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PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT
Isoket 0.1% ampoules
Isoket 0.1% bottle
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ampoule isosorbide dinitrate (ISDN) i.v. 0.1 % contains 10 mg isosorbide dinitrate in 10 ml sterile isotonic sodium chloride solution.
1 bottle isosorbide dinitrate (ISDN) i.v. 0.1 % (50 ml) contains 50 mg isosorbide dinitrate in 50 ml sterile isotonic sodium chloride solution.
Each ml contains 3.54 mg (0.154 mmol) sodium (as sodium chloride).
For list of excipients, see section 6.1.
3. PHARMACEUTICAL FORM
Solution for infusion.
The solution is a clear, colourless and odourless liquid.
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Isoket 0.1% 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.

4.2 Posology and method of administration
The posology must be adjusted to suit the patient's needs and the response of the clinical and haemodynamic variables must be monitored.
Initially treatment is started with a dose of 1–2 mg/h; then the dose can be adjusted to the individual requirements. The maximum dose does not normally exceed 8 (-10) mg/h.
Higher doses of 10 mg/h - and up to 50 mg/h in individual cases - may be necessary in patients suffering from heart failure.
Mode of administration
Isoket 0.1 % solution can be used either diluted in a continuous intravenous infusion by means of automated equipment, or undiluted using a syringe pump, in a hospital setting; the cardiac and circulatory parameters must constantly be monitored.
Isoket 0.1 % solution is compatible with the infusion solutions common in clinical practice such as physiological saline, 5 - 30 % glucose solution, Ringer's solution, protein-containing solutions. When combining Isoket 0.1 % solution with infusion solutions, observe the manufacturers' information on their infusion solutions, specifically the information concerning the compatibility, contraindications, side-effects and interactions.
Depending on the type and severity of the clinical picture, invasive haemodynamic measurements are indicated to supplement the usual controls (symptoms, blood pressure, heart rate, urine output).
Dosage table for diluted solutions:

100 µg/ml: 5 ampoules of 10 ml or 1 bottle of 50 ml topped up to produce 500 ml			**200 µg/ml: 10 ampoules of 10 ml or 2 bottles of 50 ml topped up to produce 500 ml**	
infusion rate		**intended dosage**	infusion rate	
microdrops/min ml/h	drops/min	mg/hour	microdrops/min ml/h	drops/min
10	3–4	**1 mg/h**	5	1–2
20	7	**2 mg/h**	10	3
30	10	**3 mg/h**	15	5
40	13	**4 mg/h**	20	7
50	17	**5 mg/h**	25	8
60	20	**6 mg/h**	30	10
70	23	**7 mg/h**	35	12
80	27	**8 mg/h**	40	13
90	30	**9 mg/h**	45	15
100	33	**10 mg/h**	50	17

