

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 (equivalent to 401.14 mg of meldonium).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Hard capsule (23.3 mm in length), with a white body and cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant treatment of mild chronic cardiac insufficiency in adults.

4.2 Posology and method of administration

Posology

Adults

The usual daily dose is 500-1000 mg (1 - 2 capsules) of meldonium dihydrate. The daily dose of 1000 mg 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. The capsules should be swallowed whole with water.

It is advised to take 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.

Anti-doping warning

Athletes must be aware that this medicinal product may cause a positive reaction to "anti-doping tests".

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.

Lactation

It is unknown whether meldonium/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meldonium therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of meldonium on fertility are available (see section 5.3).

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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 the HPRA Pharmacovigilance Website: www.hpra.ie.

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 conditions of increased load and when the load decreases, the content of fatty acids is quickly restored. Meldonium "trained" cells survive conditions of real 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.

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 T_{\max} but did not affect the C_{\max} and AUC at a single oral dose of 400 mg.

Distribution

Meldonium concentration in the blood plasma reached its maximum level (C_{\max}) within 1 to 2 hours after administration. It was determined that the observed C_{\max} 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. a-rapid and b-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 a-phase ($t_{1/2a}$) equals 2.1 hours, and in b-phase ($t_{1/2b}$) 21 hours, and after i.v. administration 0.7 and 14.8 hours, respectively. In dogs after i.v. administration $t_{1/2a}$ was 1.3 and $t_{1/2b}$ 14.3 hours.

5.3 Preclinical safety data

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. Environmental risk assessment studies have shown that meldonium may pose a risk to aquatic environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Potato starch, dried
Silicon dioxide
Calcium stearate

Capsule shell

Titanium dioxide (E171)
Gelatin

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

PVC/PVdC//Alu blisters containing 20 or 60 hard capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AS Grindeks
Krustpils Iela 53
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA22992/025/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th October 2023

10 DATE OF REVISION OF THE TEXT

May 2024