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30.08.2019 № 1925

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, colloidal anhydrous silica, hydroxypropyl methyl cellulose.

Pharmaceutical form. Coated tablets.
Basic physical and chemical properties:
tablets 500 mg, 850 mg: white or almost white coated, round, biconvex tablets, plain on both sides;
tablets 1000 mg: white or almost white coated, oval, biconvex tablets, plain on both sides.

Pharmacotherapeutic group. Oral hypoglycemic agents, excluding insulins. Biguanides. ATC code A10B A02.

Pharmacological properties.
Pharmacodynamics.
Metformin is a biguanide with antihyperglycemic effect. Decreases baseline plasma glucose and plasma glucose after meal. Does not stimulate insulin secretion, and has no hypoglycemic effect.
Metformin acts in 3 ways:
– decreases the production of glucose in the liver by inhibiting gluconeogenesis and glycogenolysis;
– increase insulin sensitivity in muscles by improving the capture and utilization of peripheral glucose;
– slows down the intestinal absorption of glucose.
Metformin stimulates intracellular glycogen synthesis by affecting glycogen synthetase.
Increases transport capacity of all types of membrane glucose transporters (GLUT).
Regardless of its effect on glycemia, metformin shows positive effect on lipid metabolism: reduces total cholesterol, low density lipoproteins and triglycerides.
During clinical studies, body weight of individuals on metformin tended to remain stable or even decrease somewhat.
Pharmacokinetics.
Absorption. After oral administration of metformin, the maximum concentration is reached within approximately 2.5 hours (T_{max}). The absolute bioavailability of 500 mg or 800 mg tablets is

approximately 50-60 % in healthy volunteers. After oral administration, the fraction which was not absorbed and is excreted with the feces is 20-30 %.
After oral administration, metformin absorption is saturable and incomplete.
It is assumed that the pharmacokinetics of metformin absorption is nonlinear. When using the recommended doses of metformin and dosage regimens, stable plasma concentrations are reached within 24-48 hours and are less than 1 μg/ml. In controlled clinical trials, maximum plasma levels metformin levels (C_{max}) did not exceed 5 μg/ml even when using maximum doses.
When using together with food, absorption of metformin is reduced and somewhat slowed down.
After oral administration of 850 mg, a 40% reduction in maximum plasma concentration, a 25% reduction in AUC and a 35 min increase in time required to reach maximum plasma concentrations have been observed. The clinical significance of these changes is unknown.
Distribution. Binding to plasma proteins is insignificant. Metformin penetrates red blood cells. The maximum concentration levels lower than the maximum concentration in plasma and reached approximately the same time. Red blood cells most likely represent a second cell division. The average volume of distribution (Vd) varies in the range of 63-276 liters.
Metabolism. Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination. Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine, and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Clinical characteristics.
Indications.
Type 2 diabetes mellitus if diet therapy and physical activity regimen are ineffective, especially in overweight patients;
- as monotherapy or combined therapy together with other oral hypoglycemic agents or together with insulin for treatment of adults.
- as monotherapy or combined therapy with insulin for treatment of children older than 10 years and adolescents.

For reduction of complications of diabetes in adult patients with type 2 diabetes mellitus and excessive body weight as the first line drug after ineffective diet therapy.

Contraindications.
– Hypersensitivity to metformin or any other component of the drug;
– any type of acute metabolic acidosis (e.g. lactic acidosis, diabetic ketoacidosis);
- diabetic precoma;
– severe renal insufficiency (glomerular filtration rate (GFR) <30 ml/min;
– acute conditions with risk of impairment of renal function, such as: body dehydration severe infectious diseases, shock;
– diseases that may cause hypoxia (especially acute diseases or exacerbation of a chronic disease): decompensated heart failure, respiratory failure, resent myocardial infarction, shock;
– hepatic failure, acute poisoning with alcohol, alcoholism.

