

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MILDRONĀTS 250 mg hard capsules

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule contains 250 mg or 500 mg of meldonium dihydrate (*Meldonium dihydricum*).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White hard gelatin capsules, contents of the capsule - white crystalline powder with faint odour. The powder is hygroscopic.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Meldonium is used in combination therapy in the following cases:

- cardiovascular diseases: stable angina pectoris, chronic heart failure (NYHA functional class I-III), cardiomyopathy, functional cardiovascular disorders;
- acute and chronic ischaemic cerebrovascular disorders;
- decreased work performance, physical and psychoemotional overload;
- during recovery period after cerebrovascular disorders, head trauma and encephalitis.

4.2 Posology and method of administration

Posology

Adults

Cardiovascular diseases, cerebrovascular disorders

The daily dose is 500-1000 mg. The daily dose may be used as a single dose or divided into two single doses. The maximum daily dose is 1000 mg.

Decreased performance, overload and recovery period

The daily dose is 500 mg. The daily dose may be used as a single dose or divided into two single doses. The maximum daily dose is 500 mg.

Course of treatment is 4 to 6 weeks. The course of treatment can be repeated 2 to 3 times a year.

Older people

Elderly patients with hepatic and/or renal impairment may require lower doses of meldonium (see section 5.2.).

Patients with renal disorders

As the medicine is eliminated through the kidneys, in patients with mild to moderate renal disorders, reduced meldonium doses should be used (see section 4.4 and 5.2.).

Patients with hepatic disorders

In patients with mild to moderate hepatic disorders, reduced meldonium doses should be used (see section 4.4 and 5.2.).

Paediatric population

There are no data on meldonium safety and efficacy in children and adolescents under 18 years of age, therefore this medicine in children and adolescents is contraindicated (see section 4.3.).

Method of administration

For oral administration. The capsules should be swallowed with water. The medicine can be used before or after the meal. It is advised to take the medicine in the first half of the day because of possible stimulating effect.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic and/or renal insufficiency (there are no sufficient data on safety).
- Pregnancy and breast-feeding.
- In children and adolescents under 18 years of age (the safety has not been established).

4.4. Special warnings and precautions for use

In patients with a history of hepatic and/or renal disorders, using this medicine caution should be exercised (monitoring of liver and/or kidney functions should be performed).

4.5. Interaction with other medicinal products and other forms of interaction

Meldonium can be used concurrently with long-acting nitrates and other antianginal agents to treat stable effort angina pectoris, cardiac glycosides and diuretics to treat heart failure. Furthermore, it may be combined with anticoagulants, antiaggregants, antiarrhythmic agents and other microcirculation improving medicines.

Meldonium may intensify the action of glyceryl trinitrate containing medicines, nifedipine, beta adrenoblockers, other hypotensive agents and peripheral vasodilators.

There is evidence of positive effect (main artery vasodilatation, improvement of peripheral circulation and life quality, physical and mental stress reduction) of combined administration of lisinopril and meldonium in patients with chronic cardiac insufficiency symptoms.

The combination of orotic acid and meldonium possesses additive pharmacological effects on recovery from ischemia/reperfusion injury.

Concomitant use of *Sorbifer* and meldonium in patients with iron deficiency anemia improves fatty acid composition in red blood cells.

Meldonium helps to prevent azidothymidine (AZT) induced cardiopathologic changes and indirectly acts on AZT caused oxidative stress reactions leading to mitochondrial dysfunction. Meldonium combined use with AZT or other medicines for acquired immune deficiency syndrome (AIDS) treatment, positive impact AIDS therapy.

Meldonium inhibited the sleeping time in ethanol induced loss of righting reflex test. In a pentylenetetrazole induced seizure test, significant anticonvulsant activity of meldonium was observed. However, the anticonvulsant activity of meldonium was completely blocked after pre-treatment with 2 mg/kg α_2 adrenergic receptor antagonist yohimbine and 10 mg/kg nitric oxide synthase (NOS) inhibitor N-(G)-nitro-L-arginine.

Overdose of meldonium may aggravate cyclophosphamide-induced cardiotoxicity.

Carnitine deficiency resulting from the use of D-carnitine (pharmacologically inactive isomer)-meldonium increases the ifosfamide-induced cardiotoxicity.

Meldonium shows a protective effect of indinavir-induced cardiotoxicity and efavirenz-induced neurotoxicity case.

It is not recommended to use with other meldonium containing medicines because of increased risk of adverse effects.

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal studies are insufficient with respect to meldonium effects on pregnancy, embryonal/foetal development, parturition or postnatal development. The potential risk for humans is unknown, therefore this medicine should not be used during pregnancy (see section 4.3).

