INSTRUCTION
for the medical use of the medicinal product

METONAT®

Composition:
active ingredient: metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate);
1 capsule contains 250 mg of metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate);
excipients: potato starch, colloidal anhydrous silica, calcium stearate;
the capsule shell contains: gelatin, titanium dioxide (E 171).

Pharmaceutical form: Capsules.
Principal physico-chemical properties: hard gelatin capsules of white color, containing white or white with a yellowish tint powder with a specific smell.

Pharmacotherapeutic group: Agents affecting the cardiovascular system. 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 by 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 a decrease in 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 adenosine triphosphate (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 an increase in the 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 a decrease in the concentration of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, 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 3-(2,2,2-trimethylhydrazinium) propionate dihydrate action lies in increasing tolerance to cellular load (with a change in the amount of fatty acids).
2. Mediator Function in the Hypothetical GBB-ergic System
A hypothesis has been proposed that there exists a system for the neuronal signal transmission – the GBB-ergic system, which facilitates the transfer of nerve impulses between cells. The mediator of this system is the last precursor of carnitine – GBB-ester. As a result of the action of GBB-esterase, the mediator donates an electron to the cell, thereby transferring the electrical impulse, and is converted into GBB. The hydrolyzed form of GBB is actively transported to the liver, kidneys, and ovaries, where it is converted into carnitine. In somatic cells, in response to stimulation, new GBB molecules are synthesized, ensuring the propagation of the signal.
With a decrease in carnitine concentration, GBB synthesis is stimulated, resulting in an increased concentration of GBB ester.

Metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate), as mentioned earlier, is a structural analogue of GBB and can perform the functions of a “mediator”. Contrarily, GBB-hydroxylase “does not recognize” 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, so the concentration of carnitine does not increase but decreases. Thus, 3-(2,2,2-trimethylhydrazinium) propionate dihydrate itself, replacing the “mediator” and contributing to 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

Animal studies have shown that 3-(2,2,2-trimethylhydrazinium) propionate dihydrate positively affects myocardial contractile activity, possesses cardioprotective action (including against catecholamines and alcohol), can prevent rhythm disturbances, and reduce the myocardial infarction area.

Ischemic Heart Disease (Stable Angina)

An analysis of clinical data on the course of treatment with 3-(2,2,2-trimethylhydrazinium) propionate dihydrate for stable angina has shown that the drug reduces the frequency and intensity of angina attacks, as well as the amount of glyceryl trinitrate used. The drug exhibits a pronounced antiarrhythmic effect in patients with ischemic heart disease (IHD) and ventricular extrasystoles, with less effect observed in patients with supraventricular extrasystoles.

Particularly important is the drug's ability to reduce oxygen consumption at rest, considered an effective criterion for antianginal therapy of IHD.

3-(2,2,2-trimethylhydrazinium) propionate dihydrate favorably affects atherosclerotic processes in coronary and peripheral vessels, reducing the overall cholesterol level in blood serum and the atherogenic index.

Chronic Heart Failure

In a relatively large number of clinical studies, the role of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate in treating 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.

The effectiveness of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate in the case of heart failure NYHA I-III functional class of moderate severity has been tested. Under the influence of therapy with 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, 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 3-(2,2,2-trimethylhydrazinium) propionate dihydrate improves the inotropic function of the myocardium and increases tolerance to physical exertion, improving the quality of life of patients without causing severe side effects. However, it is noted that 3-(2,2,2-trimethylhydrazinium) propionate dihydrate may cause slight hypotension.

In cases of severe heart failure, 3-(2,2,2-trimethylhydrazinium) propionate dihydrate should be used in combination with other traditional heart failure therapy methods.

Effect on the CNS

In animal experiments, the antihypoxic effect of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate and its action promoting cerebral blood flow have been established. 3-(2,2,2-trimethylhydrazinium) propionate dihydrate optimizes the redistribution of cerebral blood flow volume in favor of ischemic areas, enhancing the resilience of neurons under hypoxic conditions.

3-(2,2,2-trimethylhydrazinium) propionate dihydrate exhibits a stimulating effect on the CNS – increasing motor activity and physical endurance, stimulating behavioral responses, as well as an anti-stress effect – stimulating the sympathoadrenal system, accumulating catecholamines in the brain and adrenal glands, protecting internal organs against changes induced by stress.

