects over 65 years and patients with mild to moderate renal failure (creatinine clearance 30 – 80 mL/min) have 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

- 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.

Children and adolescents

The use of GLICLAZIDE MR ZYDUS in children is contraindicated (see section 4.3).

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to gliclazide, other sulphonylureas, sulphonamides, or to any of the excipients of GLICLAZIDE MR ZYDUS listed in section 6.1.
- Type 1 diabetes (juvenile insulin-dependent diabetes mellitus), diabetic ketoacidosis, and diabetic pre-coma and coma.
- Children.
- 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

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

Hypoglycaemia

This treatment should only be prescribed 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 medicines is being used.

Hypoglycaemia may occur following administration of sulphonylureas, including GLICLAZIDE MR ZYDUS (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 MR ZYDUS,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency (these disorders should be controlled by appropriate therapy before introducing GLICLAZIDE MR ZYDUS),
- 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.

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 MR ZYDUS, 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 GLICLAZIDE MR ZYDUS and a fluoroquinolone at the same time.

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 sulphonylurea medicines can lead to haemolytic anaemia. Since gliclazide belongs to the chemical class of sulphonylurea medicines, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

Porphyric patients:

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

GLICLAZIDE MR ZYDUS contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total 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

Contraindicated combination

Miconazole (systemic route, oromucosal 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 (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use a different anti-inflammatory medicine, 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 medicine.

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 medicines is taken: other antidiabetic medicines (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, ketoconazole, angiotensin-converting enzyme (ACE)

inhibitors (captopril, enalapril), H2 receptor antagonists (cimetidine, ranitidine), monoamine oxidase inhibitors (MAOIs), sulphonamides, clarithromycin, chloramphenicol and nonsteroidal anti-inflammatory drugs (NSAIDs).

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 medicine during and after treatment with danazol.

Combinations requiring precautions during use

Chlorpromazine (neuroleptic medicine): High doses (> 100 mg chlorpromazine per day) 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 medicine.

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 [intravenous (IV)] 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.

St John's wort (Hypericum perforatum) preparations: Gliclazide exposure is decreased by St John's wort (*Hypericum perforatum*). Emphasise the importance of blood glucose monitoring.

The following products may cause dysglycaemia

Combinations requiring precautions during use

Fluoroquinolones: In case of concomitant use of GLICLAZIDE MR ZYDUS 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): Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary. Regular monitoring of the international normalised ratio (INR) may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

It is unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the product is therefore contraindicated in breastfeeding mothers. A risk to the newborns/infants cannot be excluded.

Fertility

No effect on fertility or reproductive performance was noted in male and female rats.

4.7 Effects on ability to drive and use machines

GLICLAZIDE MR ZYDUS has no or negligible influence on the 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

Summary of the safety profile

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As for other sulphonylureas, treatment with GLICLAZIDE MR ZYDUS 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 dysrhythmia.

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.

Blood and lymphatic system disorders

Less frequent: Anaemia, leukopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.

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, dyspepsia, diarrhoea and constipation have been reported: if these should occur, they can be avoided or minimised if GLICLAZIDE MR ZYDUS is taken with breakfast.

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: Rash, pruritus.

Less frequent: Urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis and autoimmune bullous disorders), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).

Description of selected adverse reactions

Class attribution effects:

As for other sulphonylureas, the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, 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 sulphonylurea or led to life-threatening liver failure in isolated cases.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP

(Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

An overdose of GLICLAZIDE MR ZYDUS 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 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 IV 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 5,5 mmol/L. Patients should be monitored closely, long enough to be sure that hypoglycaemia will not reoccur 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

Category and class: A 21.2 Oral hypoglycaemics.

Pharmacotherapeutic group: Sulphonamides, urea derivative.

ATC code: A10BB09.

Mechanism of action

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.

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 GLICLAZIDE MR ZYDUS 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate (E572)

Anhydrous sodium carbonate

Hypromellose

Anhydrous colloidal silica.

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.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVDC/silver aluminium blister strips packed into an outer carton.

Pack sizes:

GLICLAZIDE MR 30 mg ZYDUS: 60 tablets.

GLICLAZIDE MR 60 mg ZYDUS: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

GLICLAZIDE MR 30 mg ZYDUS: 53/21.2/0553.551

GLICLAZIDE MR 60 mg ZYDUS: 53/21.2/0554.552

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

26 November 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.