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INSTRUCTION
for medical use

GLIMAX®

Composition:
active substance: glimepiride;
1 tablet contains glimepiride 2 mg or 3 mg, or 4 mg;
excipients (2 mg tablets): lactose monohydrate, sodium starch glycolate (type A), povidone K-30, microcrystalline cellulose, magnesium stearate, ferric oxide yellow (E 172);
excipients (3 mg tablets): lactose monohydrate, sodium starch glycolate (type A), povidone K-30, microcrystalline cellulose, magnesium stearate;
excipients (4 mg tablets): lactose monohydrate, sodium starch glycolate (type A), povidone K-30, microcrystalline cellulose, magnesium stearate, ferric oxide red (E 172), ferric oxide yellow (E 172).

Pharmaceutical form. Tablets.
Main physico-chemical properties:
2 mg tablets: round, flat, light-yellow tablets with a score line on one side and smooth on the other side;
3 mg tablets: round, flat, white tablets with a score line on one side and smooth on the other side;
4 mg tablets: round, flat, light-pink tablets with a score line on one side and smooth on the other side.

Pharmacotherapeutic group.
Hypoglycemic agents except for insulins. Sulfonamides, urea derivatives.
ATC code A10B B12.

Pharmacological properties.
Pharmacodynamics.
Glimepiride is an orally active hypoglycemic substance, which belongs to the group of sulfonylureas. It may be used in type II diabetes mellitus.
Glimepiride acts mainly by stimulating the release of insulin from pancreatic beta-cells.
As with other sulfonylureas, this effect is based on an increase in the sensitivity of pancreatic cells to physiological glucose stimulus. Besides, glimepiride has a pronounced extrapancreatic effect, which is also specific for other sulfonylureas.
Insulin release. Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the pancreatic beta-cell membrane. Closing of the potassium channel induces depolarization of the beta-cell and, by opening calcium channels, results in an increased influx of calcium into the cell, which in its turn results in insulin release through exocytosis.
Glimepiride binds with a high exchange rate to the beta-cell membrane protein, which is associated with the ATP-sensitive potassium channel, however, its binding site differs from the usual sulfonylurea binding site.
Extrapancreatic activity. Extrapancreatic effects include, for example, increased insulin sensitivity of peripheral tissues and decreased insulin uptake by the liver.