Efficacy in Neurological Diseases

It has been proven that metonat (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) is an effective agent in the complex therapy of acute and chronic cerebral circulation disorders (ischemic stroke, chronic cerebral circulation insufficiency). 3-(2,2,2-trimethylhydrazinium) propionate dihydrate normalizes the tone and resistance of capillaries and arterioles in the brain, restoring their reactivity.
The rehabilitation process of patients with neurological disorders (after diseases of the cerebral vessels, brain surgeries, traumas, and tick-borne encephalitis) has been studied.
The results of the therapeutic activity evaluation of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate indicate its dose-dependent positive effect on physical endurance and restoration of functional independence during recovery.
Analysis of changes in individual and total intellectual functions after the drug application has revealed a positive effect on the restoration process of intellectual functions during recovery.
It has been established that 3-(2,2,2-trimethylhydrazinium) propionate dihydrate improves the convalescent quality of life (mainly due to the renewal of the physical function of the organism) and also facilitates the elimination of mental disorders.
3-(2,2,2-trimethylhydrazinium) propionate dihydrate has a positive effect on the nervous system function – reducing disturbances in patients with neurological deficit 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

Absorption

After a single oral dose, the maximum concentration in blood plasma (Cmax) is 2.23-2.43 μg/ml, and after repeated doses – 2.77 μg/ml. The time to reach the maximum concentration in blood plasma (tmax) is 1-3 hours. The bioavailability of oral administration is 78%. Food slightly delays absorption.

Distribution

3-(2,2,2-trimethylhydrazinium) propionate dihydrate is rapidly distributed in tissues from the bloodstream. The volume of distribution is 88.07±8.56 liters, and the binding with blood plasma proteins is 78%. 3-(2,2,2-trimethylhydrazinium) propionate dihydrate and its metabolites partially cross the placental barrier.

Biotransformation

Experimental animal metabolism studies have shown that 3-(2,2,2-trimethylhydrazinium) propionate dihydrate is primarily metabolized in the liver.

Elimination

The elimination of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate and its metabolites from the body involves renal excretion. After a single oral dose, the early elimination half-life (t1/2) is approximately 3.5-4 hours. With repeated doses, the elimination half-life differs. These results indicate the potential accumulation of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate in blood plasma.

Special Patient Groups

Elderly Patients

Elderly patients with liver or kidney function impairments, which increase bioavailability, should reduce the dose of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate.

Kidney Function Impairment

Patients with kidney function impairments, where bioavailability is increased, should reduce the dose of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate. There is an interaction between renal reabsorption of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate or its metabolites (for example, 3-hydroxy meldonium) and carnitine, which results in increased renal clearance of carnitine. There is no direct effect of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, GBB,

and the combination of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate/GBB on the renin-angiotensin-aldosterone system.

Liver Function Impairment

Patients with liver function impairments, where bioavailability is increased, should reduce the dose of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate. During toxicity studies in rats with the administration of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate at doses greater than 100 mg/kg, liver discoloration to yellow and fat denaturation were observed. Histopathological studies in animals after the administration of high doses of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate (400 mg/kg and 1600 mg/kg) showed lipid accumulation in liver cells. No changes in liver function indicators were observed in humans after the administration of large doses of 400-800 mg. The potential infiltration of fats into liver cells cannot be excluded.

Children

There is no data on the safety and efficacy of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate administration to children under 18 years of age, hence its use in this patient category is contraindicated.

Clinical Characteristics

Indications

For use in complex therapy in cases of:

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

Contraindications

Hypersensitivity to 3-(2,2,2-trimethylhydrazinium) propionate dihydrate and/or any of the excipients of the drug;

Increased intracranial pressure (due to impaired venous outflow, intracranial tumors);

Severe liver and/or kidney failure (insufficient data on safety of use).

Interaction with Other Medicinal Products and Other Forms of Interaction

Meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) can be used in conjunction with long-acting nitrates and other antianginal agents (stable angina pectoris), cardiac glycosides, and diuretic drugs (heart failure). It can also be combined with anticoagulants, antiplatelet agents, antiarrhythmic drugs, and other drugs that improve microcirculation. Meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) may enhance the effect of drugs containing glyceryl trinitrate, nifedipine, beta-blockers, and other antihypertensive drugs and peripheral vasodilators. ***In patients with chronic heart failure using meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) and lisinopril to reduce symptoms, the combined therapy showed positive effects (vasodilation of main arteries, improvement of peripheral circulation and quality of life, reduction of mental and physical stress).***

Simultaneous use of iron preparations and meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) in patients with anemia caused by iron deficiency improved the fatty acid composition of erythrocytes.

Using meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) in combination with orotic acid to address damages caused by ischemia/reperfusion observed an additional pharmacological effect.

Meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) helps to eliminate pathological changes in the heart caused by zidovudine (AZT) and indirectly affects oxidative stress reactions caused by AZT, leading to mitochondrial dysfunction. The use of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) in combination with AZT or other drugs for AIDS

treatment has a positive effect on AIDS treatment. In the test of balance reflex loss caused by ethanol, meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) reduced sleep duration. During seizures induced by pentylenetetrazol, a pronounced anticonvulsant effect of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) was established. Conversely, when used before treatment with meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate), 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 completely blocked the anticonvulsant action of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate).
Overdose of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) may enhance the cardiotoxicity caused by cyclophosphamide.
Carnitine deficiency formed by the use of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) may enhance the cardiotoxicity caused by ifosfamide.
Meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) exerts a protective effect in case of cardiotoxicity caused by indinavir and neurotoxicity caused by efavirenz.
Do not use meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) capsules together with other drugs containing 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, as this may increase the risk of side effects.

