Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isoket 0.5 mg/ml Solution for Infusion or Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide dinitrate 0.05% w/v, equivalent to 25 mg/50 ml (500 micrograms/ml).
Each millilitre also contains 3.54mg sodium (as sodium chloride)
Each 50ml bottle contains 177mg sodium (as sodium chloride)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion or injection
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Intravenous

Isoket is indicated in the treatment of unresponsive left ventricular failure secondary to acute myocardial infarction, unresponsive left ventricular failure of various aetiologies and severe or unstable angina pectoris.

Intra-coronary

Isoket is indicated during percutaneous transluminal coronary angioplasty to facilitate prolongation of balloon inflation and to prevent or relieve coronary spasm.

4.2 Posology and method of administration

Adults, including the elderly

Intravenous route:
Isoket 0.5 mg/ml (undiluted) is intended for intravenous administration by slow infusion via a syringe pump. Alternatively it can be administered as an admixture with a suitable vehicle such as Sodium Chloride Injection B.P. or Dextrose Injection B.P.

A dose of between 2 mg and 12 mg per hour is usually satisfactory. However, dosages up to 20 mg per hour may be required. In all cases the dose administered should be adjusted to the patient response.

Intra-coronary route:
Isoket 0.5 mg/ml can be injected directly by this route according to the proposed dosage schedule.

The usual dose is 1 mg given as a bolus injection prior to balloon inflation. Further doses may be given not exceeding 5 mg within a 30 minute period.

Older People
There’s no evidence that dose adjustment in elderly patients is needed.

Paediatric Population
The safety and efficacy of Isoket has not yet been established in children.

Isoket can be administered as an intravenous admixture with a suitable vehicle, see section 6.6.

4.3 Contraindications

These are common to all nitrates: hypersensitivity to isosorbide dinitrate, other nitrates or to any of the excipients, marked anaemia, cerebral haemorrhage, head trauma, diseases associated with an increased intracranial pressure, hypovolaemia, severe hypotension (systolic blood pressure less than 90 mmHg), aortic and/or mitral valve stenosis, closed angle glaucoma.

Use in circulatory collapse or low filling pressure is also contraindicated.

Isoket should not be used in the treatment of cardiogenic shock (unless some means of maintaining an adequate diastolic pressure is undertaken, for example by concurrent administration of an inotrope), hypertrophic obstructive cardiomyopathy, constrictive pericarditis or cardiac tamponade.

Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) have been shown to potentiate the hypotensive effects of nitrates. Therefore, Isoket must not be given to patients receiving phosphodiesterase-5 inhibitors (see section 4.4 and 4.5).

During nitrate therapy, the soluble guanylate cyclase stimulator riociguat must not be used (see section 4.5).

4.4 Special warnings and precautions for use

Isoket should be used with caution and under medical supervision in patients who are suffering from:
- hypothyroidism,
- malnutrition,
- severe liver or renal disease
- hypothermia.
- orthostatic syndrome

The development of tolerance (decrease in efficacy) as well as cross tolerance towards other nitrate-type drugs (decrease in effect in case of a prior therapy with another nitrate drug) has been described. For a decrease in, or loss of, effect to be prevented, continuously high dosages must be avoided.

Blood pressure and pulse rate should always be monitored and the dose adjusted according to the patient’s response.

Isoket contains 0.15 mmol (3.54 mg) of sodium per ml and should be taken into consideration by patients on a controlled sodium diet.

Patients who undergo a maintenance treatment with isosorbide dinitrate should be informed that they must not use phosphodiesterase inhibitors-containing products (e.g. sildenafil, tadalafil, vardenafil). Isosorbide dinitrate therapy should not be interrupted to take phosphodiesterase inhibitors containing products (e.g. sildenafil, tadalafil, vardenafil), because the risk of inducing an attack of angina pectoris could increase by doing so (see Sections 4.3 and 4.5).

Acute therapy with isosorbide dinitrate (0.5 mg/ml, 1 mg/ml, tablets 5 and 10 mg, or oromucosal spray) must not be used in patients who have recently taken phosphodiesterase inhibitors (e;g; sildenafil, tadalafil, vardenafil). Patients who receive isosorbide dinitrate as acute therapy must be warned not to take phosphodiesterase inhibitor-containing products (e. g. sildenafil, vardenafil, tadalafil) (see Sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent intake of drugs with blood pressure lowering properties e.g. beta-blockers, calcium antagonists, vasodilators etc. and /or alcohol may potentiate the hypotensive effect of Isoket. This might also occur with

neuroleptics and tricyclic antidepressants.