The uptake of blood glucose by peripheral (muscle and fat) tissues occurs via special transport proteins in cell membranes. The transport of glucose in these tissues is limited by the rate of glucose uptake. Glimepiride increases very rapidly the number of active glucose transporter molecules on the plasma cell membranes of muscle and fat tissues, which results in stimulated glucose uptake.
Glimepiride increases the activity of glycosyl-phosphatidylinositol-specific phospholipase C, which may correlate with the drug-induced lipogenesis and glycogenesis in isolated muscle and fat cells.
Glimepiride inhibits glucose production in the liver by increasing intracellular concentrations of fructose-2,6-biphosphate, which, in its turn, inhibits gluconeogenesis.
General characteristics. In healthy individuals, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, that is, the reduction of insulin secretion, is maintained under glimepiride.
There was no significant difference in the effect of glimepiride when the drug was used 30 minutes or immediately before a meal. In patients with diabetes mellitus, proper metabolic control for 24 hours was provided with a single daily dose of the drug.
Although the hydroxy metabolite causes a small but significant decrease in blood glucose levels in healthy individuals, it is only a minor part of the overall drug effect.
Use in combination with metformin. In one study, improved metabolic control was demonstrated in concomitant treatment with glimepiride compared to metformin monotherapy in patients whose diabetes was not properly controlled when administering maximum metformin doses.
Use in combination with insulin. Data on the use of the drug in combination with insulin are limited. Concomitant treatment with insulin may be initiated in patients whose diabetes is not properly controlled when administering maximum glimepiride doses. In two studies, this combination allowed to achieve the same improvement in metabolic control as with insulin monotherapy; however, a lower average dose of insulin is required in combination therapy.
Pharmacokinetics.
Absorption. Glimepiride has 100 % bioavailability after oral administration. Food intake has no significant effect on absorption, but only slightly slows down its rate. Maximum serum concentrations (Cmax) are reached approximately 2.5 hours after oral administration (mean 0.3 μg/ml during multiple dosing of 4 mg daily). There is a linear correlation between dose and Cmax, as well as dose and AUC (area under the "concentration – time curve»).
Distribution. Glimepiride has a very low distribution volume (about 8,8 l), which is roughly equal to the albumin distribution volume, a high degree of binding to plasma proteins (over 99 %) and low clearance (about 48 ml/min).
In animals, glimepiride is excreted in milk. Glimepiride crosses the placenta. Passage of the blood-brain barrier is low.
Metabolism and elimination. Mean dominant serum elimination half-life, which is relevant for multiple dosing, is about 5 to 8 hours. A slightly longer elimination half-life was noted after administering high doses.
After a single dose of radiolabelled glimepiride, 58 % of the radioactive substance was detected in the urine and 35 % in the feces. The unchanged substance was not detected in the urine. There are two metabolites in the urine and feces, which most likely originated due to metabolism in the liver (major enzyme CYP2C9), one of which is the hydroxy derivative, and the other is the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.
Comparison of single and multiple once-daily dosing revealed no significant differences in the pharmacokinetics. The intraindividual variability was very low. No relevant cumulation was observed.
<u>Special categories of patients.</u>
Pharmacokinetic parameters were similar in men and women, as well as in young and elderly patients (above 65 years). In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for mean serum concentrations to decrease, which is most likely caused by more rapid elimination due to lower protein binding. Renal elimination of both metabolites was impaired. Overall, no additional risk of cumulation is to be assumed in such patients.

Pharmacokinetics in patients after bile duct surgery was similar to that in healthy volunteers.
Children including adolescents. The study of the pharmacokinetics, safety and tolerability after a single dose of 1 mg glimepiride in a fed state in 30 children (4 children aged 10–12 years and 26 children aged 12–17 years) with type II diabetes mellitus showed that the average values of AUC(0-last), Cmax and $t^1/_2$ were similar to those earlier observed in adults.
Preclinical safety data. Preclinical effects observed occurred at exposures considerably exceeding the maximum human exposures, which indicates their little relevance to clinical use, or were caused by pharmacodynamic effect of the drug (hypoglycemia). These results were obtained in conventional safety, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity studies. In the latter studies (covering embryotoxicity, teratogenicity and developmental toxicity), adverse reactions were considered to result from hypoglycemic effects induced by the drug in dams and offspring.

Clinical characteristics.
Indications.
Type II diabetes mellitus in adults when blood sugar levels cannot be maintained by diet, physical exercise, and weight reduction alone.

Contraindications.
The drug is not indicated for treatment of type I insulin-dependent diabetes mellitus, diabetic ketoacidosis, diabetic coma. The use of the drug is contraindicated in patients with severe renal or hepatic impairment. In case of severe renal or hepatic impairment, a change over to insulin is required.
The drug should not be used in patients with hypersensitivity to glimepiride or any of the excipients in the composition, to sulfonylurea derivatives or other sulfonamides (risk of hypersensitivity reactions).
Pregnancy or breastfeeding (see section “Use during pregnancy or breastfeeding”).

