SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isomex 30 mg prolonged-release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide mononitrate 30 mg

For a full list of excipients, see section 6.1.

Contains lactose 113 mg/tablet

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white oval tablet, 7 x 13 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isomex is intended for prophylactic treatment of angina pectoris in adults.

4.2 Posology and method of administration

Nitrate therapy entails a risk of developing tolerance. It is thus important to dose Isomex once daily in order to obtain intervals with low nitrate concentrations in order to reduce the risk of tolerance development.

Isomex can be combined with beta-adrenoceptor blocking agents and calcium channel blockers.

Dosage

Adults

Isomex should be taken once daily in the morning.

To minimize the risk of headache, treatment can be initiated with 30 mg daily as starting dose the first 2-4 days of treatment. The normal dose is 60 mg (two tablets) once daily, which can be further increased to 120 mg daily if needed.

Elderly

There is no evidence that the normal dose needs to be changed for elderly patients.

Paediatric population

The safety and efficacy in children and adolescents (less than 18 years old) have not been established. No data available.

Method of administration

The tablet should not be chewed or crushed. It must be swallowed whole with at least half a glass of water. . The tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- simultaneous treatment with phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)
- acute myocardial infarction with low filling pressure
- constrictive pericarditis, pericardial tamponade or constrictive cardiomyopathy
- acute circulatory failure (shock, vascular collapse)
- co-administration with riociguat (see section 4.5)

4.4 Special warnings and precautions for use

Isomex is indicated as prophylaxis for angina and not for the treatment of acute angina attacks.

Caution should be exercised in patients with:

- hypotension and hypovolemia
- severe cerebrovascular insufficiency
- elevated intracranial pressure
- aortic stenosis, mitral stenosis
- hypertrophic obstructive cardiomyopathy
- anaemia
- hypoxaemia
- hypothyroidism

Concomitant administration of Isomex and phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) can potentiate the vasodilatory effect of Isomex with the potential result of serious side effects such as syncope or myocardial infarction (see section 4.3 and section 4.5)

Nitrate therapy entails a risk of developing tolerance. In order to reduce the risk of tolerance development, it is important to dose Isomex as described in section 4.2.

Special care may be needed with individuals who have increased risk of hypotension.

Patients with any of the following rare hereditary conditions: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption; should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interactions

- Intake of phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated when treating with nitrate preparations that potentiate the vasodilator efficacy of the drug; this may lead to serious undesirable effects such as syncope or myocardial infarction.
- The effect of vasodilator and anti-hypertensive drugs may be potentiated if given concomitantly with isosorbide mononitrate.
- Alcohol may increase the antihypertensive effect of Isosorbide mononitrate.
- The use of isosorbide mononitrate with riociguat, a stimulator of soluble guanylate cyclase, is contra-indicated (see section 4.3), since concomitant use can cause hypotension.
- Isosorbide mononitrate may increase blood level of dihydroergotamine and hence enhance the blood pressure.

4.6 Fertility, pregnancy and breast feeding

Pregnancy
There is limited clinical experience with pregnant women. Data from animal experiments do not indicate an increased risk for foetal injury.
As a precautionary measure, it is preferable to avoid the use of Isomex during pregnancy.

Breastfeeding
There is no data about excretion into human milk. A risk to the suckling child cannot be excluded. Isomex should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

In cases where patients have headaches or dizziness associated with the initial treatment of Isomex, the condition should be allowed to stabilise before driving a vehicle or using machinery.

4.8 Undesirable effects

Most of the undesirable effects are pharmacodynamically mediated and dose-dependent.
Headaches may occur when the treatment is initiated and be due to the vasodilating effect; however it usually disappears within a week. The headache can be avoided by giving 30 mg for the first 2 to 4 days. Hypotension with symptoms such as dizziness and nausea, and with occasional cases of syncope, have been reported.

The incidence of undesirable effects is classified as follows: 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) and Very rare (<1/10,000), Rate not known (cannot be estimated from available data).