Special Instructions
Patients with mild or moderate liver and/or kidney function impairments in their history need to exercise caution when using the drug (liver and/or kidney functions should be monitored).
Long-term experience in treating acute myocardial infarction and unstable angina in cardiology departments shows that meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) is not a first-line drug in acute coronary syndrome.
Due to the possible development of an excitatory effect, the drug is recommended to be used in the first half of the day.

Use During Pregnancy or Breastfeeding
Pregnancy: There is insufficient research on animals to assess the impact of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) on pregnancy, embryonic/fetal development, childbirth, and postnatal development. The potential risk to humans is unknown, thus meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) is contraindicated during pregnancy.
Breastfeeding: Available animal data indicate that meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) penetrates into breast milk. It is unknown whether meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) penetrates human breast milk. The risk to newborns/infants cannot be excluded, thus meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) is contraindicated during breastfeeding.

Ability to Influence Reaction Speed When Driving or Operating Machinery
Studies to evaluate the effect on the ability to drive vehicles and operate machinery have not been conducted.

Method of use and doses
For oral use. Due to the potential excitatory effect, it is recommended to use the drug in the first half of the day.
Adults:
For heart and vascular system diseases, cerebrovascular disorders:
The dose is 500 - 1000 mg per day. The daily dose can be taken all at once or divided into 2 administrations. The maximum daily dose is 1000 mg.
For reduced work capacity, stress, and recovery period:
The dose is 500 mg per day. The daily dose can be taken all at once or divided into two doses. The maximum daily dose is 500 mg.

The duration of treatment is 4-6 weeks. The course of treatment can be repeated 2-3 times a year.
Elderly Patients:
Elderly patients with liver and/or kidney function impairments may require a dose reduction of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate).
Patients with Kidney Function Impairment:
As the drug is excreted through the kidneys, patients with mild to moderate kidney function impairment should use a lower dose of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate).
Patients with Liver Function Impairment:
Patients with mild to moderate liver function impairment should use a lower dose of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate).

Children:
There is no data on the safety and efficacy of meldonium for children (under 18 years of age), therefore its use in this patient category is contraindicated.

Overdose
There have been no reported cases of overdose with meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate). The drug is low-toxic and does not cause life-threatening side effects.
In case of reduced blood pressure, 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 the case of meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) overdose due to its strong binding to blood proteins.
Side Effects
Meldonium (3-(2,2,2-trimethylhydrazinium) propionate dihydrate) is generally well-tolerated.
Side effects are classified according to organ systems and frequency of occurrence according to MedDRA: common (≥1/100, <1/10), rare (≥1/10000, <1/1000).
Reported side effects in clinical studies and post-marketing period include:
Immune system: allergic reactions; hypersensitivity, including allergic dermatitis; hives; angioedema; anaphylactic reactions up to shock.
Psychiatry: agitation, fear, obsessive thoughts, sleep disorders.
Nervous system: headache, paresthesia, tremor, hypoesthesia, tinnitus, vertigo, dizziness, gait disturbances, presyncope, syncope.
Heart: changes in heart rhythm, palpitations, tachycardia/sinus tachycardia, atrial fibrillation, arrhythmia, chest discomfort/pain.
Blood system: increased/decreased blood pressure, hypertensive crisis, hyperemia, pallor.
Respiratory, thoracic, and mediastinal disorders: respiratory infections, sore throat, cough, dyspnea, apnea.
Gastrointestinal tract: dyspepsia, dysgeusia (metallic taste in the mouth), loss of appetite, nausea, vomiting, flatulence, diarrhea, abdominal pain, dry mouth or hypersalivation.
The skin and subcutaneous tissue: rash, generalized/macular/papular rash, itching.
The musculoskeletal and related system: back pain, muscle weakness, muscle spasms.
The kidneys and urinary system: pollakiuria.
General disorders and reactions at the injection site: general weakness, chills, asthenia, swelling, swelling of the face, swelling of the legs, feeling of heat, feeling of cold, cold sweat.
Research: dyslipidemia, increased level of C-reactive protein, deviation in the electrocardiogram (ECG), acceleration of the heart, eosinophilia.
Upper abdominal pain and migraine have been reported with 3-(2,2,2-trimethylhydrazinium) propionate dihydrate.

Expiration date.
4 years.

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

Packaging.
10 capsules in a blister, 5 blisters in a pack.

Leave category.
By prescription.

Manufacturer. Monfarm PJSC.

The location of the manufacturer and its address of the place of its activity. Ukraine, 19161, Cherkasy region, Uman district, Avramivka village, st. Zavodska, 8.

The applicant LLC "Pharmaceutical company "Salutaris".

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

Date last viewed.