

Summary Public Assessment Report

Generics

Meldonium Pharmexon 500mg hard capsules
Meldonium dihydrate

MT/H/0388/001/DC

Summary Public Assessment Report

Generics

General guidance:

In principle information from the PL should be included and standard texts/sentences should be used where possible.

Meldonium Pharmexon 500 mg hard capsules

Meldonium dihydrate, hard capsules 500mg

This is a summary of the public assessment report (PAR) for Meldonium Pharmexon. It explains how Meldonium Pharmexon was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Meldonium Pharmexon.

For practical information about using Meldonium Pharmexon, patients should read the package leaflet or contact their doctor or pharmacist.

What is Meldonium Pharmexon and what is it used for?

Meldonium Pharmexon is a 'generic medicine'. This means that Meldonium Pharmexon is similar to a 'reference medicine' already authorised in the European Union (EU) called Mildronate 500mg kietosios kapsulės.

Meldonium Pharmexon is used in the treatment as supplementary treatment for mild long-term heart failure.

How does Meldonium Pharmexon work?

Meldonium is a structural analogue of gamma-butyrobetaine (GBB), substance that can be found in each cell of the body. Under the conditions of poor cardiac (heart) blood flow, Meldonium Pharmexon widens the blood vessels, positively affects metabolism of the heart muscle and restores the balance between oxygen delivery and its consumption in the cells. In the case of heart failure, Meldonium Pharmexon improves the ability of heart muscle to contract and increases the tolerance to physical overload.

How is Meldonium Pharmexon used?

The pharmaceutical form of Meldonium Pharmexon is hard capsules and the route of administration is oral administration.

Meldonium Pharmexon can be taken with food, preferably in the morning.

Adults

The recommended dose is 500-1000 mg of meldonium daily. The daily dose can be divided into two single doses. The maximum daily dose is 1000 mg. The length of treatment varies from 4 to 6 weeks.

Elderly

Elderly patients with liver and/or kidney impairment may require lower doses.

Patients with liver and/or kidney disorders

In patients with liver and/or kidney disorders reduced doses should be used.

The medicine can only be obtained with a prescription.

What benefits of Meldonium Pharmexon have been shown in studies?

Because Meldonium Pharmexon is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Mildronate 500 mg kietosios kapsulēs. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Meldonium Pharmexon?

Because Meldonium Pharmexon is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

Why is Meldonium Pharmexon approved?

It was concluded that, in accordance with EU requirements, Meldonium Pharmexon has been shown to have comparable quality and to be bioequivalent to Mildronate 500 mg kietosios kapsulēs. Therefore, the Medicines Authority decided that, as for reference medicine called Mildronate 500 mg kietosios kapsulēs, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Meldonium Pharmexon?

A risk management plan has been developed to ensure that Meldonium Pharmexon is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Meldonium Pharmexon, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Meldonium Pharmexon

The marketing authorisation for Meldonium Pharmexon was granted on 9th January 2020

The full PAR for Meldonium Pharmexon can be found on the website <http://mri.cts-mrp.eu/Human/>

For more information about treatment with Meldonium Pharmexon, read the package leaflet <http://www.medicinesauthority.gov.mt/advanced-search> or contact your doctor or pharmacist.

This summary was last updated in 03-2020.

Public Assessment Report

Scientific discussion

Meldonium Pharmexon 500mg hard capsules Meldonium dihydrate

MT/H/0388/001/DC

This module reflects the scientific discussion for the approval of Meldonium Pharmexon 500mg hard capsules. The procedure was finalised at 7th January 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Meldonium Pharmexon 500mg hard capsules, from Pharmexon Consulting s.r.o.

The product is indicated for: Adjuvant treatment of mild chronic cardiac insufficiency.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form

Hard Capsule

Formulation

Capsule content

Potato starch, dried

Silica, colloidal anhydrous (Syloid 244 FP)

Calcium stearate

Capsule shell

Titanium dioxide (E171)

Gelatine

Container system

Meldonium dihydrate 500 mg hard capsules are packed in blister consisting of aluminium foil and polyvinylchloride / polyvinylidene chloride (PVC/PVDC) film packed in a cardboard box.

II.2 2.2 Drug Substance

INN

Meldonium dihydrate

Chemical features like chemical class

Nomenclature

Systematic Chemical Name (IUPAC nomenclature)

3-(2,2,2-Trimethylhydrazinium)propionate dihydrate

· Other Names

3-(2,2,2-Trimethyldiazaniumyl)propanoate dihydrate

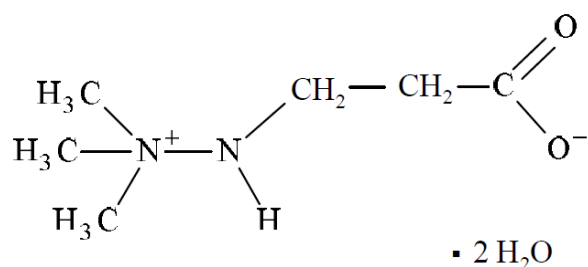
3-(2,2,2-Trimethylhydrazinium)propionate dihydrate (English)

3-(2,2,2-Trimethylhidrazinii)propionati dihydricum (in Latin)

Other Name for Final Dosage Forms

Mildronate

Structure



Manufacturing, specifications and stability:

The active substance Meldonium dihydrate is described in the European Pharmacopoeia, reference 01/2015:2624. The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph. This procedure is meant to ensure that the quality of substance is guaranteed and that these substances comply with Ph.Eur. The Chemical-pharmaceutical documentation and quality overall summary in relation to Meldonium dihydrate 500mg hard capsules is of sufficient quality in view of the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up.

