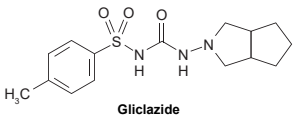
Getzid® MR
(G l i c l a z i d e)

گیٹزیڈ ایم آر

30mg, 60mg Modified Release Tablets

DESCRIPTION
Getzid MR (Gliclazide) is an oral hypoglycemic sulfonylurea. Chemically, it is 1-(hexahydrocyclopenta [c]pyrrol-2(1H)-yl)-3- [(4-methylphenyl)sulphonyl] urea. Its molecular formula is $C_{15}H_{21}N_3O_3S$ and the structural formula is:



Gliclazide

QUALITATIVE AND QUANTITATIVE COMPOSITION
Getzid MR (Gliclazide) Tablets are available for oral administration as:

Getzid MR Tablets 30mg
Each modified-release tablet contains:
Gliclazide BP... 30mg

Getzid MR Tablets 60mg
Each modified-release tablet contains:
Gliclazide BP... 60mg

CLINICAL PHARMACOLOGY
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.

Pharmacokinetics
Absorption
Gliclazide is slowly and completely absorbed from the gastro-intestinal tract (mean absolute bioavailability of 97%). After administration, plasma concentrations rise gradually and the maximum concentration is usually reached after about 6 hours, with a plateau maintained for another 4 to 6 hours. Intra- individual variability is low. Food intake does not affect the rate and extent of absorption. The relationship between the dose administered and the area under the concentration curve as a function of time is linear. Linear kinetics were observed with Gliclazide modified-release tablets 30mg in the dose range up to 120mg.

Effect of Food
Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.

Distribution
The volume of distribution is relatively small, which can partially be explained by high protein binding (about 95%). The volume of distribution is around 30 litres. A single daily dose of Gliclazide modified-release tablets 30mg maintains effective Gliclazide plasma concentrations over 24 hours.

Metabolism
Although more than 90% of unchanged Gliclazide is found in plasma following oral administration, this is extensively metabolized with little of the unchanged compound (<1%) found in urine. Six principal metabolites have been identified in urine, essentially oxidized and hydroxylated derivatives, and two glucuronoconjugates. No active metabolites have been detected in plasma.

Excretion
Gliclazide metabolites and conjugates are primarily (60-70%) eliminated via the urine, with about 10 to 20% elimination via feces. The mean elimination half-life is 16 h (range 12-20 h).

THERAPEUTIC INDICATIONS
Getzid MR (Gliclazide) Tablets are indicated for the control of hyperglycemia in Gliclazide responsive diabetes mellitus of stable, mild, non-ketosis prone, maturity onset or adult type which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.

DOSAGE & ADMINISTRATION
The daily dose may vary from 30mg to 120mg 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 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 30mg 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 60mg, 90mg or 120mg 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 120mg.

Switching from another oral antidiabetic agent to Getzid MR (Gliclazide) Tablets 30mg:
Getzid MR (Gliclazide) Tablets 30mg 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 Getzid MR (Gliclazide) Tablets 30mg. A transitional period is not generally necessary. A starting dose of 30mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above. 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 Getzid MR (Gliclazide) Tablets 30mg, *i.e.* a starting dose of 30mg/day, followed by a stepwise increase in dose, depending on the metabolic response.

Combination treatment with other antidiabetic agents:
Getzid MR (Gliclazide) Tablets 30mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin. In patients not adequately controlled with Getzid MR (Gliclazide) Tablets 30mg, concomitant insulin therapy can be initiated under close medical supervision.

Special Populations
Elderly
Getzid MR (Gliclazide) Tablets 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.

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 30mg is used.

Pediatric population
The safety and efficacy of Getzid MR (Gliclazide) Tablets in children and adolescents have not been established.

ADVERSE REACTIONS
Common:
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 sulfonylureas 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 hospitalisation 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.

Rare:
Skin and subcutaneous tissue disorders: Rash, pruritus, 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).

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.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, plese contact at dsafety@getzpharma.com or +92-21-38636363

CONTRAINDICATIONS
Gliclazide MR Tablet is contraindicated in patients with:
- Hypersensitivity to Gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients of the product.
- 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.
- Pregnancy and lactation.

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 sulfonylureas. 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 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.
- 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 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 MR Tablets 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.

Porphyric patients:
Cases of acute porphyria have been described with some other sulfonylurea drugs, in patients who have porphyria.

Effects on ability to drive and use machines:
Gliclazide MR Tablets 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.

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

DRUG INTERACTIONS
Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia 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.

Miconazole (systemic route, *oromucosal gel):* Increases the hypoglycemic effect with possible onset of hypoglycemic symptoms, or even coma.

Phenylbutazone (systemic route): Increases the hypoglycemic 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 hypoglycemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycemic coma. Avoid alcohol or medicines containing alcohol.

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 (>100mg 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 (IV): Increased blood glucose levels due to beta-2 agonist effects. Emphasise 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. Emphasise the importance of blood glucose levels monitoring.

Fluoroquinolones: In case of a concomitant use of Gliclazide MR Tablets and a fluoroquinolone, the patient should be warned of the risk of dysglycemia, and the importance of blood glucose monitoring should be emphasized.

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

OVERDOSAGE
Symptoms
An overdose of sulfonylureas 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.

Treatment
If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50mL 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 1g/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. Some sulfonylurea-induced hypoglycemias may be refractory to treatment and susceptible to relapse especially in elderly or malnourished patients. Continuous dextrose infusions for hours or days have been necessary. Dialysis is of no benefit to patients due to the strong binding of Gliclazide to proteins.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Getzid MR (Gliclazide) Tablets 30mg are available in blister pack of 30's.
Getzid MR (Gliclazide) Tablets 60mg are available in blister pack of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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