Interaction with other medicinal products and other forms of interaction.
Concomitant use of the drug Glimax® with certain medicinal products may cause both a decrease and an increase in the hypoglycemic effect of glimepiride. Therefore, other drugs should only be taken with the knowledge (or by prescription) of the doctor. Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This metabolism is known to possibly change following concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole). Results from an *in vivo* interaction study showed that the AUC of glimepiride is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.
Experience with glimepiride and other sulfonylurea derivatives is indicative of the following types of interaction.
Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycemia, may occur when glimepiride is co-administered with medicinal products such as: phenylbutazone, azapropazone and oxyphenbutazone, sulfinpyrazone, insulin and oral antidiabetic agents (such as metformin), some long-acting sulfonamides, tetracyclines, salicylates and p-amino-salicylic acid, MAO inhibitors, anabolic steroids and male sex hormones, quinolone antibiotics and clarithromycin, chloramphenicol, probenecid, coumarin anticoagulants, miconazole, fenfluramine, disopyramide, pentoxifylline (high dose parenteral), fibrates, tritoqualine, ACE inhibitors, fluconazole, fluoxetine, allopurinol, sympatholytics, cyclo-, tro- and iphosphamides.
Weakening of the hypoglycemic effect and thus raised blood glucose levels may occur when a patient concomitantly uses medicinal products such as: estrogens and progestogens; saluretics, thiazide diuretics; thyroid stimulating agents, glucocorticoids; phenothiazine derivatives, chlorpromazine; adrenaline and sympathomimetics; nicotinic acid (high doses) and its derivatives; laxatives (long term use); phenytoin, diazoxide; glucagon, barbiturates, and rifampicin; acetazolamide.
H_2-receptor antagonists, beta blockers, clonidine and reserpine may result in both potentiation and weakening of the hypoglycemic effect.
Under the effect of sympatholytics, such as beta blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycemic action of glimepiride in an unpredictable manner.
Glimepiride may both potentiate or weaken the effects of coumarin derivatives.
Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam administration. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

Administration details.
Glimax® should be taken shortly before or during the meal.
During the first weeks of treatment there may be an increased risk of hypoglycemia, therefore extremely thorough monitoring is required.
Treatment with Glimax® may cause hypoglycemia in case of irregular nutrition or skipping meals. Possible symptoms of hypoglycemia include headache, polyphagia, nausea, vomiting, fatigue, apathy, somnolence, sleep disturbances, increased motor activity, aggression, impaired concentration, anxiety and delayed response time, depression, confusion, speech disorders and eye disorders, aphasia, tremor, paresis, sensory disorders, dizziness, helplessness, loss of self-control, delirium, brain cramps, somnolence, and loss of consciousness up to coma, shallow breathing, and bradycardia. Besides, signs of adrenergic counterregulation may be present such as sweating, cold and wet skin, anxiety, tachycardia, hypertension, palpitations, angina, and cardiac arrhythmias.
The clinical picture of a severe hypoglycemic attack may resemble that of a stroke.
Symptoms of hypoglycemia can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners are ineffective.
It is known from the experience of using other sulphonylurea derivatives that, despite initially successful countermeasures, hypoglycemia may recur.
Severe or prolonged hypoglycemia, only temporarily controlled by the usual amounts of sugar, requires immediate medical treatment and occasionally hospitalization.
Factors favoring hypoglycemia include:

- unwillingness or (more commonly in elderly patients) incapacity of the patient to cooperate with the doctor;
- undernutrition, irregular mealtimes or missed meals or periods of fasting;
- alterations in the diet;
- imbalance between physical exertion and carbohydrate intake;
- consumption of alcohol, especially in combination with a skipped meal;
- impaired renal function;
- serious hepatic dysfunction;
- overdosage with the drug Glimax®;
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycemia (for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency);
- concurrent administration of certain other medicinal products (see section “Interactions with other medicinal products and other forms of interactions”).

Treatment with the drug Glimax® requires regular monitoring of glucose levels in the blood and urine. In addition, determination of the amount of glycosylated hemoglobin is recommended.
In stressful situations (for example injuries, acute operations, infections with fever) a temporary switch to insulin may be indicated.
There is no experience of using the drug Glimax® in patients with severe impairment of liver function or patients undergoing dialysis. Switch over to insulin is indicated in patients with severe impairment of renal or hepatic function. Treatment of patients with glucose-6-phosphate dehydrogenase deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be exercised when prescribing it in patients with glucose-6-phosphate dehydrogenase deficiency. Alternative products that do not contain sulfonylurea should be prescribed in such patients.

