SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mildronate 500 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 500 mg of meldonium dihydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
White hard gelatin capsules. The content – white crystalline powder with faint odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant treatment of mild chronic cardiac insufficiency.

4.2 Posology and method of administration

Posology

Adults
The usual daily dose is 500-1000 mg of meldonium. The daily dose may be divided into two single doses. The maximum daily dose is 1000 mg. The treatment course varies from 4 to 6 weeks.

Elderly
No specific recommendation for the use in this age group. Elderly patients with hepatic and/or renal impairment may require lower doses (see section 4.4).

Patients with hepatic and/or renal disorders
As the medicinal product is eliminated through the kidney, in patients with renal disorders, as well as those with liver diseases, doses should be reduced (see section 4.4).

Paediatric population
Due to lack of data on the safety and efficacy, the medicinal product is not recommended for use in children.

Method of administration

For oral administration.
It is advised to use meldonium in the morning because of the possible stimulating effect.
In order to avoid gastrointestinal disturbances the medicinal product can be taken with food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with chronic liver and renal diseases should use this medicinal product carefully because no studies were held to find out the effects on elevated risk patients.

Paediatric population
No clinical data are available on the meldonium safety to children, therefore it is not recommended for children.

4.5 Interaction with other medicinal products and other forms of interaction

- Meldonium may be used together with other cardiovascular medicinal products: antianginal medicinal products, anticoagulants, antiarrhythmics and diuretics, cardiac glycosides and etc.
- Meldonium may intensify the action of several cardiovascular medicinal products such as glyceryl trinitrate, nifedipine, beta-adrenoblockers, hypotensive agents and peripheral vasodilators. This should be taken into consideration when using these medicinal products concomitantly. It might be necessary to reduce doses.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data are available on the medicinal product safety during pregnancy. To avoid possible undesirable action on the organism of mother and foetus, meldonium is not recommended during pregnancy.
Breastfeeding
It is not known whether active substance is excreted into human milk. If mother needs to be treated with this medicinal product, she has to stop breast-feeding.

4.7 Effects on ability to drive and use machines

There are no known cases of meldonium unfavorable effect on ability to drive or use machines.

4.8 Undesirable effects

The frequency of undesirable effect is presented as following: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Not known: eosinophilia.

Immune system disorders
Common: allergic reactions (blush, rash, itching, swelling).

Nervous system disorders
Common: headache.
Not known: agitation.

Cardiac disorder
Very rare: tachycardia.

Vascular disorders
Very rare: hypotension.

Gastrointestinal disorders
Common: dyspeptic disturbances (stomach discomfort, nausea, vomiting, bitter taste in mouth).

General disorders and administration site conditions
Not known: general weakness.

The leading and concomitant diseases can cause other undesirable effects (proteinuria, granular cylinders in urine sediment, liver impairment due to inappropriate diet, mood changes); the relationship between these effects and meldonium usage is hardly possible. The frequency is not known.

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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

No data concerning overdose in humans are available. The medicinal product is of low toxicity and causes no undesirable effects that would be dangerous to patient's health. If arterial pressure considerably deviates from normal, arterial blood pressure regulating medicines should be used.

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.
Meldonium inhibits the activity of butyrobetainhydroxylase, causing a decrease of carnitine biosynthesis and long-chain fatty acids transport through cell membranes. It prevents the accumulation of the metabolites of long-chain fatty acids – Acyl-CoA and Acyl-carnitine – in cells, thus diminishing their adverse effects. Under the conditions of ischemia, meldonium activates the anaerobic glycolysis and stimulates the ATP production and transport, restores the balance between oxygen delivery and consumption.
A temporary decrease in the content of fatty acids takes place in a healthy organism´s cell upon an increased load as a result of intensive energy consumption. This activates the metabolism of fatty acids, especially the synthesis of carnitine. It is clear that the biosynthesis of carnitine is regulated by the blood plasma concentration of carnitine and stress; however the concentration of carnitine precursors in the cell has no influence. Meldonium inhibits the transformation of GBB to carnitine and so decreases its concentration in blood, thus activating the synthesis of carnitine precursors, i. e. GBB. The biosynthesis of carnitine resumes and the concentration of fatty acids become normal in the cell as the concentration of meldonium decreases. The cells

are trained regularly in this way and are stimulated to survive when the concentration of fatty acids is low under the increased metabolic conditions and when it rapidly restores. Meldonium "trained" cells survive substantial overload, whereas "untrained" cells die under the same conditions.

