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INSTRUCTION
for medical use

METAMIN®

Composition:
active substance: metformin hydrochloride;
1 tablet contains metformin hydrochloride 500 mg or 850 mg, or 1000 mg;
excipients: lactose monohydrate, povidone, magnesium stearate, silica colloidal anhydrous, hydroxypropyl methylcellulose.

Pharmaceutical form. Coated tablets.
Basic physico-chemical properties:
500 mg or 850 mg tablets: round biconvex white or off-white coated tablets smooth on both sides;
1000 mg tablets: oval biconvex white or off-white coated tablets smooth on both sides.

Pharmacotherapeutic group. Oral hypoglycemic agents except for insulins. Biguanides. ATC code A10B A02.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
Metformin is a biguanide with antihyperglycemic effect. It decreases both fasting and postprandial plasma glucose levels. It does not stimulate insulin secretion and does not cause the hypoglycemic effect mediated by this mechanism.
Metformin acts in three ways:
– results in reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
– increases insulin sensitivity in muscles, which results in improved peripheral glucose uptake and utilization;
– slows down intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by affecting the glycogen synthase. It increases the transport capacity of all known types of membrane glucose transporters.
Regardless of its effect on glycemia, metformin positively affects lipid metabolism: it reduces total cholesterol, low-density lipoprotein, and triglyceride levels.
In clinical studies during the use of metformin, the patients' body weight remained stable or decreased moderately.
Pharmacokinetics.
Absorption.
After oral administration of metformin, the peak concentration (C_{max}) is reached approximately within 2.5 hours (T_{max}). The absolute bioavailability of 500 mg or 850 mg metformin tablets is approximately 50-

60 % in healthy volunteers. After oral administration the non-absorbed fraction excreted in the feces is 20-30 %.
After oral administration, metformin absorption is saturable and incomplete.
It is assumed that metformin absorption is non-linear. When using metformin at recommended doses and dosing regimens, the steady-state plasma concentration is reached within 24-48 hours and is less than 1 μg/ml. In controlled clinical studies, peak plasma levels of metformin (C_{max}) did not exceed 5 μg/ml even at maximum doses.
The concomitant intake of food decreases and slightly slows down the absorption of metformin.
Following oral administration of an 850 mg dose, a 40 % lower peak plasma concentration, a 25 % decrease in AUC and a 35-minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.
Distribution.
Plasma protein binding is negligible. Metformin penetrates into erythrocytes. The peak blood concentration is lower than the peak plasma concentration, while they are reached within approximately the same time. Erythrocytes most likely represent a secondary compartment of metformin distribution. The mean volume of distribution (Vd) ranges between 63-276 l.
Metabolism. Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination. The renal clearance of metformin is > 400 ml/min. This indicates that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the elimination half-life is approximately 6.5 hours. If renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is increased, which results in increased plasma metformin levels.
Special groups of patients.
Renal impairment.
The available data concerning patients with moderate renal impairment are limited, therefore it is not possible to accurately assess the systemic exposure of metformin in this group of patients compared to patients with normal renal function. Therefore, dose adjustment is required according to clinical efficacy/tolerability (see section “Dosage and administration”).
Children.
After conducting a study of a single 500 mg dose of metformin hydrochloride, the pharmacokinetic profile in pediatric patients was similar to that in healthy adults.
Data concerning the use of multiple doses are limited to one study.
After re-administration of 500 mg metformin twice daily for 7 days in pediatric patients, the peak plasma concentration (C_{max}) and systemic exposure (AUC0-t) were reduced by approximately 33 % and 40 % respectively compared to those in diabetic adults who received repeated doses of 500 mg twice daily for 14 days.
As the dose is individually titrated based on glycemic control, the abovementioned information is of limited clinical relevance**.**

Clinical characteristics.
Indications.
Type 2 diabetes mellitus, especially in overweight patients, when dietary management and physical exercise are inefficient;
- as monotherapy or in combination with other oral hypoglycemic agents or with insulin to be used in adults.
- as monotherapy or in combination with insulin to be used in children over 10 years of age and adolescents.
As a first-line drug after inefficient dietary management to reduce diabetic complications in overweight adult patients with type 2 diabetes mellitus.

