MedChoice Endocrine

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Gliclazide

Zeltine-MR

30 mg Modified Release Tablet
BLOOD GLUCOSE LOWERING DRUG
(SULFONYLUREA)

FORMULATION:
Each modified-release tablet contains:
Gliclazide ..... 30 mg

PRODUCT DESCRIPTION:
White colored, round shaped, biconvex, uncoated tablet having breakline on one side and plain on other side.

PHARMACOLOGY:
PHARMACODYNAMICS:
Mechanism of action:
Gliclazide is a hypoglycemic 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.
In addition to these metabolic properties, Gliclazide has hemovascular 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.
Hemovascular 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.

PHARMACOKINETICS:
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 liters.
A single daily intake of Gliclazide (Zeltine-MR) 30 mg maintains effective gliclazide plasma concentrations over 24 hours.
Biotransformation:
Gliclazide is mainly metabolized 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.

INDICATIONS:
For non-insulin-dependent diabetes (type 2) in adults, in association with dietary measures and with exercise, when these measures alone are not sufficient.

DOSAGE AND ADMINISTRATION:
The daily dose of Gliclazide (Zeltine-MR) 30 mg 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 to swallow the dose without crushing or chewing.
If a dose is forgotten, there must be no increase in the dose taken the next day.
As with any hypoglycemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbA1c).
Initial dose: The recommended starting dose is 30 mg daily one tablet of Gliclazide (Zeltine-MR) 30 mg. 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.
Consequently the switch can be performed with careful blood monitoring.
Switching from another oral antidiabetic agent to Gliclazide (Zeltine-MR) 30 mg: Gliclazide (Zeltine-MR) 30 mg 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 (Zeltine-MR) 30 mg.
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 previously.
When switching from a hypoglycemic sulfonylurea 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 hypoglycemia. The procedure described for initiating treatment should also be used when switching to treatment with Gliclazide (Zeltine-MR) 30 mg, 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 (Zeltine-MR) 30 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.
In patients not adequately controlled with Gliclazide (Zeltine-MR) 30 mg, concomitant insulin therapy can be initiated under close medical supervision.
Special Populations:
Elderly:
Gliclazide (Zeltine-MR) 30 mg should be prescribed using the same dosing regimen recommended for patients under 65 years of age.
Renal impairment:
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.
Patients at risk of hypoglycemia:
-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 population:
The safety and efficacy of Gliclazide (Zeltine-MR) 30 mg in children and adolescents have not been established. No data are available.
Missed Dose: It is important to take the medicine everyday as regular treatment works better.
However, if the patient forgets to take a dose of Gliclazide (Zeltine-MR) 30 mg, take the next dose at the usual time.
Do not take a double dose to make up for a forgotten dose.
Discontinuation of Treatment: As the treatment for diabetes is usually life long, the patient should discuss with the doctor before stopping this medicinal product.
Stopping could cause high blood sugar (hyperglycemia) which increases the risk of developing complications of diabetes.
If the patient has any further questions on the use of this product, ask the doctor or pharmacist.

CONTRAINDICATIONS:
This medicine is contraindicated in case of:
-Hypersensitivity to Gliclazide or to any of the excipients, other sulfonylurea, 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;
-Lactation.

WARNINGS AND PRECAUTIONS:
Hypoglycemia:
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 hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycemic agents is being used.
Hypoglycemia may occur following administration of sulfonylurea. Some cases may be severe and prolonged.
Hospitalization 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 hypoglycemic episodes.
Factors which increase the risk of hypoglycemia:
-Patient refuses or (particularly in elderly subjects) is unable to cooperate;
- 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 medicinal products.
Renal and hepatic insufficiency:
The pharmacokinetics and/or pharmacodynamics of Gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.
Patient information:
The risks of hypoglycemia, 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, fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.
The hypoglycemic 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.
Dysglycemia:
Disturbances in blood glucose, including hypoglycemia and hyperglycemia 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 (Zeltine-MR) 30 mg and a fluoroquinolone.
Laboratory tests:
Measurement of glycated hemoglobin 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 hemolytic anemia. 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.
Excipients:
Gliclazide (Zeltine-MR) 30 mg should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
Driving and Using Machines:
Gliclazide (Zeltine-MR) 30 mg has no or negligible influence on the ability to drive and use machines. However, patients should be made aware of the symptoms of hypoglycemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

PREGNANCY AND LACTATION:
Pregnancy:
There is no or limited amount of data (less than 300 pregnancy outcomes) from the use of Gliclazide in pregnant women, even though there are few data with other sulfonylurea.
In animal studies, Gliclazide is not teratogenic.
As a precautionary measure, it is preferable to avoid the use of Gliclazide during pregnancy.
Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.
Oral hypoglycemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.
Breastfeeding:
It is unknown whether Gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycemia, the product is therefore contraindicated in breastfeeding mother. A risk to the newborns/infants cannot be excluded.

DRUG INTERACTIONS:
The following products are likely to increase the risk of hypoglycemia:
Contraindicated combination: Miconazole (systemic route, oromucosal gel): increases the hypoglycemic effect with possible onset of hypoglycemic symptoms, or even coma.
Combinations which are not recommended: Phenylbutazone (systemic route): increases the hypoglycemic effect of sulfonylurea (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 emphasize the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.
Alcohol: increases the hypoglycemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycemic coma. Alcohol or medicinal products containing alcohol should be avoided.
Combinations requiring precautions for use: Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur when one of the following drugs is taken: other antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and nonsteroidal anti-inflammatory agents.
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 emphasize 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 emphasize 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 emphasize 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. Emphasize the importance of monitoring blood glucose levels. If necessary, switch to insulin.
Saint John's Wort (Hypericum perforatum) preparations: Gliclazide exposure is decreased by Saint John's Wort-Hypericum perforatum. Emphasize the importance of blood glucose levels monitoring.
The following products may cause dysglycemia:
Combinations requiring precautions during use: Fluoroquinolones: in case of a concomitant use of Gliclazide (Zeltine-MR) 30 mg and a fluoroquinolone, the patient should be warned of the risk of dysglycemia, and the importance of blood glucose monitoring should be emphasized.
Combination which must be taken into account: Anticoagulant therapy (e.g. Warfarin): Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment.
Adjustment of the anticoagulant may be necessary.

ADVERSE DRUG REACTIONS:
Based on the experience with Gliclazide, the following undesirable effects have been reported.
The most frequent adverse reaction with Gliclazide is hypoglycemia.
As for other sulfonylureas, treatment with Gliclazide can cause hypoglycemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycemia 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 sulfonylurea shows that hypoglycemia can recur even when measures prove effective initially.
If a hypoglycemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalization is required.
Other undesirable effects:
Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhea, and constipation have been reported: if these should occur, they can be avoided or minimized if Gliclazide is taken with breakfast.
The following undesirable effects have been more rarely reported:
Skin and subcutaneous tissue disorders:
Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, 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:
Changes in hematology are rare. They may include anemia, 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:
As for other sulfonylureas, the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, hemolytic anemia, 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 sulfonylurea or led to life-threatening liver failure in isolated cases.

OVERDOSE AND TREATMENT:
An overdose of sulfonylurea 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 doctor 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.
If hypoglycemic 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.

SPECIAL PRECAUTIONS FOR DISPOSAL:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

"For suspected adverse drug reaction, report to the FDA: www. fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction".

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:
Alu/Alu Blister Pack x 10's (Box of 60's)

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