Also phosphodiesterase-5 inhibitors e.g. sildenafil, potentiate the hypotensive effects of Isoket. This might lead to life-threatening cardiovascular complications, see Section 4.3 and 4.4.

Patients who are on isosorbide dinitrate therapy therefore must not use phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil). Patients who have recently taken phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil) therefore must not receive acute isosorbide dinitrate therapy.

The use of ISDN with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (see section 4.3) since concomitant use can cause hypotension.

Reports suggest that, when administered concomitantly, Isoket may increase the blood level of dihydroergotamine and its hypertensive effect.

Sapropterin (Tetrahydrobiopterine, BH4) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterin containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glycerol trinitrate (GTN), isosorbide dinitrate (ISDN), isosorbide 5 mononitrate (5 ISMN) and others).

4.6 Fertility, pregnancy and lactation

Pregnancy
In reproduction studies performed in rats and rabbits, isosorbide dinitrate was associated with increase post-implantation loss and survival of offspring only as doses which were significantly higher than the max recommended human daily dose. There are, however, no adequate and well-controlled studies in pregnant women.

Since animal studies are not always predictive of human response, isosorbide dinitrate should not be used during pregnancy or lactation unless considered essential by the physician and solely under the direction and continuous supervision of a physician.

Breast-feeding
Available evidence is inconclusive or inadequate for determining infant risk when used during breastfeeding. There is data that nitrates are excreted in breast milk and may cause methemoglobinemia in infants. The extent of excretion of isosorbide dinitrate and its metabolites in human breast milk has not been determined. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Isoket therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
No data on effects on fertility are available.

4.7 Effects on ability to drive and use machines

As for other drugs which produce changes in blood pressure, patients taking Isoket should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

Isosorbide dinitrate may affect the patient's reactivity to an extent that her/his ability to drive or to operate machinery is impaired. This effect is increased in combination with alcohol.

4.8 Undesirable effects

Undesirable effects frequencies are defined as: very common (≥1/10), common (≥1/100,<1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

During administration of isosorbide dinitrate the following undesirable effects may be observed:

Nervous system disorders:
Very common: Headache
Common: Dizziness, somnolence.

Cardiac disorders:
Common: Tachycardia
Uncommon: Angina pectoris aggravated.

Vascular disorders:
Common: Orthostatic hypotension
Uncommon: Circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope).
Unknown: Hypotension

Gastrointestinal disorders:
Uncommon: Nausea, vomiting
Very rare: Heartburn

Skin and subcutaneous tissue disorders:
Uncommon: Allergic skin reactions (e.g. rash), flushing.
Very rare: Angioedema, Stevens-Johnson-Syndrome.
Not known: Dermatitis exfoliative.

General disorders and administration site conditions:
Common: Asthenia.

Severe hypotensive responses have been reported for organic nitrates including nausea, vomiting, restlessness, pallor, and excessive perspiration.

During treatment with isosorbide dinitrate, temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas. Particularly in patients with coronary artery disease this may lead to myocardial hypoxia.

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL-Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms:
- Fall of blood pressure ≤ 90 mmHg
- Pallor
- Sweating
- Weak pulse
- Tachycardia
- Postural dizziness
- Headache
- Asthenia

- Dizziness
- Nausea
- Vomiting
- Diarrhoea
- Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During isosorbide dinitrate biotransformation nitrite ions are released, which may induce methaemoglobinaemia and cyanosis with subsequent tachypnoea, anxiety, loss of consciousness and cardiac arrest. It cannot be excluded that an overdose of Isoket may cause this adverse reaction.
- In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

General procedure:
- Stop delivery of the drug
- General procedures in the event of nitrate-related hypotension:
  - The patient must be laid down with lowered head and raised legs
  - Supply oxygen
  - Expand plasma volume (i.v. fluids)
  - specific shock treatment (admit patient to intensive care unit)

Special procedure:
- Raise the blood pressure if the blood pressure is very low.
- Vasopressors should be used only in patients who do not respond to adequate fluid resuscitation
- Treatment of methaemoglobinaemia
  - Reduction therapy of choice with vitamin C, methylene-blue, or toluidine-blue
  - Administer oxygen (if necessary)
  - Initiate artificial ventilation
- Resuscitation measures

In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C01DA08 Vasodilators used in cardiac diseases.
Isosorbide dinitrate is an organic nitrate which, in common with other cardioactive nitrates, is a vasodilator. It produces decreased left and right ventricular end-diastolic pressures to a greater extent than the decrease in systemic arterial pressure, thereby reducing afterload and especially the preload of the heart.

