INSTRUCTION
for medical use of the medicinal product

METONAT®

Composition:
active substance: metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate);
5 ml of solution (1 ampoule) contains 500 mg of metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate);
excipient: water for injections.

Pharmaceutical form: Injection solution.
Principal physico-chemical properties: clear, colorless liquid.

Pharmacotherapeutic group:
Other cardiological drugs. ATC code C01EB22.

Pharmacological properties:
Pharmacodynamics:
Metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) is a precursor to carnitine, a structural analogue of gamma-butyrobetaine (GBB), in which one carbon atom is replaced with a nitrogen atom. Its effect on the body can be explained in two ways.
1. Effect on carnitine biosynthesis
Metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate), by reversibly inhibiting gamma-butyrobetaine hydroxylase, reduces the biosynthesis of carnitine and thus prevents the transport of long-chain fatty acids through cell membranes, thereby preventing the accumulation in cells of a strong detergent – activated forms of unoxidized fatty acids. Thus, it prevents damage to cell membranes.
With reduced carnitine concentration under ischemic conditions, beta-oxidation of fatty acids is delayed, and oxygen consumption in cells is optimized, stimulating glucose oxidation and restoring the transport of ATP from its biosynthesis sites (mitochondria) to consumption sites (cytosol). Essentially, cells are supplied with nutrients and oxygen, and the consumption of these substances is optimized.
On the other hand, with the increased biosynthesis of the carnitine precursor, i.e., GBB, NO-synthase is activated, resulting in improved rheological properties of blood and decreased peripheral vascular resistance.
With decreased metonat concentration, carnitine biosynthesis is again enhanced, and the amount of fatty acids in cells gradually increases.
It is believed that the basis for the efficacy of metonat action is the increased tolerance to cellular load (with the change in the amount of fatty acids).
2. Mediator function in the hypothetical GBB-ergic system
It has been hypothesized that there is a system of neuronal signal transmission in the body – the GBB-ergic system, which provides the transmission of nerve impulses between cells. The mediator of this system is the last precursor of carnitine – GBB-ester. As a result of GBB-esterase action, the mediator gives an electron to the cell, thus transferring the electrical impulse, and is converted to GBB. The hydrolyzed form of GBB is actively transported to the liver, kidneys, and ovaries, where it is converted to carnitine. In somatic cells in response to stimulation, new GBB molecules are synthesized, spreading the signal.

With decreased carnitine concentration, GBB synthesis is stimulated, resulting in increased GBB ether concentration.
Metonat®, as mentioned earlier, is a structural analogue of GBB and can perform the functions of a "mediator". In contrast, GBB-hydroxylase "does not recognize" metonat, so the concentration of carnitine does not increase, but decreases. Thus, metonat, by replacing the "mediator" and promoting the increase in GBB concentration, leads to the development of the corresponding body response. As a result, the overall metabolic activity also increases in other systems, for example, in the central nervous system (CNS).
Effect on the cardiovascular system
In animal studies, metonat has been found to positively affect the contractile activity of the myocardium, has a cardioprotective action (including against catecholamines and alcohol), can prevent arrhythmias, and reduce the area of myocardial infarction.
Ischemic Heart Disease (IHD) (stable angina pectoris)
Analysis of clinical data on the course use of metonat in the treatment of stable angina pectoris showed that the drug reduces the frequency and intensity of angina attacks, as well as the amount of glyceryl trinitrate used. The drug has a pronounced antiarrhythmic effect in patients with IHD and ventricular extrasystoles, with a lesser effect observed in patients with supraventricular extrasystoles.
Particularly important is the drug's ability to reduce oxygen consumption at rest, which is considered an effective criterion for antianginal therapy of IHD.
Metonat® favorably affects atherosclerotic processes in the coronary and peripheral vessels, reducing the total cholesterol level in serum and the atherogenic index.
Chronic Heart Failure
In a relatively large number of clinical studies, the role of metonat in the treatment of chronic heart failure resulting from IHD has been analyzed, noting its ability to increase tolerance to physical exertion, as well as the volume of work performed by patients with heart failure.
In a separate study at cardiological institutes in Latvia and Tomsk, the effectiveness of metonat in cases of heart failure NYHA I-III functional class of moderate severity was tested. Under the influence of metonat therapy, 59-78% of patients, who were initially diagnosed with class II functional heart failure, were included in the class I functional group. It has been established that the use of metonat improves the inotropic function of the myocardium and increases tolerance to physical exertion, improves the quality of life of patients, without causing severe side effects.
In cases of severe heart failure, metonat must be used in combination with other traditional heart failure therapy methods.
Effect on the CNS
In animal experiments, the antihypoxic action of metonat and its effect on cerebral blood flow have been established. The drug optimizes the redistribution of cerebral blood flow volume in favor of ischemic foci, increasing the resilience of neurons under hypoxic conditions.
The drug has a stimulating effect on the CNS - increasing motor activity and physical endurance, stimulating behavioral reactions, as well as an anti-stress effect - stimulation of the sympathoadrenal system, accumulation of catecholamines in the brain and adrenal glands, protecting internal organs from stress-induced changes.
Effectiveness in Neurological Diseases
Metonat has been proven to be an effective means in the complex therapy of acute and chronic cerebral circulation disorders (ischemic stroke, chronic cerebral circulation insufficiency). Metonat® normalizes the tone and resistance of the capillaries and arterioles of the brain, restoring their reactivity.
The impact of metonat on the rehabilitation process of patients with neurological disorders (after diseases of the blood vessels of the brain, brain surgery, injuries, and tick-borne encephalitis) has been studied.
The results of testing the therapeutic activity of metonat indicate its dose-dependent positive effect on physical endurance and the restoration of functional independence during recovery.

