Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isoket 1mg/ml Concentrate for solution for injection or infusion, 10 ml Ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1mg isosorbide dinitrate.
Each 10 ml ampoule contains 10mg isosorbide dinitrate.
Each ml of concentrated solution contains 3.54mg sodium (as sodium chloride).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion (sterile concentrate).
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 aetiology 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

Posology
Adults, including the elderly.

Intravenous route
A dose of between 2 mg and 12 mg per hour is usually satisfactory. However, dosages up to 20 mg per hour administered should be adjusted to the patient response.

Intra-coronary Route
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 in needed.

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

Method of administration
Isoket is a concentrated solution and must be diluted prior to use. The diluted solution should never be injected directly in the form of a bolus except via the intra- coronary route prior to balloon inflation. A dilution of 50% is advocated for intracoronary administration.
Isoket can be administered as an intravenous admixture with a suitable vehicle (see Section 6.6).

Example of admixture preparation

To obtain a dose of 6 mg per hour add 50 ml of Isoket 1 mg/ml to 450 ml of a suitable vehicle, under aseptic conditions. The resultant admixture (500 ml) contains 100 µg/ml (1 mg/10 ml) isosorbide dinitrate. An infusion rate of 60 ml per hour (equivalent to 60 paediatric microdrops per minute or 20 standard drops per minute) will deliver the required dose of 6 mg per hour.

Should it be necessary to reduce fluid intake, 100 ml of Isoket 1 mg/ml may be diluted to 500 ml using a suitable vehicle. The resultant solution now contains 200 µg/ml (2 mg/10 ml) isosorbide dinitrate. An infusion rate of 30 ml per hour (equivalent to 30 paediatric microdrops per minute or 10 standard drops per minute) will deliver the required doseof 6 mg per hour.

A dilution of 50% is advocated to produce a solution containing 0.5 mg/ml where fluid intake is strictly limited.
Prepared Isoket admixtures should be given by intravenous infusion or with the aid of a syringe pump incorporating a glass or rigid plastic syringe. During administration the patient's blood pressure and pulse should be closely monitored and dose adjusted according to the patient's response.

4.3 Contraindications

Hypersensitivity to the active substance, other nitrates or to any of the excipients listed in section 6.1.
These are common to all nitrates: marked anaemia, cerebral haemorrhage, head trauma, diseases associated with an increased intracranial pressure, hypovolaemia, severe hypotension (systolic blood pressure less than 90mmHg), 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.

Acute therapy with ISDN (i.v. 0.05% and 0.1%, tablets 5 and 10mg, or oromucosal spray) must not be used in patients who have recently taken phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, vardenafil) the intervening 24 hours (48 hours for tadalafil).

<u>Hypoxaemia</u>

Caution should be exercised in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure. As a potent vasodilator, ISDN could result in increased perfusion of poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

During treatment with ISDN alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of ISDN (see Section 4.5).

Patients who undergo a maintenance treatment with ISDN should be informed that they must not use phosphodiesterase inhibitors-containing products (e.g. sildenafil, tadalafil, vardenafil). ISDN 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).

Patients who receive ISDN as acute therapy must be warned not to take phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil) (see Sections 4.3 and 4.5).

Due to the fact that Isoket i.v. 0.1% are supersaturated with the active substance, a deposit of crystals may be observed when Isoket i.v. 0.1% are used in undiluted form. If crystals are observed, do not use the solution. Materials made of polyethylene (PE), polypropylene (PP) or polytetrafluorethylene (PTFE) have proven to be suitable for infusing Isoket i.v. 0.1%. However, infusion material made of polyvinyl chloride (PVC) or polyurethane (PU) has been shown to induce a loss of the active substance due to adsorption and therefore these materials should not be used.
Isoket contains 0.15mmol (3.54mg) of sodium per ml and should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

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

The concurrent intake of ISDN with ACE-inhibitors or arterial vasodilators could be a desirable interaction, unless the antihypertensive effects are excessive in which case consider reducing the dose of one or both drugs.

Also phosphodiesterase-5 inhibitors e.g. sildenafil, potentiate the hypotensive effects of Isoket. This might lead to life-threatening cardiovascular complications, see Sections 4.3 and 4.4.
Patients who have recently taken phosphodiesterase inhibitors (e.g., sildenafil, vardenafil, tadalafil) therefore must not receive acute ISDN therapy within the next 24 hours for sildenafil and vardenafil, or within the next 48 hours for tadalafil.

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

Patients who have recently taken phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil) therefore must not receive acute ISDN therapy.

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
Reproduction studies performed in rats and rabbits at doses up to maternal toxicity have revealed no evidence of harm to the foetus due to ISDN. There are, however, no adequate and well-controlled studies in pregnant women.

Since animal studies are not always predictive of human response, ISDN 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. Therefore, caution is appropriate when administering this agent to lactating women.

Fertility:

No data on effects of 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.

ISDN may affect the patient's reactivity to an extent that his/her ability to drive or 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 Isoket the following undesirable effects may be observed:
Nervous system disorders:
Very common: headache
Common: dizziness, somnolence.

Cardiac disorders:
Common: tachycardia
Uncommon: angina pector is 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.

S ki n and subcutaneous tissue disorders :
Uncommon: allergic skin reactions (e .g. rash), flushing
Very rare: angioedema , Stevens-Johnson-Syndrome
Not known:exfoliativedermatitis .

General disorders and administration site conditions:
Common: asthenia

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

During treatment with Isoket a temporary hypoxemia may occur due to are a relative redistribution of the blood flow in hypoventilated alveolar areas . Particularly in patients with coronary artery disease this may lead to a 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
Website: www.hpra.ie

4.9 Overdose

Symptoms:

• Fall of blood pressure ≤ 90m mHg
• 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. f luids)
- 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

Pharmacotherapeutic group: Vasodilators used in cardiac diseases, organic nitrates, ATC Code: CO1D A08
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

5.2 Pharmacokinetic properties

Isosorbide dinitrate (ISDN) is eliminated from plasma with a short half-life (about 0.7 h). 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 0.57 h^{-1} followed by isosorbide –2- mononitrate (IS-2-MN) with 0.27 h^{-1}, and isosorbide (IS) with 0.16 h^{-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 2.5 h) is shorter than that of IS-5-MN (about 5.1 h). The half-life of ISDN is the shortest of all and that of IS-2-MN (about 3.2 h) 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 injection
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (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 can 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 medicinal product must not be mixed with other medicina l products except those mentioned in Section 6.6.

6.3 Shelf life

Unopened 5 years.

Use diluted solution immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The solution concentrate is sterile, but not preserved. The bottle is not intended for multiple use.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For the diluted solution: Please store only unused, diluted solution in a ref rigerator and use within 24 hours.

From a microbiological point of view, the product must be used immediately. I f not used immediately, in- use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours a t 2 to 8°C , unless reconstitution/dilution has taken place in cont rolled and validated aseptic conditions .

6.5 Nature and contents of container

A clear Ph. Eur. type I glass ampoule.
10 x 10 ml ampoules.

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. No incompatibilities have so far been demonstrated.

Isoket is compatible with glass infusion bottles and infusion packs made from polyethylene. Isoket may be infused slowly using a syringe pump with glass or plastic syringe.

This product must be diluted before administration.
For an example of admixture preparation see section 4.2.
For single use only, discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA2118/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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