Interactions with other medicinal products and other forms of interactions.
Combinations that are not recommended for use.
Alcohol. Acute alcohol intoxication is associated with increased risk of lactic acidosis, especially in case of fasting or low-calorie diet, and hepatic failure. During Metamin® therapy, avoid using alcohol and any medicinal products containing alcohol.
Iodine-containing radiocontrast products. Intravenous administration of iodine-containing radiocontrast products may cause renal failure and consequently accumulation of metformin and increased risk of lactic acidosis.

Patients with GFR > 60 ml/min/1.73 m^2 should stop using metformin before or during the examination and should restart it not earlier than 48 hours after the examination, only after re-evaluation of the renal function and confirmation of absence of further deterioration in the condition of the kidneys (see section “Administration details”).

Iodine-containing radiocontrast products

Patients with metformin should be discontinued prior to or during the study and should not be renewed earlier than 48 hours after the study, only after reassessment and the establishment of a stable kidney function (see section "Dosage and administration" and "Administration details").

Combinations that should be used with caution.

Some drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase inhibitors (COX) II, angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor antagonists, and diuretics, especially loop diuretics, may have a negative effect on renal function, which may increase risk of lactic acidosis. At the beginning of treatment with the above-mentioned drugs or their use in combination with metformin, careful monitoring of renal function should be performed.

Medicinal products that have hyperglycemic effect (glucocorticosteroids,of systemic and local action sympathomimetics). Blood glucose level should be controlled more often, especially at the beginning of treatment. During and after such combined therapy, the dose of Metamin should be adjusted under the control of the glycemic level.

Organic Cation Transporter (OST).

Metformin is the substrate of both transporters - OTS1 and OTS2.

Concomitant metformin use with:

• OST1 inhibitors (such as verapamil) may reduce the effectiveness of metformin;

• inductors of OST1 (such as rifampicin) may increase gastrointestinal absorption and metformin efficiency;

• OST2 inhibitors (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isazanone) may reduce the renal excretion of metformin with subsequent increases in the concentration of metformin in plasma;

• Inhibitors of both OST1 and OST2 (such as crizotinib, olaparib) may affect the effectiveness and renal excretion of metformin.

Therefore, it is recommended that special care be taken when co-administering these drugs with metformin, especially in patients with impaired renal function, as the concentration of metformin in plasma may increase. If necessary, the possibility of adjusting the dose of metformin should be weighed, since OST inhibitors / inducers may affect metformin's efficacy.

Administration details.

Lactic acidosis is a very rare but severe metabolic complication which may occur as the result of acute deterioration of renal function, cardio-pulmonary disease or sepsis. With acute deterioration of renal function, metformin is cumulative, which increases the risk of lactic acidosis.

In the case of dehydration (severe diarrhea or vomiting, fever, or reduced fluid intake), it is recommended to temporarily stop metformin use and seek medical attention.

Patients receiving metformin should be treated with caution with agents that may severely impair the function of the kidneys (e.g., antihypertensives, diuretics and NSAIDs).

Other risk factors should be taken into account to avoid the development of lactic acidosis: poorly controlled diabetes mellitus, ketosis, prolonged fasting, excessive alcohol use, liver failure or any condition associated with hypoxia as well as concomitant use of drugs that may lead to lactic acidosis (see. section “Contraindications” and “Interactions with other medicinal products and other forms of interactions”).

Patients and/or persons caring for them should be informed about the risk of developing lactic acidosis. Characteristic signs of lactic acidosis are acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia, and later coma development is possible. In case of any symptom of lactic acidosis, the patient should stop using metformin and seek medical advice immediately.

The diagnostic results of laboratory data are reducing the pH of blood (<7,35), increasing serum lactate concentration in plasma (> 5 mmol/l) and increasing the anionic interval and increasing the ratio of lactate/pyruvate content. In case of development of lactic acidosis, the patient should be hospitalized