Contraindications.
– Hypersensitivity to metformin or to any other component of the drug;
– any type of acute metabolic acidosis (e.g. lactic acidosis, diabetic ketoacidosis),
– diabetic pre-coma;

– severe renal failure (glomerular filtration rate (GFR)< 30 ml/min);
– acute conditions that occur with the risk of developing kidney dysfunction such as: dehydration, severe infectious diseases, shock;
– diseases that may cause tissue hypoxia (especially acute diseases or exacerbation of a chronic disease): decompensated heart failure, respiratory failure, recent myocardial infarction, shock;
– hepatic impairment, acute alcohol intoxication, alcoholism.

Interaction with other medicinal products and other forms of interaction.
Combinations that are not recommended for use.
Alcohol. Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.
Iodinated radiopaque agents. Metformin should be discontinued in patients before or during the study and should not be renewed sooner than 48 hours after the study, provided that renal function has been re-evaluated and found to be stable (see sections "Dosage and administration" and "Administration details").
Combinations requiring caution.
Some medicinal products, for example, nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX) II inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and diuretics, especially loop diuretics, may negatively affect renal function, which may increase the risk of lactic acidosis. Careful monitoring of renal function should be performed at the beginning of treatment with the abovementioned medicinal products or during their use in combination with metformin.
Medicinal products with hyperglycemic effect (systemic and local glucocorticoids, sympathomimetics). More frequent blood glucose monitoring is required, especially at the beginning of treatment. During such concomitant therapy and upon its discontinuation the dose of Metamin® should be adjusted.
Organic cation transporters (OCT).
Metformin is a substrate of both transporters – OCT1 and OCT2.
Co-administration of metformin with:
• OCT1 inhibitors (such as verapamil) may reduce the efficacy of metformin;
• OCT1 inducers (such as rifampicin) may increase gastrointestinal absorption and the efficacy of metformin;
• OCT2 inhibitors (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease renal elimination of metformin and result in increased metformin plasma concentrations;
• inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may affect the efficacy and renal elimination of metformin.
Therefore, it is recommended to exercise particular caution when co-administering these drugs with metformin, especially in patients with renal impairment, as metformin plasma concentrations may increase. If necessary, dose adjustment of metformin should be considered, as OCT inhibitors/inducers may affect the efficacy of metformin.

Administration details.
Lactic acidosis is a very rare but severe metabolic complication, which most often occurs in acute deterioration of renal function, in a cardio-pulmonary disease, or sepsis. Metformin accumulation occurs upon acute deterioration of renal function, which increases the risk of lactic acidosis.
In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), it is recommended to temporarily discontinue metformin and seek medical attention.
Treatment with agents that may acutely impair renal function (e.g. hypotensive agents, diuretics, and NSAIDs) should be initiated with caution in patients receiving metformin.
Other risk factors for lactic acidosis include inadequately controlled diabetes mellitus, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment, and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections "Contraindications" and "Interaction with other medicinal products and other forms of interaction").
Patients and/or their caregivers should be informed about the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, muscle cramps, asthenia, and hypothermia, possibly