System organ classification	**Frequency**	**Undesirable effects**
Cardiac disorders	Common	Tachycardia
Nervous system disorders	Common	Headache, dizziness
	Rare	Syncope
Vascular disorders	Common	Hypotension
Gastrointestinal tract disorders	Common	Nausea
	Uncommon	Vomiting, diarrhoea
Musculoskeletal system and connective tissue disorders	Very rare	Myalgia
Skin and subcutaneous tissue disorders	Rare	Skin rash, itching

Reporting of suspected undesirable effects
It is important to report suspected adverse reactions once a drug is approved. This permits continuous monitoring of the medicinal product's benefit-risk ratio. Health professionals are encouraged to report each suspected adverse reaction to:

Medical Products Agency
Box 26
751 03 UPPSALA
www.lakemedelsverket.se

4.9 Overdose

Symptoms
Throbbing headache. More serious symptoms include excitation, redness, cold sweats, nausea, vomiting, dizziness, syncope, tachycardia and hypotension. Extremely large doses can cause methaemoglobinaemia. (Very rare).

Treatment
Induction of vomiting, activated carbon. In the case of pronounced hypotension, the patient must first be placed in the supine position with the legs highly elevated. If necessary, administer intravenous fluids. (In the event of cyanosis as a result of methaemoglobinaemia, administer methylthionine (methylene blue) 1–2 mg/kg slowly, intravenously). Expert opinion should be sought.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiac disease, organic nitrates, ATC code: C01DA14

Isomex is a prolonged-release formulation of isosorbide mononitrate, which is an active metabolite of isosorbide dinitrate.
As with other organic nitrates, the primary pharmacological mechanism of action of isosorbide mononitrate is the release of nitric oxide (NO), which induces protein phosphorylation resulting in relaxation of smooth muscle in the vascular wall. This results in venous and arterial peripheral vasodilation, and may even have direct dilating effect on the coronary vessels. The effect is dose dependent. Low doses give venous dilatation and decreased venous return to the heart (reduced preload), while higher doses also result in arterial dilation and reduced arterial vascular resistance (reduced afterload). By reducing the end diastolic pressure and volume, the intramural pressure decreases leading to an improved subendocardial perfusion. The net effect of isosorbide mononitrate is therefore reduced cardiac work and improving oxygenation of the myocardium.

Tolerance development, that varies individually, may develop in maintenance treatment of nitrates. Isomex should therefore be administered once daily, to allow for an interval with low nitrate concentration each day. (see sections 4.2 4.4).

5.2 Pharmacokinetic properties

Absorption
The active ingredient is released independently of pH.
Isosorbide mononitrate is rapidly and completely absorbed after oral administration. The absorption is not affected by simultaneous intake of food. In contrast to many other nitrates, isosorbide mononitrate is not subject to first-pass metabolism and its oral bioavailability is therefore nearly 100%. This property very likely contributes to the relatively low variation in plasma levels seen among individuals after ingesting the drug. Peak plasma concentration of isosorbide mononitrate after oral administration of a modified-release tablet occurs within 3.1 to 4.5 hours.

Distribution
The volume of distribution of isosorbide mononitrate is approx. 0.6 l/kg and has negligible plasma protein binding (approx. 4%).

Metabolism
Isosorbide mononitrate is metabolised in the liver to several inactive metabolites.

Elimination
Elimination principally occurs through denitrification and conjugation in the liver. The metabolites are excreted principally through the kidneys. Only 2% of the administered dose is excreted unchanged via the kidneys. The half-life of isosorbide mononitrate in plasma in both healthy volunteers and most patients is about 6.5 hours after administration of prolonged-release tablets.

Special patient populations
Neither kidney or liver diseases changes the pharmacokinetics of isosorbide mononitrate.

5.3 Preclinical safety data

No information of relevance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose.
Lactose monohydrate.
Pregelatinised starch
Magnesium stearate
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Alu blister packs with 28 or 98 tablets.
HDPE bottle and PP cap with 100 tablets, child resistant

Not all pack sizes may be marketed.

6.6 Special precautions for destruction

No special instructions.

7. MARKET AUTHORISATION HOLDER

RPH Pharmaceuticals AB
Lagervägen 7
136 50 Jordbro
Sweden

8. MARKETING AUTHORISATION NUMBER.

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

18 January 2017

10. DATE OF REVISION OF THE TEXT

20 September 2018