Glimax® contains lactose monohydrate. Patients with intolerance of some sugars should consult their doctor before taking this medicinal product.

Use during pregnancy or breastfeeding.
Pregnancy.
Risk associated with diabetes. Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. Therefore, blood glucose levels must be closely monitored in pregnant women to avoid teratogenic risk.
Pregnant women with diabetes mellitus should be switched to insulin. Women with diabetes mellitus who consider pregnancy should inform their physician in order to adjust the treatment and switch to insulin.
Risk associated with glimepiride. There are no adequate data regarding the use of glimepiride in pregnant women. Preclinical studies have shown reproductive toxicity which was likely related to the pharmacologic action (hypoglycemia) of glimepiride. Therefore, glimepiride should not be used in women during the entire duration of pregnancy (see section "Contraindications").
If the patient taking glimepiride is planning a pregnancy or is pregnant, the treatment should be switched to insulin therapy as soon as possible.
Breastfeeding.
It is unknown whether the drug is excreted in human milk. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in breast milk and considering the risk of hypoglycemia in breastfed infants, breastfeeding is not advised during treatment with glimepiride.

Effect on reaction rate when driving motor transport or using other mechanisms.
No studies of the effect of the drug on the ability to drive and use mechanisms have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia or, for example, as a result of visual impairment. This may constitute a risk in situations where this ability is especially important (e.g. driving a car or operating mechanisms).
Patients should be advised to take precautions to avoid developing hypoglycemia whilst driving motor transport. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or those who have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate mechanisms in these circumstances.

Dosage and administration.
Successful treatment of diabetes mellitus depends on maintaining an appropriate diet, regular physical activity, as well as routine checks of blood and urine glucose levels. Tablets or insulin cannot compensate if the patient does not follow the recommended diet.
The dose is determined based on the results of blood and urinary glucose tests.
Monotherapy.
The starting dose is 1 mg (½ of 2 mg tablet) glimepiride per day. If good control is achieved, this dosage should be used for maintenance therapy.
If glycemic control is unsatisfactory, the dosage should be increased to 2 or 3, or 4 mg glimepiride per day in a stepwise manner (with an interval of 1 to 2 weeks).
A dose of more than 4 mg per day demonstrates better results only in exceptional cases. The maximum recommended dose is 6 mg of the drug Glimax® per day.
Combination with metformin
If the maximum dose of metformin does not provide adequate glycemic control, concomitant glimepiride therapy may be initiated.
While maintaining the previous metformin dose, glimepiride treatment is started at a low dose which may then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.
Combination with insulin
If the maximum daily dose of the drug Glimax® does not provide adequate glycemic control, concomitant insulin therapy can be initiated if necessary. While maintaining the previous glimepiride

dose, insulin treatment should be started at a low dose which may then be titrated up depending on the desired level of metabolic control.
The combination therapy should be initiated under close medical supervision.
Normally, 1 daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or – if none is taken – shortly before or during the first main meal. Mistakes in administering the drug, for example missing a dose, should never be corrected by increasing the next dose. The tablet should be swallowed without chewing, with a liquid.
If a patient has a hypoglycemic reaction in response to 1 mg glimepiride daily, this indicates that diabetes mellitus can be controlled by diet alone.
Improvement in diabetes control is associated with higher insulin sensitivity, therefore, glimepiride requirements may decrease in the course of treatment. To avoid hypoglycemia, gradual dose reduction or cessation of therapy must be considered. Changing the dosage may also be necessary if the patient's bodyweight or lifestyle change, or if other factors that increase the risk of hypo- or hyperglycemia are present.
Switch over from other oral hypoglycemic agents to the drug Glimax®.
A switch over from other oral hypoglycemic agents to the drug Glimax® can generally be done. During such switch over, the strength and the half-life of the previous medication has to be taken into account. In some cases, especially in antidiabetic medicines with a long half-life (e.g. chlorpropamide), it is advisable to wait for a few days before using the drug Glimax®**.** This will allow to minimize the risk of hypoglycemic reactions due to the additive effect of the two medicinal products.
The recommended starting dose is 1 mg glimepiride per day. As mentioned above, the dosage may be increased stepwise based on the response.
Switch over from insulin to the drug Glimax®.
In exceptional cases, a changeover to Glimax® may be indicated in type 2 diabetic patients taking insulin. The switch over should be performed under close medical supervision.

