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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

AZUKON MR

Gliclazide Modified Release Tablets

COMPOSITION

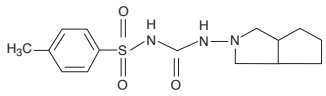
Each uncoated modified release tablet contains :
Gliclazide I.P. 30 mg

PROPERTIES

Gliclazide is a second-generation sulphonylurea drug, having hypoglycemic and potentially useful in hemobiological action.

Chemically Gliclazide is identified as 1-(hexahydro-cyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4-methylphenyl) sulphonyl]urea.

The empirical formula is $C_{15}H_{21}N_3O_3S$ with a molecular weight of 323.4. The chemical structure of Gliclazide is as follows:



Gliclazide is an oral sulfonylurea hypoglycemic agent which stimulates insulin secretion.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans.

In type 2 diabetes, 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.

In addition to these metabolic properties, gliclazide also has haemovascular properties. Gliclazide decreases microthrombosis by partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B_2) and an action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

PHARMACOKINETICS

Plasma levels increase progressively during the first 6 hours, reaching a plateau which is maintained from the sixth to the twelth hour after administration. Intra-individual variability is low. Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption. The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear. Plasma protein binding is approximately 95%. 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. The elimination half-life of gliclazide varies between 12 and 20 hours. The volume of distribution is around 30 litres.

No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients. A single daily dose of Gliclazide 30 mg MR Tablets maintains effective gliclazide plasma concentrations over 24 hours.

INDICATIONS

Therapy of maturity onset Diabetes Mellitus (non-insulin dependent or Type II), where dietary management alone has been insufficient.

CONTRAINDICATIONS

Hypersensitivity to gliclazide or to any of the excipients, other sulphonylureas, sulphonamides. Not to be used for: juvenile onset diabetes; diabetes complicated by ketosis or acidosis; diabetics undergoing surgery, after severe trauma or during infections; diabetic precoma and coma; severe renal or hepatic insufficiency; In patient on Miconazole, porphyria, hyperthyroidism, pregnancy and lactation.

WARNINGS AND PRECAUTIONS

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 sulphonylureas. 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 30 mg MR Tablets,
- Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- Concomitant administration of certain other medicines.

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.

Pregnancy

There is no experience with the use of gliclazide during pregnancy in humans, even though there are few data with other sulphonylureas. In animal studies, gliclazide is not teratogenic. 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.

Lactation

It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, the product is contra-indicated in breast-feeding mothers.

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.

Drug abuse and dependence

Gliclazide has no known potential for abuse or dependence.

ADVERSE EFFECTS

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

Hypoglycaemia

As for other sulphonylureas, treatment with Gliclazide 30 mg MR Tablets 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 hospitalisations are required.

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation have been reported: if these should occur they can be avoided or minimised if gliclazide is taken with breakfast.

The following undesirable effects have been more rarely reported:

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.

Blood and lymphatic system disorders

Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.

Hepato-biliary disorders

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

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Class attribution effects

Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas.

With other sulphonylureas cases were also observed of 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.

DRUG INTERACTIONS

1.Risk of hypoglycaemia

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 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.

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken, for example: Other anti-diabetic agents (insulins, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulphonamides, and non-steroidal anti-inflammatory agents.

2. The following products may cause an increase in blood glucose levels

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.

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.

Other:

Anticoagulant therapy (Warfarin...): Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary.

DOSAGE AND METHOD OF ADMINISTRATION

Adults

The daily dose may vary from 1 to 4 tablets per day, i.e. from 30 to 120 mg taken orally in a single intake at breakfast time.

It is recommended that the tablet(s) be swallowed whole.

If a dose is forgotten, there must be no increase in the dose taken the next day.

As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbA_{1C})

Initial dose

The recommended starting dose is 30 mg daily. If blood glucose is effectively controlled, this dose may be used for maintenance treatment. If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month except in patients whose blood glucose has not reduced after two weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment. The maximum recommended daily dose is 120 mg.

Switching from Gliclazide 80 mg tablets to Gliclazide 30 mg modified release tablets

1 tablet of Gliclazide 80 mg is comparable to 1 tablet of Gliclazide 30 mg MR Tablets. Consequently the switch can be performed provided a careful blood monitoring.

Switching from another oral antidiabetic agent to Gliclazide 30 mg MR Tablets

Gliclazide 30 mg MR Tablets can be used to replace other oral antidiabetic agents. The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to Gliclazide 30 mg MR Tablets. A transitional period is not generally necessary. A starting dose of 30 mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above. When switching from a hypoglycaemic sulphonylurea with a prolonged half-life, a treatment free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycaemia. The procedure described for initiating treatment should also be used when switching to treatment with Gliclazide 30 mg MR Tablets, i.e. a starting dose of 30 mg/day, followed by a stepwise increase in dose, depending on the metabolic response.

Combination treatment with other antidiabetic agents

Gliclazide 30 mg MR Tablets can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

In patients not adequately controlled with Gliclazide 30 mg MR Tablets, concomitant insulin therapy can be initiated under close medical supervision.

In the elderly (over 65)

Gliclazide 30 mg MR Tablets should be prescribed using the same dosing regimen recommended for patients under 65 years of age. 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.

In 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.

Pediatric

There are no data and clinical studies available in children.

SWITCHING OF GLICLAZIDE 80 MG TO GLICLAZIDE 30 MG MR TABLETS

DOSE OF GLICLAZIDE 80 MG	DOSE OF GLICLAZIDE 30 MG MR
80 mg once daily	30 mg once daily
80 mg BID	60 mg once daily
160 mg a.m. and 80 mg p.m.	90 mg once daily
160 mg BID	120 mg once daily

DIRECTIONS FOR USE

Tablet or divided halves of the tablet to be swallowed whole. Do not chew or crush.

OVERDOSE AND ITS TREATMENT

An overdose of sulphonylureas may cause hypoglycemia. Moderate symptoms of hypoglycemia, 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 physician is sure that the patient is out of danger.

Severe hypoglycemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalization.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store in a dry place at a temperature not exceeding $25^{o}C$, protected from light.

Keep all medicines out of the reach of children

PRESENTATION

AZUKON MR is available in blister strip of 10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS (SIKKIM)
32 No. Middle Camp, NH-31A, East District,
Gangtok, Sikkim-737 135.