Use of the diluted solution:
– Concentration 100 µg/ml (0.01 %):
Dilute 50 ml of Isoket 0.1 % solution (5 ampoules of 10 ml or 1 pierce-cap bottle of 50 ml) to produce 500 ml of ready-made solution.
– Concentration 200 µg/ml (0.02 %):
Dilute 100 ml of Isoket 0.1 % solution (10 ampoules of 10 ml or 2 pierce-cap bottles of 50 ml) to produce 500 ml of ready-made solution.
Use of the undiluted solution:
Isoket 0.1 % solution can also be administered undiluted using a perfusor. Of this solution, 1 ml contains 1 mg of isosorbide dinitrate.
Children
The safety and efficacy of Isoket has not yet been established in children.
4.3 Contraindications
These are common to all nitrates:
Hypersensitivity to ISDN, other nitrates or 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), 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 4.5).
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.
Materials of polyethylene (PE), polypropylene (PP) and polytetrafluorethylene (PTFE) have proved to be suitable for being used for the infusion of isoket 0.1% solution. 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. If these materials are used the dose must be adjusted to suit patient's needs. Due to the fact that ISDN i.v. 0.1 % is supersaturated with the active substance, a deposit of crystals may be observed when ISDN i.v. 0.1 % is used in undiluted form. If crystals are observed, it is safer not to use the solution, although under normal conditions, efficacy is not impaired.
Blood pressure and pulse rate should always be monitored and the dose adjusted according to the patient's response.
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 Interactions 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 0.1 % solution. 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).
Reports suggest that, when administered concomitantly, Isoket may increase the blood level of dihydroergotamine and its hypertensive effect.
4.6 Pregnancy and Lactation
No data have been reported which would indicate the possibility of adverse effects resulting from the use of isosorbide dinitrate in pregnancy. Safety in pregnancy, however, has not been established. Isosorbide dinitrate should only be used in pregnancy and during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the possible hazards.
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.
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) or very rare (<1/10,000).
During administration of ISDN i.v. 0.1 % the following undesirable effects may be observed:
Nervous system disorders: very common: headache; common: dizziness, light headedness, drowsiness, somnolence.
Cardiac disorders: common: tachycardia; uncommon: angina pectoris aggravated.
Vascular disorders: common: orthostatic hypotension; uncommon: collapse (sometimes accompanied by bradyarrhythmia and syncope).
Gastrointestinal disorders: uncommon: nausea, vomiting; very rare: heartburn.
Skin and subcutaneous tissue disorders: uncommon: allergic skin reactions (e.g. rash), flush; very rare: angioedema, Stevens-Johnson-Syndrome; in single cases: exfoliative dermatitis.
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.

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During treatment with ISDN i.v. 0.1 %, a 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 a myocardial hypoxia. If the patient does not show spontaneous recovery, actions to support the heart and circulation such as elevation of the legs and volume expansion may be necessary.

4.9 Overdose

Animal experience:

In mice, significant lethality (LD50) at single intravenous doses of 33.4 mg/kg were observed.

Human experience:

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 isosorbide dinitrate 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
- Additional administration of norepinephrine HCl or other vasoconstrictors. The use of epinephrine in this setting is likely to do more harm than good.
- Treatment of methaemoglobinaemia
  - Reduction therapy of choice with vitamin C, methylene-blue, or toluidine-blue
  - Administer oxygen (if necessary)
  - Initiate artificial ventilation
  - Hemodialysis (if necessary)
- Resuscitation measures

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

ATC code: C01 DA 08 Vasodilatators used in cardiac diseases – organic nitrates.

Isosorbide dinitrate (ISDN) causes a relaxation of vascular smooth muscle thereby inducing a vasodilatation.

Both peripheral arteries and veins are relaxed by ISDN. The latter effect promotes venous pooling of blood and decreases venous return to the heart, thereby reducing ventricular end-diastolic pressure and volume (preload).

The action on arterial and at higher doses arteriolar vessels, reduces the systemic vascular resistance (afterload). This in turn reduces the cardiac work.

The effects on both preload and afterload lead subsequently to a reduced oxygen consumption of the heart.

Furthermore, ISDN causes redistribution of blood flow to the subendocardial regions of the heart when the coronary circulation is partially occluded by arteriosclerotic lesions. This last effect is likely to be due to a selective dilation of large coronary vessels. Nitrate induced dilation of collateral arteries can improve the perfusion of poststenotic myocardium. Nitrates also dilate eccentric stenoses as they can counteract possible constricting factors acting on the residual arch of compliant smooth muscle at the site of the coronary narrowing. Furthermore, coronary spasms can be relaxed by nitrates.

Nitrates were shown to improve resting and exercise hemodynamics in patients suffering from congestive heart failure. In this beneficial effect several mechanisms including an improvement of valvular regurgitation (due to the lessening of ventricular dilatation) and the reduction of myocardial oxygen demand are involved.

By decreasing the oxygen demand and increasing the oxygen supply, the area of myocardial damage is reduced. Therefore, ISDN may be useful in selected patients who suffered a myocardial infarction.