followed by coma. In case of any symptom of lactic acidosis, the patient should discontinue the use of metformin and immediately seek medical advice.
Lactic acidosis is characterized by diagnostic laboratory findings: decreased blood pH (<7.35), increased serum concentration of plasma lactate (>5 mmol/l), an increased anionic gap and increased lactate/pyruvate ratio.
Patients with known or suspected mitochondrial diseases: in patients with known mitochondrial diseases such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS syndrome) as well as maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications, which may result in worsening of the disease. In case of signs and symptoms suggestive of MELAS syndrome or MIDD following administration of metformin, treatment with metformin should be discontinued immediately and prompt diagnostic evaluation should be performed.
Renal function. GFR should be evaluated before initiation of treatment and regularly thereafter (see section "Dosage and administration"). The use of metformin is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of diseases affecting renal function (see section "Contraindications").
Cardiac function. Patients with heart failure have a higher risk of hypoxia and renal impairment. Metformin may be used under regular monitoring of cardiac and renal function in patients with stable chronic heart failure. Metformin is contraindicated in patients with acute and unstable heart failure (see section "Contraindications").
Iodinated radiopaque agents. Intravascular administration of iodinated contrast substances may cause contrast-induced nephropathy, which results in metformin accumulation and an increased risk of lactic acidosis.
The use of metformin should be discontinued in patients before or during the investigation and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections "Dosage and administration" and "Interaction with other medicinal products and other forms of interaction").
Surgery. Metformin should be discontinued during surgery performed under general, spinal, or epidural anesthesia, and should not be restarted earlier than 48 hours following surgery or resumption of oral nutrition, provided that renal function has been re-evaluated and found to be stable.
Children. The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. The effect of metformin on growth and puberty in children has not been determined in one-year controlled clinical studies. However, no data concerning the effect of metformin on growth and puberty during prolonged use of metformin are available, therefore careful monitoring of these parameters is recommended in children treated with metformin, especially during puberty.
Children from 10 to 12 years of age. In controlled clinical studies conducted in 15 children from 10 to 12 years of age, the efficacy and safety of metformin in this group of patients did not differ from those in older children and adolescents. The drug should be prescribed with particular caution in children from 10 to 12 years of age.
Other precautions. Patients should adhere to a diet, regular distribution of carbohydrate intake throughout the day. Overweight patients should continue their low-calorie diet. The carbohydrate metabolism indicators should be regularly controlled.
Metformin may reduce serum vitamin B_{12} levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration and/or in case a patient has risk factors known to cause vitamin B_{12} deficiency. In case of suspected vitamin B_{12} deficiency (e.g., anemia or neuropathy), serum vitamin B_{12} levels should be controlled. Monitoring of vitamin B_{12} levels may be required in patients with risk factors for vitamin deficiency. Therapy with metformin should be continued for as long as it is tolerated and not contraindicated, and appropriate corrective treatment of vitamin B_{12} deficiency is provided according to current clinical guidelines.
Monotherapy with metformin does not cause hypoglycemia, however caution should be exercised when co-administering metformin with insulin or other oral hypoglycemic agents (e.g., sulfonylureas or meglitinides).
If you have an established intolerance to some sugars, you should consult a physician before using this medicinal product as the drug contains lactose.

Use during pregnancy or breastfeeding.
Pregnancy. Uncontrolled hyperglycemia during the preconception period and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, pre-eclampsia and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout the entire pregnancy to reduce the risk of adverse consequences of hyperglycemia for the mother and her child.
Metformin crosses the placenta in amounts that can be as high as maternal concentrations.
A large amount of data on pregnant women (more than 1000 exposure outcomes) from a register-based cohort study and published data of meta-analyses and clinical studies indicates no increased risk of congenital abnormalities or fetal/neonatal toxicity after exposure to metformin in the periconception period and/or during pregnancy.
There are some unconfirmed data on the long-term effect of metformin on weight of children exposed in utero. Metformin does not appear to affect motor and social development of children under 4 years of age, who were exposed in utero, although data on long-term outcomes are limited.
If clinically needed, the use of metformin can be considered during pregnancy and in the preconception period as an addition or an alternative to insulin.
Breastfeeding. Metformin is excreted in breast milk, but no adverse effects have been observed in breast-fed newborns/infants. However, as data on the safety of the drug are insufficient, breastfeeding is not recommended during treatment with metformin. When deciding whether to discontinue breastfeeding, the benefits of breastfeeding and the potential risk of adverse effects for the child should be considered.
Fertility. Metformin did not affect the fertility of animals when administered at doses of 600 mg/kg per day, which is almost 3 times the maximum recommended daily dose in humans based on body surface area.

Effect on reaction rate when driving motor transport or using other mechanisms.
Monotherapy with metformin does not affect the reaction rate when driving motor transport or using other mechanisms, as the drug does not cause hypoglycemia.
However, caution should be exercised when using metformin in combination with other hypoglycemic agents (sulfonylureas, insulin or meglitinides) due to the risk of hypoglycemia.