The analysis of changes in individual and total intellectual functions after the use of the drug has established a positive effect on the recovery process of intellectual functions during recovery.
It has been established that metonat improves the quality of convalescence (mainly by renewing the physical function of the body) and also eliminates psychological disorders.
Metonat® has a positive effect on the function of the nervous system to reduce disturbances in patients with neurological deficits during recovery.
The overall neurological condition of patients improves (reduction of brain nerve damage and reflex pathology, regression of paresis, improvement of movement coordination and autonomic functions).

Pharmacokinetics

The pharmacokinetics were studied in healthy volunteers with the administration of metonat intravenously and orally.

Absorption

Bioavailability is 100%. The maximum concentration in blood plasma (Cmax) is reached immediately after administration. After intravenous administration of multiple doses, Cmax reaches 25.5±3.63 μg/ml.
Intravenous administration shows a difference in the area under the concentration-time curve (AUC) after single and repeated doses of metonat, indicating possible accumulation of metonat in blood plasma.

Distribution

Metonat® is quickly distributed in tissues from the bloodstream with high cardiac affinity. Metonat® and its metabolites partially cross the placental barrier. Animal studies have shown that metonat penetrates into mother's milk.

Biotransformation

Metabolism studies on experimental animals have shown that metonat is mainly metabolized in the liver.

Excretion

The excretion of metonat and its metabolites from the body involves renal excretion. After a single intravenous administration of metonat doses of 250 mg, 500 mg, and 1000 mg, the early elimination half-life of metonat is 5.56-6.55 hours, with a terminal elimination period of 15.34 hours.

Special Patient Groups

Elderly Patients

Elderly patients with liver and kidney function impairments, in whom bioavailability increases, need to reduce the dose of metonat.

Renal Function Impairment

Patients with renal function impairments, in whom bioavailability increases, need to reduce the dose of metonat. There is an interaction between renal reabsorption of metonat or its metabolites (e.g., 3-hydroxymeldonium) and carnitine, resulting in increased renal clearance of carnitine. There is no direct effect of metonat, GBB, and the metonat/GBB combination on the renin-angiotensin-aldosterone system.

Liver Function Impairment

Patients with liver function impairments, who experience increased bioavailability, need to reduce the dose of metonat. Toxicity studies on rats using metonat at doses higher than 100 mg/kg have shown liver discoloration to yellow and fat denaturation. Histopathological studies on animals after administering high doses of metonat (400 mg/kg and 1600 mg/kg) revealed lipid accumulation in liver cells. Changes in liver function indicators in humans after using high doses (400-800 mg) were not observed. The potential infiltration of fats into liver cells cannot be excluded.