Breast-feeding

The available data in animals have shown that meldonium is excreted into breast milk. It is not known whether the medicine is excreted into human breast milk. The risk for newborns/infants cannot be excluded, therefore this medicine should not be used during breast-feeding period (see section 4.3).

4.7. Effects on ability to drive and use machines

No data on the effects on the ability to drive and use machines.

4.8. Undesirable effects

In the table below presents adverse reactions that have occurred in previous uncontrolled clinical trials and post-marketing period.

Adverse reactions are presented according to the MedDRA system organ classes and frequency convention: common ($\geq 1/100$ to $< 1/10$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$).

Adverse reactions reported in clinical trials and post-marketing period

Immune system disorders	
<i>Common</i>	Allergic reactions*
<i>Rare</i>	Hypersensitivity, allergic dermatitis, urticaria, angioedema, anaphylactic reaction
Psychiatric disorders	
<i>Rare</i>	Agitation, fear, obsessive thoughts, sleep disorders
Nervous system disorders	
<i>Common</i>	Headache*
<i>Rare</i>	Formication, tremor, hypoaesthesia, tinnitus, <i>vertigo</i> , dizziness, gait disturbances, presyncope, loss of consciousness
Cardiac disorders	
<i>Rare</i>	Heart rhythm changes, palpitations, tachycardia/sinus tachycardia, atrial fibrillation, arrhythmia, chest discomfort/chest pain
Vascular disorders	
<i>Rare</i>	Blood pressure increased/decreased, hypertensive crisis, hyperaemia, pallor
Respiratory, thoracic and mediastinal disorders	
<i>Rare</i>	Throat irritation, cough, dyspnoea, apnoea
Gastrointestinal disorders	
<i>Common</i>	Dyspepsia*
<i>Rare</i>	Dysgeusia (taste metallic), appetite loss, retching, nausea, vomiting, flatulence, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	
<i>Rare</i>	Rash, macular/papular/generalized rash, pruritus
Musculoskeletal and connective tissue disorders	
<i>Rare</i>	Back pain, muscle weakness, muscle spasms
Renal and urinary disorders	
<i>Rare</i>	Pollakiuria
General disorders and administration site conditions	
<i>Rare</i>	General weakness, chills, asthenia, oedema, face oedema, oedema of legs, feeling hot, feeling cold, cold sweat
Investigations	
<i>Rare</i>	Abnormal electrocardiogram (ECG), heart rate increased, eosinophilia*

* Adverse reactions reported during previous uncontrolled clinical studies.

In connection with meldonium use upper abdominal pain and migraine have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via State Agency of Medicines, Jersikas Street 15, Riga, LV-1003 Tel. +371 67078400; Fax +371 67078428. Website: www.zva.gov.lv

4.9. Overdose

No cases of overdose have been reported. The medicine is of low toxicity and causes no patient health-threatening side effects.

In case of hypotension, headache, dizziness, tachycardia and general weakness may occur. The treatment is symptomatic.

In case of severe overdose, hepatic and renal functions should be monitored.

Haemodialysis is of no value because the medicine is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: other cardiac preparations, ATC code: C01EB22

Meldonium is a structural analogue of a precursor of carnitine, gamma-butyrobetaine (GBB), which has one carbon atom replaced by nitrogen atom. Its effect on the body may be explained in two ways.

- Effect of carnitine biosynthesis

Meldonium, by reversibly inhibiting the activity of gamma butyrobetainhydroxylase, causes a decrease of carnitine biosynthesis and thus prevents long-chain fatty acid transport through the cell membranes. Accordingly, it prevents the accumulation of strong detergents, activated forms of un-oxidised fatty acids, in cells thus diminishing damage of the cells membranes.

Under the decrease of carnitine concentration in ischemic conditions, β -oxidation of fatty acids is inhibited and oxygen consumption in cells is optimized, the oxidation of glucose is stimulated and ATP transport from their sites of biosynthesis (in mitochondria) to the sites of consumption (in cytosol) is restored. Essentially, the cells are supplied with nutrients and oxygen, as well as the usage of these substances is optimized.

In turn, by increasing of biosynthesis of the precursor of carnitine i.e. GBB, NO-synthetase is activated, that results in improved blood rheological properties and reduced peripheral vascular resistance.

When meldonium concentration lowers, the carnitine biosynthesis is again intensified and the level of cell fatty acids is gradually restored.

It is considered that meldonium efficacy is based on enhancing cells tolerance to load (by changes in fatty acid level).