The effect on the cardiovascular system

It is established that meldonium increases the blood flow, left ventricular volume and cardiac output, almost does not affect venous pressure or diminishes it. These evidences show the positive effect of meldonium on myocardium contractility.
Under the conditions of ischemia, meldonium diminishes the negative effect of hypoxia on myocardium. It was determined, that meldonium decreases the area of infarcted myocardium.
The medicine helps also to prevent arrhythmias such as ventricular fibrillation.

Chronic heart failure

The study of effect of treatment with meldonium in chronic heart failure caused by CHD was based upon a large number of clinical trials. The data show that the medicine increases tolerance to physical exertion and physical load size of the patients suffering from heart failure. The medicinal product efficacy in treatment of average severity heart failure (NYHA II functional class) was studied separately in Latvia's and Tomsk's cardiology institutes. After the treatment with meldonium the diagnoses of 59-78 % patients who had II functional class heart failure were reassigned with a new I functional class diagnoses. It was determined that meldonium strengthens the inotropic myocardium function and increases tolerance to physical work, enhance patients life quality and does not cause serious adverse effects. However, it is noticed, that meldonium can cause moderate hypotension, allergic skin reactions, headache, chest discomfort.
Meldonium should be administered together with traditional treatment of this illness if the heart failure is severe.

5.2 Pharmacokinetic properties

Absorption
The absorption and excretion dynamics of meldonium was studied by oral, i.p. and i.v. administrations of an active substance containing carbon radioactive isotope (^{14}C) in experimental animals. The bioavailability of the medicine at oral application accounted for 78 %. The food intake delayed the Tmax but did not affect the Cmax and AUC at a single oral dose of 400 mg.

Distribution
Meldonium concentration in the blood plasma reached its maximum level (Cmax) within 1 to 2 hours after administration. It was determined that the observed Cmax and area under the time-concentration curve (AUC) of meldonium increases proportionally to the dose.

Biotransformation
Experimental studies have shown that in the organism of animals meldonium undergoes biotransformations.
The medicine is metabolized mainly in the liver. No information on the metabolism in humans has been published.

Elimination
Renal excretion plays a substantial role in elimination of meldonium and its metabolites. Two phases can be detected on the elimination curves of radioactive products, i.e. α-rapid and β-slow phases which, probably, are related to different kinetics of meldonium and its metabolites. In

rabbits after the medicine oral administration an elimination half-life in α-phase ($t_{1/2}\alpha$) equals 2,1 hours, and in β-phase ($t_{1/2}\beta$) 21 hours, and after i.v. administration 0,7 and 14,8 hours, respectively. In dogs after i.v. administration $t_{1/2}\alpha$ was 1,3 and $t_{1/2}\beta$ 14,3 hours.

5.3 Preclinical safety data

Meldonium is of low toxicity. For active substance, LD_{50}, was more than 18000 mg/kg after oral administration to mice and rats. The blood count, biochemical blood and urine tests and weight of the rats and dogs did not showed any adverse change after a continuous administration of the medicinal product for 6 month period. Liver and kidney hemorrhage were observed in the dogs after they had been taken high doses of meldonium, however the function of these organs was not impaired.
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Potato starch, dried
Silica, colloidal anhydrous (Syloid 244 FP)
Calcium stearate

Capsule shell
Titanium dioxide (E171)
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 in order to protect from moisture.

6.5 Nature and contents of container

10 hard capsules per PVC/PVDC/Al blister.
2 or 6 blisters (20 or 60 hard capsules) per cardboard box.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

MA1419/00401

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th January 2020

10. DATE OF REVISION OF THE TEXT

31th January 2023