Children

There is no data on the safety and efficacy of metonat use in children under 18 years of age, therefore the use of the drug in this patient category is contraindicated.

Clinical Characteristics

Indications:

For use in the complex therapy of diseases such as:

- Heart and vascular system diseases: stable effort angina, chronic heart failure (NYHA functional class I-III), cardiomyopathy, functional disorders of the heart and vascular system;
- Acute and chronic ischemic disorders of cerebral circulation;
- Reduced work capacity, physical and psycho-emotional overstrain;
- During the recovery period after cerebrovascular disorders, head injuries, and encephalitis.

Contraindications:

- Increased sensitivity to metonat and/or any of the excipients of the drug;
- Increased intracranial pressure (due to venous outflow disorders, intracranial tumors);
- Severe liver and/or renal failure (insufficient data on safety of use).

Interaction with other medicinal products and other forms of interaction:

Metonat® can be used together with long-acting nitrates and other antianginal drugs (stable effort angina), cardiac glycosides, and diuretic drugs (heart failure).

It can also be combined with anticoagulants, antiplatelet agents, antiarrhythmic drugs, and other medications that improve microcirculation.

Metonat® may enhance the effect of drugs containing glyceryl trinitrate, nifedipine, beta-blockers, and other antihypertensive and peripheral vasodilators.

The concurrent use of iron supplements and metonat in patients with anemia caused by iron deficiency improved the fatty acid composition in erythrocytes.

When used in combination with orotic acid to mitigate damage caused by ischemia/reperfusion, an additional pharmacological effect is observed.

Metonat® helps to eliminate pathological changes in the heart caused by azidothymidine and indirectly affects oxidative stress reactions caused by azidothymidine, leading to mitochondrial dysfunction. The use of metonat in combination with azidothymidine or other drugs for the treatment of acquired immunodeficiency syndrome (AIDS) has a positive effect in the treatment of AIDS.

In the balance reflex loss test caused by ethanol, metonat reduced sleep duration. During seizures caused by pentylenetetrazole, a pronounced anticonvulsant effect of metonat was observed. On the other hand, the use of the alpha2-adrenoceptor blocker yohimbine at a dose of 2 mg/kg and the nitric oxide synthase inhibitor N-(G)-nitro-L-arginine at a dose of 10 mg/kg before metonat therapy completely blocked the anticonvulsant action of metonat.

Metonat overdose may enhance the cardiotoxicity caused by cyclophosphamide.

Carnitine deficiency, formed by the use of metonat, may enhance the cardiotoxicity caused by ifosfamide.

Metonat® has a protective effect in cases of cardiotoxicity caused by indinavir and neurotoxic effect caused by efavirenz.

Do not use metonat together with other drugs containing meldonium, as this may increase the risk of side effects.

Special Instructions for Use

Patients with mild to moderate liver function impairments and/or a history of kidney impairments should exercise caution when using this medication (monitoring of liver and/or kidney functions is recommended). Years of experience in treating acute myocardial infarction and unstable angina in cardiological departments show that meldonium is not a first-line drug for acute coronary syndrome.

Use During Pregnancy or Breastfeeding
Pregnancy
There is insufficient animal study data to assess the impact of metonat on pregnancy, embryo/fetal development, childbirth, and postnatal development. The potential risk to humans is unknown, therefore metonat is contraindicated during pregnancy.
Breastfeeding Period
Available data on animals indicate that metonat penetrates into mother's milk. It is unknown whether metonat penetrates human breast milk. The risk to newborns/infants cannot be excluded, therefore metonat is contraindicated during the breastfeeding period.

Ability to Influence Reaction Speed When Driving or Operating Machinery
Studies to assess the impact on the ability to drive or operate machinery have not been conducted.

