APPROVED SPC

For

Gliclazide Unicorn MR 30 mg

Registration No.: 38/21.2/0224

Date Approved: November 2017

Confidential Information

Gliclazide Unicorn MR 30 mg

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

Gliclazide Unicorn MR 30 mg, modified release tablet.

COMPOSITION:

Each modified release tablet contains 30 mg of gliclazide.

The other excipients are: calcium hydrogen phosphate dihydrate, hypromellose, maltodextrin, magnesium stearate and silica colloidal anhydrous.

CATEGORY AND CLASS:

A 21.2 Oral Hypoglycaemics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:
Gliclazide is a sulphonylurea hypoglycaemic agent, which reduces blood glucose levels by stimulating insulin secretion from the ß-cells of the islets of Langerhans. In addition to this pancreatic action, it has been demonstrated that gliclazide administration may improve the metabolic utilisation of glucose at a peripheral level.

Pharmacokinetic properties:
Plasma levels increase progressively until the sixth hour, resulting in a plateau-shaped curve from the sixth to the twelfth hour after administration. Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption. The relationship between the dose administered and the area under the concentration curve, as a function of time, is linear up to 120 mg. Plasma protein binding is approximately 95 %.

Gliclazide is 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. No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients.
A single daily dose (varying from 1 – 4 tablets) of **Gliclazide Unicorn MR 30 mg** maintains glucose lowering effects over 24 hours.

INDICATIONS:

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.

CONTRAINDICATIONS:

This medication is contraindicated in the following cases:

- Hypersensitivity to gliclazide, other sulphonylureas, sulphonamides, or to any of the excipients,
- Type 1 diabetes (Juvenile Insulin Dependent Diabetes Mellitus), diabetic keto-acidosis, and diabetic pre-coma and coma,
- Children,
- Severe renal or hepatic insufficiency,
- Treatment with miconazole (see INTERACTIONS),
- Pregnancy,
- Lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

A reduction in dosage may be necessary in patients with mild to moderate renal dysfunction. (see CONTRAINDICATIONS and DOSAGE AND DIRECTIONS FOR USE).

Hypoglycaemiamay occur following administration of sulphonylureas including **Gliclazide Unicorn MR 30 mg** (see SIDE 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.
The administration of oral hypoglycaemics may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

Factors favouring hypoglycaemia include:

- Patient refusing or (particularly elderly patients) 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 **Gliclazide Unicorn MR 30 mg,**
- Concomitant administration of certain other medicines (see INTERACTIONS),
- 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 INTERACTIONS), fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.
The hypoglycaemic effect of **Gliclazide Unicorn MR 30 mg**, 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 **Gliclazide Unicorn MR 30 mg** and a fluoroquinolone.

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

Effects on ability to drive and use machines:
Gliclazide Unicorn MR 30 mg 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.

INTERACTIONS:

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 CONTRAINDICATIONS).

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.
- Cimetidine, ranitidine.
- Other antidiabetic agents (insulin, acarbose, biguanides)
- ACE-inhibitors (captopril, enalapril)
- Sulphonamides.
- NSAIDS
- Mono-amine-oxidase inhibitors.
- Chloramphenicol.

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

Combination which is not recommended

- Danazol: diabetogenic effect of 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 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 following products may cause dysglycaemia:

Combinations requiring precautions during use:

- **Fluoroquinolones:** in case of concomitant use of **Gliclazide Unicorn MR 30 mg** 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 **Gliclazide Unicorn MR 30 mg** may lead to potentiation of anticoagulation during concurrent treatment. Regular monitoring of the INR.

HUMAN REPRODUCTION:

Safety in pregnancy and lactation has not been established. (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

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 **Gliclazide Unicorn MR 30 mg** 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 Gliclazide Unicorn MR 30 mg:

In patients stabilised on gliclazide 80 mg, the replacement of gliclazide 80 mg by **Gliclazide Unicorn MR 30 mg** may initially be based on: 1 tablet gliclazide 80 mg = 1 tablet of **Diaglucide MR**
30 mg.

Replacement of another sulphonylurea with Gliclazide Unicorn MR 30 mg:

Gliclazide Unicorn MR 30 mg can replace other sulphonylurea treatment. For the transition to **Gliclazide Unicorn MR 30 mg**, the dosage and the half-life of 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 **Gliclazide Unicorn MR 30 mg**, 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:

Gliclazide Unicorn MR 30 mg, 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 Unicorn MR 30 mg** alone.

Elderly patients and patients with renal failure:

The efficacy and tolerance of **Gliclazide Unicorn MR 30 mg**, 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) 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:

- 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.

SIDE EFFECTS:

Based on the experience with gliclazide and with other sulphonylureas, the following side effects have to be mentioned.

The following frequency rating has been used:

Very common (≥ 1/10);

Common (≥ 1/100, < 1/10);

Uncommon (≥ 1/1 000, < 1/100);

Rare (≥ 1/10 000, < 1/1000);

Very rare (≤ 1/ 10 000),

Not known (cannot be estimated from available data).

Gastrointestinal disorders:

Common (≥ 1/100 and < 1/10).

Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea and constipation have been reported: if these should occur, they can be avoided or minimised if **Gliclazide Unicorn MR 30 mg** is taken with breakfast.

Skin and subcutaneous tissue disorders:

Common (≥ 1/100 and < 1/10): Rash, pruritus.

Very rare (< 1/10 000): 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).

Blood and lymphatic system disorders:

Very rare (< 1/10 000): Changes may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.

Hepato-biliary disorders:
Very rare (< 1/10 000): 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.

Eye disorders:
Very rare (< 1/10 000): Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

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 **Gliclazide Unicorn MR 30** mg 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.

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT:
An overdose of **Gliclazide Unicorn MR 30 mg** 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.
Strict monitoring should be continued until the patient is out of danger.

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.

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

PRESENTATION:
Aluminium/PVC blister packs of 60 tablets.

STORAGE INSTRUCTIONS:
Store at or below 30 °C.
Keep out of reach of children.

REGISTRATION NUMBER:
38/21.2/0224

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