immediately (see section "Overdose"). The doctor should warn patients about the risk of development and symptoms of lactic acidosis.
Kidney function. GFR should be evaluated before and regularly after treatment, before starting treatment (see section "Administration and dose"). The use of metformin is contraindicated in patients with GFR <30 ml/min and should be temporarily discontinued in the presence of diseases that alter the function of the kidneys (see section "Contraindications").
Heart function. Patients with heart failure have a higher risk of hypoxia and renal insufficiency. Metformin can be used for patients with stable congestive heart failure at regular monitoring of cardiac and renal function. Metformin is contraindicated in patients with acute and unstable heart failure (see section "Contraindications").
Iodine-containing radiocontrast products. Intravascular administration of iodine-containing contrast agents may cause contract-induced nephropathy, which leads to accumulation of metformin and an increased risk of lactic acidosis.
The use of metformin should be discontinued before or during the study and not renewed earlier than 48 hours after the study, only after reassessment and the establishment of a stable kidney function (see "Dosage and Administration" and "Administration details").
Surgical interventions. Metformin should be discontinued during surgical intervention under general, spinal or epidural anesthesia and should not be renewed earlier than 48 hours after surgery or restoration of oral nutrition, only after re-evaluation and stable renal function.
Children. Before the start of treatment with metformin, the diagnosis of type 2 diabetes mellitus must be confirmed. No effect of metformin on growth and puberty has been detected in children. However, there are no data on the effect of metformin on growth and puberty in more prolonged use of metformin; therefore, close supervision over these parameters in children treated with metformin is recommended, especially during puberty.
Children aged 10 to 12 years. Efficacy and safety of use of metformin in patients of this age did not differ from that in older children and adolescents. Special caution is required when prescribing the drug in children aged 10 to 12 years.
Other precautions. Patients should keep to a diet, stable consumption of carbohydrates during the day and control the laboratory parameters. Overweight patients should continue their low-calorie diet. Carbohydrate metabolism parameters should be regularly controlled.
Monotherapy with metformin does not cause hypoglycemia; however, caution is required when using metformin concomitantly with insulin or other oral hypoglycemic agents (e.g., sulfonylurea derivatives or meglitinides).
The presence of fragments of tablet coating in the feces is possible. This is normal and has no clinical significance.
If you have a diagnosed intolerance of some sugars, consult the doctor before taking this medicinal product, since the drug contains lactose.

Use during pregnancy or breast feeding.
Pregnancy. Uncontrolled diabetes during pregnancy (gestational or permanent) increases the risk of development of congenital abnormalities and perinatal mortality. There are limited data on use of metformin in pregnant women, which do not reveal the increased risk of congenital abnormalities. Preclinical studies have revealed no negative effect on pregnancy, development of the embryo or fetus, childbirth and postnatal development. In case of planning pregnancy or in case of pregnancy, for treatment of diabetes, insulin is recommended instead of metformin for maintaining blood glucose level maximally close to the normal to reduce the risk of fetal malformations.
Breastfeeding. Metformin is excreted into the breast milk, but no adverse effects have been observed in breast-fed newborns/infants. However, as the drug safety data are insufficient, breastfeeding is not recommended during the metformin therapy. Decision on discontinuation of the breastfeeding should be taken considering the benefits of the breastfeeding and potential risk of adverse effects for the child.
Fertility. Metformin had no effect on fertility of animals when using the doses of 600 mg/kg/day, which is almost three times the maximum daily dose, recommended for use in humans and is calculated on the basis of the body surface area.

Effect on reaction rate when driving motor transport or operating other mechanisms.
Monotherapy with metformin has no effect on the reaction rate when driving motor transport or working with other mechanisms, since the drug does not cause hypoglycemia.
However, caution required when using metformin in combination with other hypoglycemic agents (sulfonylurea derivatives or meglitinides) because of the risk of hypoglycemia.

