SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
MILDRONĀTS 0.5 g/5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution contains 100 mg meldonium dihydrate (Meldonium dihydricum).
One ampoule (5 ml) contains 500 mg meldonium dihydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
A clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Meldonium is used in combination therapy in the following cases:
– cardiovascular diseases: stable effort angina pectoris, chronic heart failure (NYHA functional class I-III), cardiomyopathy, functional cardiovascular disorders;
– acute and chronic ischaemic cerebrovascular disorders;
– decreased performance, physical and psychoemotional overload;
– during recovery period after cerebrovascular disorders, head trauma and encephalitis.

4.2 Posology and method of administration

Posology

Adults
The daily dose is 500-1000 mg (5-10 ml) intravenously, used as a single dose or divided into two single doses. The duration of treatment is usually 10-14 days, thereafter continuing treatment with oral dosage forms.

The duration of treatment course is 4-6 weeks. The course of treatment can be repeated 2-3 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 dose should be used (see section 4.4 and 5.2).

**Patients with hepatic disorders**
In patients with mild to moderate hepatic disorders, reduced meldonium dose 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 (up to 18 years of age), therefore this medicine in children and adolescents is contraindicated (see section 4.3).  

**Method of administration**

Intravenously. The use of the medicine does not provide special preparation prior to administration. 
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.
- Children and adolescents up to 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, this medicine should be used with caution (regular monitoring of liver and/or kidney functions should be performed).

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

Meldonium may be used concurrently with long-acting nitrates and other antianginal agents to treat stable effort angina pectoris, with cardiac glycosides and diuretics to treat heart failure.
Meldonium 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 life quality and peripheral circulation, 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 of 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 pentylentetrazole 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 α2 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 ifosfamide-induced cardiotoxicity.

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

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 and 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 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

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 (≥1/100 to <1/10), rare (≥1/10 000 to <1/1 000).
<table>
<thead>
<tr>
<th>Adverse reactions reported in clinical trials and post-marketing period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
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<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
</tbody>
</table>

* Adverse reactions reported during previous uncontrolled clinical trials.
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 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 on 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, i.e. GBB-ergic system which ensures the transmission of nervous impulses to somatic cells. The mediator of this system is a direct 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 a hypothetical "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 myocardiotropic 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. After the treatment with meldonium, 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 medication 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.

Efficacy 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 elimination 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 intravenous administration of multiple doses \( C_{\text{max}} \) reached 25.50±3.63 µg/ml. The apparent bioavailability was increased in individuals with \( C_{\text{max}} \), AUC and \( t_{1/2} \) increases, in patients with liver cirrhosis and in patients with severe renal insufficiency. Administered intravenously, AUC following single and repeated doses of meldonium is different. These results suggest a possible meldonium accumulation of blood plasma.

Distribution
Meldonium is rapidly distributed from the circulation to the tissues with high affinity to the heart. 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. After meldonium single dose of 250 mg, 500 mg and 1000 mg intravenous administration, early elimination half-life is 5.56-6.55 hours, terminal elimination half-life is 15.34 hours.

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). There is meldonium or its metabolites (e.g. 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 examination of animals after large doses of meldonium (400 mg/kg and 1600 mg/kg) received, revealed changes in lipids of liver cells. Abnormal 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 (up to 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. LD$_{50}$ after active substance oral administration to mice and rats was more than 18 000 mg/kg.

Chronic toxicity
The body weight, blood count, biochemical 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
Water for injections

6.2 Incompatibilities
In absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life
4 years.

6.4 Special precautions for storage
Do not store above 25 °C. Do not freeze.

6.5 Nature and contents of container
5 ml of solution in clear glass ampoule.
5 ampoules in a PVC liner.
2 liners (10 ampoules) in a cardboard box.

6.6 Special precautions for disposal and other handling
Unused medicines or waste material should be disposed of in accordance with local 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)
98-0259

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of authorisation: 09 November 1992
Date of latest renewal: 20 June 2008

10. DATE OF REVISION OF THE TEXT
12/2015