Isosorbide dinitrate influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions by selective dilatation of large epicardial vessels.

It reduces the requirement of the myocardium for oxygen by increasing venous capacitance, causing a pooling of blood in peripheral veins, thereby reducing ventricular volume and heart wall distension.

5.2 Pharmacokinetic properties

Isosorbide dinitrate (ISDN) is eliminated from plasma with a short half-life (about 0.7h).
The metabolic degradation of ISDN occurs via denitration and glucuronidation, like all organic nitrates. The rate of formation of the metabolites has been calculated for isosorbide-5-mononitrate (IS-5-MN) with $0.57h^{-1}$ followed by isosorbide-2-mononitrate (IS-2-MN) with $0.27h^{-1}$and isosorbide (IS) with $0.16h^{-1}$. IS-5-MN and IS-2-MN are the primary metabolites which are also pharmacologically active. IS-5-MN is metabolised to isosorbide-5-mononitrate-2-glucuronide (IS-5-MN-2-GLU). The half-life of this metabolite (about 2.5h) is shorter than that of IS-5-MN (about 5.1h). The half-life of ISDN is the shortest of all and that of IS-2-MN (about 3.2h) lies in between.

5.3 Preclinical safety data

Acute toxicity:
Acute toxicity of isosorbide dinitrate was related to an exaggerated pharmacodynamic effect. Animal studies showed good local tolerability of the undiluted isosorbide dinitrate solution.

Chronic toxicity:
In chronic oral toxicity studies in rats and dogs, toxic effects including CNS symptoms and an increase in liver weight, were observed at exposures considered sufficiently in excess of the maximum human exposure levels indicating little relevance to clinical use.

Reproduction studies:
There is no evidence from animal studies suggesting a teratogenic effect of isosorbide dinitrate. At high maternally toxic oral doses, isosorbide dinitrate was associated with increased post-implantation loss and reduced survival of offspring.

Mutagenicity and carcinogenicity:
No evidence for mutagenic effect was found in both in vitro and in vivo tests.
A long-term study in rats did not provide any evidence for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid (diluted) (for pH-adjustment)
Sodium hydroxide (diluted) (for pH-adjustment)

6.2 Incompatibilities

The use of polyurethane (PU) or polyvinyl chloride (PVC) giving sets and containers should be avoided since significant losses of the active ingredient by adsorption occur. Therefore, these materials should not be used as it has not been verified how the dose can be adjusted to suit the patient’s needs due to this adsorption.

Materials made of polyethylene (PE), polypropylene (PP) or polytetrafluorethylene (PTFE) have proven to be suitable for infusing Isoket i.v. 0.1%.

This medicine product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

Unopened: 5 years, as packaged for sale.

Once opened/diluted: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened: This medicinal product does not require any special storage conditions.

Once diluted: See Section 6.3 for storage conditions of the diluted solution.

6.5 Nature and contents of container

50 ml glass bottles (Type I glass) with a laminated rubber stopper. The grey rubber stopper consists of bromobutyl polymer.
Pack size: 1

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Isoket contains isosorbide dinitrate in isotonic solution and is compatible with commonly employed infusion fluids, such as sodium chloride solution, 5-30% glucose solution, Ringer's solution and solutions containing albumin.

Isoket must be diluted under aseptic conditions immediately after opening. The diluted solution is to be used immediately. Any unused contents of the container should be discarded.

Bottles of Isoket are for single use only and should not be regarded as multi-dose containers. Discard any remaining solution after use.

7 MARKETING AUTHORISATION HOLDER

Merus Labs Luxco II S.à.R.L.
26-28 rue Edward Steichen
L-2540
Luxembourg

8 MARKETING AUTHORISATION NUMBER

PA2118/003/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 January 1989

Date of last renewal: 09 January 2009

10 DATE OF REVISION OF THE TEXT

August 2016