▪ Mediator function in hypothetical GBB-ergic system

A hypothesis was advanced that the organism has a neural signal transmission system - GBB-ergic system which ensures the transmission of nervous impulses to somatic cells. The mediator of this system is a last carnitine precursor – GBB ester. As a result of GBB-esterase action this mediator gives up an electron to the cell, thus transmitting electric impulse, but itself transforms into GBB. Then the hydrolyzed form of GBB with participation of active transport enters the liver, kidneys and testicles, where it transforms into carnitine. Somatic cells in response to stimuli, synthesize new GBB molecules, thus providing signal spreading. When carnitine concentration lowers, the GBB synthesis is stimulated, resulting in increased GBB ester concentration.

As indicated above, meldonium is a structural analog of GBB and is able to perform the functions of "mediator", while GBB-hydroxylase does not "recognize" meldonium. Consequently, carnitine level does not increase but lowers. Thus meldonium both by replacing the "mediator", and contributing to rise of GBB concentration, promotes the development of body's response. As a result, the overall metabolic activity in other systems also, e.g. central nervous system (CNS), increases.

The effect on the cardiovascular system

Animal studies have shown that meldonium has positive effect on myocardial contractility, it exerts cardioprotective action (including that against catecholamines and alcohol), it can prevent heart rhythm disorders and reduce myocardial infarct zone.

Coronary heart disease (stable effort angina pectoris)

The analysis of the clinical data on meldonium use in repeated courses for the treatment of stable effort angina pectoris shows that the medicine reduces the frequency and intensity of angina attacks, as well as intake of glyceryl trinitrate. The medicine has pronounced antiarrhythmic effect in patients with coronary heart disease (CHD) and ventricular extrasystoles, it is less effective in patients with supraventricular extrasystoles. Particularly important is the medicine's ability to decrease oxygen consumption at rest, which is considered as efficacy criterion of antianginal therapy in CHD.

Meldonium favourably affects atherosclerotic processes in coronary and peripheral blood vessels by lowering total serum cholesterol levels and atherogenicity index.

Chronic heart failure

A relatively large number of clinical trials analyzed the role of meldonium in the treatment of CHD-induced chronic heart failure, and marked its ability to increase the tolerance to physical loads, as well as the amount of doable work in patients with heart failure.

The efficacy of meldonium in the treatment of moderate heart failure (NYHA functional class II) was studied in cardiology institutes in Latvia and Tomsk. Meldonium therapy affects, 59-78 % of patients with initially diagnosed functional class II heart failure were reclassified in functional class I group. It was found that meldonium improves myocardial inotropic function and increases tolerance to physical load, improves patients' life quality by causing no severe adverse effects.

The effect on CNS

Antihypoxic and brain perfusion improving effect of meldonium was noticed during the animal studies. Meldonium optimizes the volume of redistribution of cerebral blood flow for the benefit of ischemic lesions, increases neuronal resistance under hypoxic conditions.

The medicine has CNS stimulating activity – increase in movement activity and physical performance, stimulation of behavioural reactions. It has also antistress activity – stimulation

of sympathoadrenal system, the accumulation of catecholamines in the brain and adrenal glands, protection against stress-related changes in the internal organs.

Efficiency in cerebrovascular disorders and neurological diseases

It has been demonstrated that meldonium is effective in complex therapy in the management of acute and chronic cerebrovascular disorders (ischaemic stroke, chronic cerebrovascular insufficiency). Meldonium normalizes brain capillary and arteriolar tone and resistance, restores their reactivity.

The effect of meldonium on the rehabilitation process in patients with neurological disorders (following cerebrovascular diseases, brain surgery, trauma, tick-borne encephalitis) has been studied.

The results of therapeutic efficacy test with meldonium show evidence of positive dose-dependent effect on patients' physical ability to work and functional self-support recovery during the convalescence period.

A positive effect on intellectual function recovery during the rehabilitation period was found while studying distinct and integral intellectual functional changes following medicine administration.

It has been established that meldonium improves quality of life in convalescent patients (most of all because of the recovered physical functions) and also contributes to liquidation of mental disorders.

Meldonium has positive effect on regression of nervous system function disorders in patients with neurological deficit during the recovery period. General neurological status of patients improves (the diminishing of brain nerve damage and pathological reflexes, the regression of pareses, the improvement of movement coordination and vegetative functions).

5.2. Pharmacokinetic properties

The pharmacokinetics was studied in normal human subjects using meldonium intravenously and orally.