Dosage and administration.
Adult patients with normal renal function (GFR ≥ 90 ml/min).
Monotherapy or combined therapy with other oral hypoglycemic agents.
Usually the initial dose is 500 mg or 850 mg (Metamin® coated tablets, 500 mg or 850 mg) 2-3 times per day during or after meal.
After 10-15 days, the dose should be adjusted according to the results of measuring serum glucose level.
Slow dose increase helps reduce adverse effects on the digestive tract.
In treatment with high doses (2000-3000 per day) every 2 tablets of the drug Metamin®, 500 mg may be replaced by 1 tablet of the drug Metamin®, 1000 mg.
The maximum recommended dose is 3000 mg per day, divided into 3 doses.
In case of transfer from another antidiabetic agent, this drug should be stopped and metformin should be administered, as described above.
Combined therapy with insulin.
To achieve a better control of blood glucose level, metformin and insulin may be used in a combined therapy. The usual initial dose is 500 mg or 850 mg of the drug Metamin® 2-3 times per day, while the dose of insulin should be adjusted according to the results of measuring blood glucose level.
Renal failure. GFR should be evaluated prior to treatment with metformin-containing drugs and after initiation of treatment at least annually. Patients with an increased risk of further progression of renal insufficiency and elderly patients should carefully monitor kidney function as often as possible, for example every 3-6 months.

GFR (ml/min)	Total maximum daily dose (should be divided into 2-3 daily doses)	Additional Information
60-89	3000 mg	In the case of reduced kidney function, it is recommended to consider the possibility of reducing the dose.
45-59	2000 mg	Before starting metformin, factors that may increase the risk of lactic acidosis should be considered (see section "Administration details").
30-44	1000 mg	The initial dose is not more than half the maximum dose.
<30	-	The use of metformin is contraindicated.

Children.
Monotherapy or combined therapy with insulin.
The drug Metamin® is administered in children aged from 10 years and adolescents. The usual initial dose is 500 mg or 850 mg of the drug Metamin® 1 time per day during or after meal. After 10-15 days the dose should be adjusted according to the results of measuring serum glucose level.
Slow dose increase helps reduce adverse effects on the digestive tract.
The maximum recommended dose is 2000 mg per day, divided into 2-3 doses.
Elderly patients may have reduction in renal function, therefore, the dose of metformin should be chosen on the basis of the renal function evaluation, which should be conducted on a regular basis (see section “Administration details”).

Children.
The drug Metamin® is used for treatment of children from 10 years old.

Overdose.
Hypoglycemia was not observed while using metformin at a dose of 85 g. But in this case lactic acidosis was observed. In case of lactic acidosis, Metamin therapy should be stopped and the patient should be hospitalized immediately. The most effective method to remove lactate and metformin from the organism is hemodialysis. Significant doses of metformin or associated risks may cause appearance of lactic acidosis. Lactic acidosis is an emergency condition and should be treated in a hospital. The most effective measure for withdrawal from the body of lactate and metformin is hemodialysis.

Adverse reactions.
The most common undesirable reactions at the beginning of treatment are nausea, vomiting, diarrhea, abdominal pain, and lack of appetite. These symptoms usually disappear on their own. To prevent the occurrence of these side effects, a slow increase in dosage and the use of a daily dose of the drug in 2-3 doses is recommended.
Metabolism and nutrition disorders: lactat acid acidosis (see section "Administration details").
Long-term drug administration in patients with megaloblastic anemia may decrease the absorption of vitamin B_{12}, which is accompanied by reducing its level in the blood serum. It is recommended to take into account such possible reason of B_{12} hypovitaminosis is the patient has megaloblastic anemia.
Nervous system: taste perversion.
Gastrointestinal tract: disorders of the digestive system, nausea, vomiting, diarrhea, abdominal pain, lack of appetite. Most of these side effects occur at the beginning of treatment and usually disappear spontaneously. To avoid gastrointestinal adverse effects, it is recommended to increase the dose slowly and use the drug during or after meal 2-3 times per day.
Hepatobiliary system: impaired liver functions or hepatitis, which completely disappear after withdrawal of metformin.
Skin and subcutaneous tissue: allergic skin reactions, including rash, erythema, itching, urticaria.

Shelf life. 3 years.

Storage conditions.
Store below 25°C in original package.
Keep out of reach of children.

Package.
Tablets 500 mg, 850 mg: 10 tablets are in a blister. 3, or 6, or 10 blisters in a carton package.
Tablets 1000 mg: 15 tablets are in a blister. 2, or 4, or 6 blisters are in a carton package.

Conditions of supply. On prescription.

Manufacturer.
LLC "KUSUM PHARM".

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