II.3 Medicinal Product

The description of the development of the finished product, meldonium dihydrate 500mg hard capsules was improved following several clarifications requested during the procedure. The *Pharmaceutical Section* is considered adequate. The choice of excipients is justified, and their functions explained.

The proposed product specifications have been improved and are considered appropriate for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three production scale batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are considered adequate. The shelf-life granted is 4 years if stored at a temperature not above 25 degrees Celsius. The approved packaging is PVC/PVDC/Al blister.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

III. NON-CLINICAL ASPECTS

III.1 Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.

III.2 Pharmacology

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 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, whereas "untrained" cells die under substantial overload/ disease conditions.

The effect on the cardiovascular system

It is established that meldonium increases the blood flow, left ventricular volume and cardiac output, 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

III.3 Pharmacokinetics

The applicant has submitted one comparative bioequivalence study (dated 21 February 2019). This was a two way, randomised, single centre, open-label, balanced, two-period, two sequence, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Meldonium dihydrate 500mg hard capsules (Test) and Mildronate 500mg hard capsules (Reference) in healthy, adult subjects under fasting conditions.

The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of meldonium 500mg preparations. The studies were conducted between 31 March 2019 and 17 April 2019. The bioanalytical part was conducted between 06 May 2019 and 21 May 2019. Both the test product and the reference product were well tolerated.

The 90% confidence intervals calculated for the primary parameters C_{max} and AUC_{0-t} for meldonium fall within the 80.00 – 125.00% acceptance range after single dose administration under fasting conditions.

III.4 Toxicology

No special toxicological concerns are raised concerning the use of this formulation, when using the

recommended doses for treatment indicated in the SmPC of the product.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Meldonium Pharmexon 500mg hard capsules is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

This decentralised application concerns a generic version of meldonium dihydrate, under the trade name Meldonium Pharmexon 500mg hard capsules in accordance with article 10(1). Pharmacodynamic, pharmacokinetic and toxicological properties of meldonium dihydrate are well known. As meldonium dihydrate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies were not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant has submitted a comparative bioequivalence study in order to support the approval of the product. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of meldonium 500mg preparations.

Based on the submitted bioequivalence study results, meldonium 500mg hard capsules of the test and reference products are considered to be bioequivalent in healthy, adult, subjects under fasting conditions.

IV.2 Pharmacology

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. 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.

Meldonium should be administered together with recommended standard therapies if the heart failure is severe.

IV.3 Pharmacokinetics

Bioequivalence study

Study design (500mg) MELD-C0219/13

This was a two way, randomised, single centre, open-label, balanced, two-period, two sequence, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of

Meldonium dihydrate 500mg hard capsules and Mildronate 500mg hard capsules (AS Grindeks Latvia) in healthy adult subjects under fasting conditions.

Blood samples were collected at the times specified under study design and appropriately analysed.

The 90% confidence intervals for the ratio (or difference) between the test and reference product and pharmacokinetic parameters of AUC_{0-t} and C_{max} were determined for meldonium.

PK Parameter	Geometric Means Arithmetic Means (CV %)		Ratio of Geometric Means	90% Confidence Interval	ANOVA CV (%)**
	Test (Treatment A)	Reference (Treatment B)			
AUC _{0→t} [ng.h/ml] (n= 23)	40728.0	40370.6	100.72	95.75-105.95	9.98
	41803.7 (22.47)	41460.9 (23.63)			
C _{max} [ng /ml] (n= 23)	5480.106	5841.547	93.97	86.20-102.45	17.13
	5675.093 (27.87)	6030.155 (27.86)			
t _{max} * [h] (n= 23)	1.67	1.33			
	1.00-5.50	0.75-5.50			

*Present as median and range

$$** \% CV_{res} = 100 \cdot \sqrt{\exp(\sigma^2) - 1}$$

Conclusion on bioequivalence study:

Based on the submitted bioequivalence study (MELD-C0219/13) results, Meldonium dihydrate 500mg hard capsules and Mildronate (meldonium) 500mg hard capsules are considered to be bioequivalent in healthy adult subjects under fasting conditions.

IV.4 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.5 Clinical efficacy

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.6 Clinical safety

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.7 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Meldonium Pharmexon 500mg hard capsules.

Safety specification

Table Summary of safety concerns

List of important risks and missing information	
Important identified risks	Hypersensitivity reactions
Important potential risks	None
Missing information	Use in patients with severe hepatic insufficiency Use in patients with severe renal insufficiency Use in pregnancy Use in lactation Use in the paediatric population (under 18 years of age)

IV.8 Discussion on the clinical aspects

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was acceptable. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Meldonium Pharmexon 500mg hard capsules contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A positive benefit -risk ratio comparable to the reference product can therefore be concluded.