Dosage and administration.
Adult patients with normal renal function (GFR ≥ 90 ml/min).
Monotherapy or combination therapy with other oral hypoglycemic agents.
The usual starting dose is 500 mg or 850 mg (Metamin®, coated tablets, 500 mg or 850 mg) 2-3 times daily during or after meals.
After 10-15 days the dose should be adjusted according to the measurements of serum glucose levels.
A slow increase of dose reduces adverse gastrointestinal effects.
During treatment with high doses (2000-3000 mg daily), every 2 tablets of the drug Metamin®, 500 mg, may be substituted with 1 tablet of the drug Metamin®, 1000 mg.
The maximum recommended dose is 3000 mg daily taken as 3 divided doses.
In case of transfer from another oral antidiabetic agent, this agent should be discontinued and metformin should be prescribed as indicated above.
Combination therapy with insulin.
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is 500 mg or 850 mg of the drug Metamin® 2-3 times daily, while insulin dose should be adjusted according to the measurements of blood glucose levels.
Renal impairment. GFR should be evaluated before initiating treatment with medicinal products containing metformin and at least annually during treatment. Close monitoring of renal function should be performed as frequently as possible, for example every 3-6 months, in patients with an increased risk of further progression of renal impairment and in elderly patients.
A decline in renal function may occur *in elderly patients*, therefore the dose of metformin should be adjusted based on the evaluation of renal function, which should be performed regularly (see section "Administration details").

GFR (ml/min)	Total maximum daily dose (should be divided into 2-3 doses)	Additional information
60-89	3000 mg	Dose reduction should be considered in case of a decline in renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis should be considered before initiating the use of metformin (see section "Administration details).
30-44	1000 mg	The starting dose is at most half of the maximum dose.
<30	-	The use of metformin is contraindicated.

Children.
Monotherapy or combination therapy with insulin.
The drug Metamin® is used in children over 10 years of age and adolescents. The usual starting dose is 500 mg or 850 mg of the drug Metamin® once daily during or after meals. After 10-15 days the dose should be adjusted according to the measurements of serum glucose levels.
A slow increase of dose reduces adverse gastrointestinal effects.
The maximum recommended dose is 2000 mg daily taken as 2-3 divided doses.

Children.
The drug Metamin® should be used for treatment of children over 10 years of age.

Overdose.
Hypoglycemia has not been observed when using the drug at a dose of 85 g. However, lactic acidosis has been observed in such circumstances. Considerable overdose with metformin or concomitant risk factors may result in lactic acidosis. Lactic acidosis is a medical emergency and should be treated in hospital. The most effective method to eliminate lactate and metformin is hemodialysis.

Adverse reactions.
The most common undesirable reactions at the beginning of treatment are nausea, vomiting, diarrhea, abdominal pain, loss of appetite. These symptoms resolve spontaneously in most cases. To prevent the mentioned adverse events, it is recommended to increase the dose slowly and take the daily dose of the drug in 2-3 divided doses.
The adverse reactions observed during the use of the drug are listed below according to organ systems and frequency: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 1/10000 and < 1/1000), very rare (< 1/10000), unknown (cannot be estimated from the available data).
In each system and organ class the adverse reactions are listed in order of decreasing clinical relevance.
Metabolism disorders.
Common: vitamin B_{12} decrease/deficiency (see section "Administration details").
Very rare: lactic acidosis (see section "Administration details").
Nervous system disorders.
Common: dysgeusia.
Gastrointestinal disorders.
Very common: gastrointestinal disorders such as nausea, vomiting, diarrhea, abdominal pain, loss of appetite. These adverse events occur most frequently during initiation of treatment and resolve spontaneously in most cases. To prevent gastrointestinal adverse events, it is recommended to increase the dose slowly and take a daily dose of the drug in 2-3 divided doses during or after meals.
Hepatobiliary disorders.
Very rare: abnormalities of liver function tests or hepatitis completely resolving upon discontinuation of metformin.
Skin and subcutaneous tissue disorders.
Very rare: skin reactions including erythema, pruritus, urticaria.

Children.
In published and post-marketing data and in controlled clinical studies in a limited pediatric population aged 10–16 years receiving metformin for 1 year, the reported adverse effects in children were similar in nature and severity to those reported in adults.

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.
500 mg, 850 mg tablets: 10 tablets are in a blister. 3, 6 or 10 blisters are in a carton box.
1000 mg tablets: 15 tablets are in a blister. 2, 4, or 6 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.
“GLADPHARM LTD” LLC.

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

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