Effects on other organ systems include a relaxation of the bronchial muscle, the muscles of the gastrointestinal, the biliary and the urinary tract. Relaxation of the uterine smooth muscles is reported as well.

Mechanism of action

Like all organic nitrates, ISDN acts as a donor of nitric oxide (NO). NO causes a relaxation of vascular smooth muscle via the stimulation of guanylyl cyclase and the subsequent increase of intracellular cyclic guanosine monophosphate (cGMP) concentration. A cGMP-dependent protein kinase is thus stimulated, with resultant alteration of the phosphorylation of various proteins in the smooth muscle cell. This eventually leads to the dephosphorylation of the light chain of myosin and the lowering of contractility.

5.2 Pharmacokinetic properties

The half-life of intravenously infused ISDN amounts to 10 min. ISDN is metabolized to isosorbide 2-mononitrate and isosorbide 5-mononitrate having a half-life of 1.5 to 2 and 4 to 6 h, respectively. Both metabolites are pharmacologically active.

The bioavailability of ISDN solution is defined 100 % as all intravenously applied drugs.

5.3 Preclinical safety data

Acute toxicity:

Investigations on the acute toxicity have not revealed any particular risks. Animal studies showed good local tolerability of the undiluted ISDN solution. Similarly, in humans local tolerability was found to be good following administration of both undiluted and diluted solution.

Chronic toxicity:

Chronic toxicity studies in rats and dogs revealed toxic effects such as CNS symptoms and an increase of liver weight when ISDN was administered in doses as high as 480 and 90 mg/kg b.w. per day, respectively.

Reproduction studies:

There is no evidence from animal studies suggesting a teratogenic effect of ISDN.

Mutagenicity:

No evidence for mutagenic effects was found in several tests undertaken both in vitro and in vivo.

Carcinogenicity:

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

6.2 Incompatibilities

Isoket 0.1 % is compatible with all infusion solutions usually administered in hospital such as physiological sodium chloride solution, 5 - 30% glucose solution, Ringer's solution, solutions containing albumin. Isoket 0.1 % does not contain propylenglycol, ethanol, and potassium ions. Incompatibilities have not been reported.

6.3 Special precautions for storage

Store below 30°C.

For the reconstituted solution: please store the diluted solution in a refrigerator as long as it is not used within 24 hours.

The diluted solution must be administered within 24 hours.

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

From a microbiological point of view, the product must be used immediately. If 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 at 2 to 8°C.

6.4 Nature and contents of container

Isoket 0.1 % ampoules: 10 ml colourless, O(ne) P(oint) C(ut) glass ampoule. Pack size – 10 ampoules.

Isoket 0.1% bottle: 50 ml colourless glass vial. Pack size – 1 vial.

6.5 Special precautions for handling

ISDN i.v. 0.1 % may be administered either diluted in a continuous intravenous infusion by means of an automatic infusion device, or undiluted using a syringe pump, in a hospital setting under constant cardiovascular monitoring.

Depending on the type and the severity of the disease, the usual follow-up examinations (symptoms, blood pressure, heart rate, urine) must be completed using invasive hemodynamic measurements.

Isoket 0.1 % must be diluted under aseptic conditions immediately after opening. The diluted solution is to be used immediately.

Concentration 0.1 mg/ml (0.01 %):

50 ml ISDN i.v. 0.1 % (5 ampoules of 10 ml each or 1 bottle of 50 ml) made up to 500 ml of ready-for-use solution

Concentration 0.2 mg/ml (0.02 %):

100 ml ISDN i.v. 0.1 % (10 ampoules of 10 ml or 2 bottles of 50 ml each, respectively) made up to 500 ml of ready-for-use solution

Isoket 0.1 % can also be used in undiluted form.

1 ml of this solution contains 1 mg ISDN.

7. MANUFACTURER

Aesica Pharmaceuticals GmbH, Monheim, Germany

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd.
25 Basel St., Petach Tikva

9. License Number

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