Lowzid® XR

Gliclazide

FORMS AND PRESENTATION

Lowzid®XR: Extended release tablets. Box of 30.

COMPOSITION

Lowzid®XR: Each extended release tablet contains Gliclazide 60mg.

Excipients: Calcium hydrogen phosphate dihydrate, povidone, hypromellose, magnesium stearate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides,urea derivatives, ATC code: A10BB09.

Mechanism of action

Gliclazide is a hypoglycemic, sulfonylurea, oral anti-diabetic 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. An increase in postprandial insulin and C-peptide secretion persists after two years of treatment.

In addition to these metabolic properties, gliclazide has hemovascular properties.

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 B_2).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

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 liters. A single daily intake of this medicine 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.

Special populations

Elderly

No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.

INDICATIONS

Lowzid®XR is indicated for non-insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise, and weight loss alone are not sufficient to control blood glucose.

CONTRAINDICATIONS

- Hypersensitivity to gliclazide or to any of the excipients, other sulfonylureas or sulfonamides
- Insulin-dependent diabetes (Type 1)
- 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

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 carbohydrates. 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 the 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, the dose used, and clear patient directions are necessary to reduce the risk of hypoglycemic episodes.

Factors that 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 this medicine
- 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, along 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, taking regular exercise, and regularly monitoring 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 anti-diabetic agent, including gliclazide, is attenuated over time in many patients. This may be due to progression in the severity of 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 a 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 this medicine 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 glucose-6-phosphate (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.

Lactose

Lowzid® XR modified release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

Lowzid® XR 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 data with other sulfonylureas.

In animal studies, gliclazide is not teratogenic. As a precautionary measure, it is preferable to avoid the use of Lowzid® XR 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 the first choice for the treatment of diabetes during pregnancy. It is recommended that oral hypoglycemic therapy is changed to insulin before pregnancy is attempted, or as soon as pregnancy is discovered.

Breast-feeding

It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycemia, the product is contraindicated in breastfeeding mothers. A risk to the newborns/infants cannot be excluded.

DRUG INTERACTIONS

The following products are likely to increase the risk of hypoglycemia:

Contra-indicated combination

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

Combinations that are not recommended

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 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. Avoid alcohol or medicines containing alcohol.

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 anti-diabetic 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; monoamine oxidase inhibitors (MAOIs); sulfonamides; clarithromycin; and non-steroidal anti-inflammatory agents.

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

Combinations that are 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 anti-diabetic 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 anti-diabetic active substance during and after treatment with the neuroleptic agent.

Glucocorticoids (systemic and local route: intra-articular, cutaneous, and rectal preparations) and tetracosactrin: increase 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 anti-diabetic active substance during and after treatment with glucocorticoids.

Ritodrine, salbutamol, and 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 level monitoring.

The following products may cause dysglycemia

Combinations requiring precautions during use

Fluoroquinolones: in case of concomitant use of Lowzid® XR 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 EFFECTS

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

The most frequent adverse reaction with gliclazide is hypoglycemia. As with other sulfonylureas, treatment with Lowzid® XR 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 hospitalization is required.

Other undesirable effects

Gastrointestinal disorders

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, 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

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) and 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.

DOSAGE AND ADMINISTRATION

Posology

The daily dose of Lowzid® XR may vary from 30 to 120 mg taken orally in a single intake at breakfast time.

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, HbAlc).

Initial dose

The recommended starting dose is 30 mg daily (half a 60 mg tablet).

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.

One Lowzid® XR 60 mg modified-release tablet corresponds to two Gliclazide 30 mg modified-release tablets.

Switching from another oral anti-diabetic agent to Lowzid® XR

Lowzid® XR can be used to replace other oral anti-diabetic agents. The dosage and the half-life of the previous anti-diabetic agent should be taken into account when switching to this medicine.

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. 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 Lowzid® XR, 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 anti-diabetic agents

Lowzid®XR can be given in combination with biguanides, alpha glucosidase inhibitors, or insulin. In patients not adequately controlled with this medicine, concomitant insulin therapy can be initiated under close medical supervision.

Special Populations

Elderly

Lowzid®XR 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 patients
- Patients with severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency)
- Following the withdrawal of prolonged and/or high dose corticosteroid therapy
- Patients with severe vascular disease (severe coronary heart disease, severe carotid impairment, or diffuse vascular disease)

It is recommended that the minimum daily starting dose of 30 mg be used.

Pediatric population

The safety and efficacy of this medicine in children and adolescents have not been established. No data and clinical studies are available in children.

Method of administration

Oral use.

Lowzid® XR is to be taken as a single dose at breakfast time.

It is recommended that the tablet(s) is swallowed in one piece (whole or half tablet).

OVERDOSAGE

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.

If a 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.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of Revision: July 2023.

Marketing Authorization Holder and Manufacturer:

Benta S.A.L. – Lebanon

PI318/1