Method of Administration and Dosage
Intravenously. The use of the drug does not require special preparation before administration.
Due to the possible stimulating effect of the drug, it is recommended to use it in the first half of the day.
Adults
The dose is 500–1000 mg (5-10 ml), administered intravenously at once or divided into two administrations. The duration of treatment typically lasts 10-14 days, after which treatment continues with an oral form.
The duration of the treatment course is 4–6 weeks. The treatment course can be repeated 2–3 times a year.
Elderly Patients
Elderly patients with liver and/or kidney function impairments may require a reduced dose of metonat.
Patients with Kidney Function Impairments
Since the drug is excreted by the kidneys, patients with mild to moderate kidney function impairments should use a lower dose of metonat.
Patients with Liver Function Impairments
Patients with mild to moderate liver function impairments should use a lower dose of metonat.
Children
There is no data on the safety and efficacy of metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) use in children under 18 years of age, therefore the use of metonat in this patient category is contraindicated.

Overdose
There have been no reported cases of metonat overdose. The drug is low in toxicity and does not cause life-threatening side effects.
In case of lowered blood pressure, symptoms such as headache, dizziness, tachycardia, and general weakness may occur. Treatment is symptomatic.
In the case of severe overdose, liver and kidney functions should be monitored.
Hemodialysis is not significantly effective in metonat overdose due to its pronounced binding to blood proteins.

Adverse Reactions
Adverse reactions are classified according to organ systems and frequency of occurrence according to MedDRA: common (≥1/100, <1/10), rare (≥1/10000, <1/1000).
Adverse reactions observed in clinical studies and post-marketing period:

From the side of the immune system

Often *Rarely*	Allergic reactions* Hypersensitivity, including allergic dermatitis, urticaria, angioedema, anaphylactic reactions to shock
From the side of the psyche	
Rarely	Agitation, feelings of fear, obsessive thoughts, sleep disturbances
From the side of the nervous system	
Often *Rarely*	Headache* Paresthesia, tremor, hypoesthesia, tinnitus, vertigo, dizziness, gait disturbance, preconscious state, fainting
From the side of the heart	
Rarely	Cardiac arrhythmia, palpitations, tachycardia/sinus tachycardia, atrial fibrillation, arrhythmia, chest discomfort/chest pain
From the circulatory system	
Piðko	Increase/decrease in blood pressure, hypertensive crisis, hyperemia, pallor
From the respiratory organs, chest and mediastinum	
Often *Rarely*	Respiratory tract infections Sore throat, cough, dyspnea, apnea
From the gastrointestinal tract	
Often *Rarely*	Dyspepsia* Dysgeusia (metallic taste in the mouth), loss of appetite, nausea, vomiting, flatulence, diarrhea, abdominal pain, dry mouth, or hypersalivation
From the side of the skin and subcutaneous tissue	
Rarely	Rash, generalized/macular/papular rash, pruritus
From the side of the skeletal-muscular and accompanying system	
Rarely	Back pain, muscle weakness, muscle spasms
From the kidneys and urinary system	
Rarely	Pollakiuria
General disorders and administration site conditions	
Rarely	General weakness, chills, asthenia, edema, face edema, leg edema, feeling hot, feeling cold, cold sweat, injection site reactions including injection site pain
Research	
Often *Rarely*	Dyslipidemia, increased level of C-reactive protein Deviations in the electrocardiogram (ECG), acceleration of the heart, eosinophilia*

* Adverse reactions observed in previously conducted uncontrolled clinical trials.

Expiration date.
4 years.

Storage conditions.
Store at a temperature not higher than 25 °C in a place inaccessible to children.
Do not freeze.

Incompatibility. Metonat® solution should not be mixed in the same syringe with other drugs.

Packaging.
5 ml in ampoules, 5 ampoules in a one-sided blister, 2 blisters in a cardboard pack.

Leave category.

By prescription.

Manufacturer. PJSC "Lekhim-Kharkiv".

The location of the manufacturer and the address of the place of its activity.
Ukraine, 61115, Kharkiv region, Kharkiv city, Severina Pototskogo Street, building 36.

The applicant LLC "Pharmaceutical company "Salutaris".

Location of the applicant.
01042, Kyiv, Druzhby Narodov Boulevard, 9.

Date last viewed.