Absorption

Following a single 25, 50, 100, 200, 400, 800 or 1500 mg high-dose oral administration meldonium peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) increased proportionally to the administered dose. The time to reach maximum concentration in plasma (t_{max}) was 1-2 hours. With multiple dosing, the plasma levels reached steady state 72-96 hours after the first dosing. Meldonium accumulation in blood plasma is possible. Food delays meldonium absorption without affecting the C_{max} and AUC scores.

Distribution

Meldonium is rapidly distributed from the circulation to the tissues. The plasma protein binding ratio increases depending on the time after dosing. Meldonium and its metabolites partially cross the placental barrier. Animal studies have shown that meldonium excreted into breast milk.

Biotransformation

Metabolism studies in experimental animals have shown that meldonium metabolized mainly in the liver.

Elimination

Renal excretion plays a substantial role in elimination of meldonium and its metabolites. Meldonium elimination half-life ($t_{1/2}$) is approximately 4 hours. Following repeated dosing elimination half-life is different.

Special populations

Elderly

Meldonium dose should be reduced in elderly patients with hepatic or renal impairment in whom the apparent bioavailability is increased (see section 4.2.)

Renal impairment

Meldonium dose should be reduced in patients with renal impairment in whom the apparent bioavailability is increased (see section 4.2). Non-clinical studies show that meldonium, administered orally in rats at doses of 20, 100 and 500 mg/kg is low toxicity and does not affect renal function. There is meldonium or its metabolites (3-hydroxymeldonium) interaction with renal reabsorption of carnitine, leading to increased renal carnitine clearance. Meldonium, GBB and meldonium/GBB combination does not have the direct action on rennin-aldosterone-angiotensine system.

Hepatic impairment

Meldonium dose should be reduced in patients with hepatic impairment in whom the apparent bioavailability is increased (see section 4.2). During toxicity study in rats, in groups that were treated with meldonium dose more than 100 mg/kg, yellow coloration of liver and denaturation of fats were observed. Histopathological studies in animals after large doses of meldonium (400 mg/kg and 1600 mg/kg) received, observed lipid accumulation in liver cells. Changes of hepatic function in human at doses of 400-800 mg were not observed. The possibility of fat infiltration in liver cells cannot be excluded.

Paediatric population

There are no data on meldonium safety and efficacy in children and adolescents (under 18 years of age), therefore the medicine is contraindicated in children and adolescents (see section 4.3).

5.3. Preclinical safety data

Acute toxicity

Meldonium is of low toxicity. LD₅₀ after active substance oral administration to mice and rats was more than 18 000 mg/kg.

Chronic toxicity

The body weight, blood count, blood and urine tests of the rats did not showed any adverse changes after a continuous administration of meldonium for more than six month period. 20, 100 or 500 mg/kg oral meldonium doses had no effect on haematopoiesis, functional status of liver and kidneys, and did not cause changes in the structure of tissue of internal organs.

Carcinogenicity, mutagenicity

The medicine has no mutagenic and carcinogenic properties.

Reproductive toxicity

Specific toxicity studies showed no teratogenic and embryotoxic action of meldonium. In reproductivity studies with adult experimental animals it was stated that there were no effects on the number of *corpora lutea*, estrous cycle, mating rate and conception rate that could have been caused by meldonium administration. From the results of the studies it was concluded that the dose that causes no toxicological effects is 400 mg/kg/daily, and the dose that causes no effects on reproductive function is 1600 mg/kg. Toxicity on foetal development has not been observed using doses exceeding 1600 mg/kg/daily.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule content

Potato starch
Silicon dioxide
Calcium stearate

The hard gelatin capsule (body and cap)

Titanium dioxide
Gelatine

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

Do not store above 25 °C.
Store in the original package. Protect from moisture.

6.5. Nature and contents of container

250 mg hard capsules

10 capsules in PVC/PVDC/Al blister.
4 or 6 blisters (40 or 60 capsules) in a carton box.

500 mg hard capsules

10 capsules in PVC/PVDC/Al blister.
6 blisters (60 capsules) in a carton box.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AS GRINDEKS.

Krustpils iela 53, Rīga, LV-1057, Latvia

Tel.: +371 67083205

Fax: +371 67083505

E-mail: grindeks@grindeks.lv

8. MARKETING AUTHORISATION NUMBER(S)

250 mg hard capsules: 00-0406

500 mg hard capsules: 99-0095

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

250 mg hard capsules

Date of authorisation: 09 November 1992

Date of latest renewal: 28 July 2011

500 mg hard capsules

Date of authorisation: 20 January 1999

Date of latest renewal: 28 May 2009

10. DATE OF REVISION OF THE TEXT

11/2015