Children.
The existing data on the safety and efficacy of the drug in children are insufficient and therefore its use in this category of patients is not recommended.

Overdose.
Overdosage may lead to hypoglycemia lasting from 12 to 72 hours, which may recur after an initial recovery. Symptoms may not be present for up to 24 hours after absorption of the drug. In general hospital observation is recommended for such patients. Nausea, vomiting and epigastric pain may occur. Hypoglycemia may be often accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, somnolence, coma and convulsions.
Management of overdose. Treatment primarily consists of preventing the absorption of the drug. This is done by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium sulphate (laxative). If large quantities of glimepiride have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium sulphate. In case of severe overdosage hospitalization in an intensive care unit is indicated. Administration of glucose should be started as soon as possible: if necessary, first an intravenous injection of 50 ml of a 50 % solution, followed by an infusion of a 10 % solution with strict monitoring of blood glucose levels. Further treatment should be symptomatic.
When treating hypoglycemia caused by accidental intake of the drug Glimax® in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycemia, and blood glucose should be closely monitored.

Adverse reactions.
Experience with Glimax® and other sulfonylureas from clinical studies was associated with the adverse reactions listed below by system organ class and in order of decreasing incidence: very

common: ≥ 1/l0; common: ≥1/100 to <1/10; uncommon: ≥ 1/1000 to <1/100; rare: ≥1/10000 to <1/1000; very rare: < 1/10000), frequency unknown (cannot be estimated from the available data).
Blood and lymphatic system disorders.
Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, hemolytic anemia and pancytopenia, which are usually reversible upon discontinuation of the drug.
Frequency unknown: severe thrombocytopenia with a platelet count under 10000/μl and thrombocytopenic purpura.
Immune system disorders.
Very rare: leukoplastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnea, drops in blood pressure and sometimes shock.
Frequency unknown: possible cross-allergenicity with sulfonylureas, sulfonamides or related substances.
Metabolism and nutrition disorders.
Rare: hypoglycemia.
Such hypoglycemic reactions mostly occur immediately, may be severe and are not always easy to correct. As with other hypoglycemic therapies, the occurrence of such reactions depends on individual factors such as dietary habits and dosage (see further in section "Administration details").
Eye disorders.
Frequency unknown: transient visual disturbances may occur especially upon initiation of treatment, due to changes in blood glucose levels.
Gastrointestinal disorders.
Very rare: nausea, vomiting, diarrhea, abdominal distension, abdominal discomfort, abdominal pain, which seldom lead to the need to discontinue therapy.
Hepatobiliary disorders.
Frequency unknown: hepatic enzymes increased.
Very rare: hepatic function abnormal (e.g. with cholestasis or jaundice), hepatitis, hepatic failure.
Skin and subcutaneous tissue disorders.
Frequency unknown: hypersensitivity reactions may occur, including pruritus, rash, urticaria and photosensitivity.
Laboratory investigations:
Very rare: serum sodium decrease.
Reporting of suspected adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

Shelf-life. 3 years.

Storage conditions.
Store in the original package at a temperature not more than 25°C.
Keep out of reach of children.

Package.
10 tablets are in a blister; 3, or 6, or 10 blisters are in a carton box.

Conditions of supply.
By prescription.

Manufacturer.
LLC "KUSUM PHARM".

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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