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Prescribing Information

ISOKET[®] Spray

Qualitative and quantitative Composition

12.7 g solution (= 15 ml) contains:

375 mg isosorbide dinitrate.

1 dose (= 0.05 ml) contains:

1.25 mg isosorbide dinitrate.

Pharmaceutical form

Oromucosal spray

The solution is a clear, colourless liquid.

Indications

- Angina pectoris
- Congestive heart failure

Posology and method of administration

The dosage should be adjusted to suit the patient's needs.

1-3 squirts at about 30 seconds intervals are sprayed into the mouth during an attack or shortly before physical and/or mental stress that may trigger an attack.

A single dose of 3 squirts applied to treat an acute angina attack should only be exceeded upon the physician's express advice.

In acute myocardial infarction or acute heart failure one starts with 1-3 squirts. In the event of non-response within 5 minutes, an additional squirt may be given. In case there is no improvement within the subsequent 10 minutes, spray application may be repeated under close blood pressure monitoring.

Contraindications

Isoket[®] spray must not be used in:

- Hypersensitivity to ISDN, other nitro compounds or other ingredients
- Acute circulatory failure (shock, collapse)
- Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by

- appropriate measures).
- Hypertrophic obstructive cardiomyopathy.
- Constrictive pericarditis
- Cardiac tamponade
- Severe hypotension (systolic blood pressure less than 90 mmHg).
- During nitrate therapy, phosphodiesterase inhibitors (e.g. sildenafil) must not be used (see section interactions with other medicaments and other forms of interaction).

Special warnings and special precautions for use

Isoket[®] spray should be used only with particular caution and under medical supervision in:

- Low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure). Reducing systolic blood pressure below 90 mmHg should be avoided.
- Aortic and/or mitral stenosis
- Orthostatic dysfunction
- Diseases associated with an increased intracranial pressure (however, until now, a further increase of intracranial pressure has only been observed following the administration of nitroglycerin i.v. in high dosages).

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 should be avoided.

Warning: The solution contains 85 vol % of ethanol!

Patients who undergo a maintenance treatment with Isoket[®] spray should be informed that they must not use phosphodiesterase inhibitors (e.g. sildenafil)-containing products. Isoket[®] spray therapy should not be interrupted to take phosphodiesterase inhibitors (e.g. sildenafil)-containing products, because the risk of inducing an attack of angina pectoris could increase by doing so (see section interactions with other medicaments and other forms of interaction).

In case of accidental extensive skin contact with the content of the ISDN spray bottle the contaminated skin should be cleaned immediately. Otherwise the solution could be absorbed from the skin and this might cause severe undesirable effects (See also chapter Undesirable effects).

Interactions with other medicaments and other forms of interaction

Concurrent intake of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel antagonists, vasodilators etc, and/or alcohol may potentiate the hypotensive effect of Isoket[®] spray. This might also occur with neuroleptics and tricyclic antidepressants. A blood pressure lowering effect of Isoket[®] spray will be increased, if used together with phosphodiesterase inhibitors (e.g. sildenafil) which are used for erectile dysfunction (see special warnings and contraindications).

This might lead to life-threatening cardiovascular complications. Patients who are on Isoket[®] spray therapy therefore must not use phosphodiesterase inhibitors (e.g. sildenafil).

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

Pregnancy and lactation

There is no evidence from animal studies suggesting teratogenic effects of isosorbide dinitrate.

Isoket[®] spray should only be used during pregnancy if clearly needed and solely under the direction and continuous supervision of a physician.

It is not known whether isosorbide dinitrate is excreted in human milk. Because many drugs are excreted in this way, caution should be exercised when Isoket[®] spray is administered to a nursing woman.

Pregnancy Category: C

Effects on ability to drive and use machines

Isoket[®] spray 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.

Undesirable effects

Undesirable effects frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$) or very rare ($< 1/10,000$)

During administration of ISDN Spray the following undesirable effects may be observed:

Cardiac disorders:

Common: reflex tachycardia

Uncommon: enhanced angina pectoris symptoms.

Gastrointestinal disorders:

Uncommon: nausea, vomiting

Very rare: heartburn

General disorders and administration site conditions:

Common: feeling of weakness,

Application site burning of the tongue.

Nervous system disorders:

Very common: headache

Common: light headedness, dizziness, drowsiness.

Skin and subcutaneous tissue disorders:

Uncommon: allergic skin reactions (e.g. rash), flush

Very rare: angioedema, Stevens-Johnson-Syndrome

In single cases: exfoliative dermatitis.

Vascular disorders:

Common: hypotension on standing

Uncommon: collapse (sometimes accompanied by bradyarrhythmia and syncope).

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

During the treatment with Isoket[®] spray, a temporary hypoxaemia 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.

Overdose

Animal experience:

In mice, significant lethality (LD50) at single intravenous doses of 33,4 mg/kg was observed.

Human experience:

Symptoms:

- Fall of blood pressure ≤ 90 mmHg
- Paleness
- Sweating
- Weak pulse
- Tachycardia
- Light-headedness on standing
- Headache
- Weakness
- 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 can not be excluded that an overdose or 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
 - Patient should be kept horizontal with the head lowered and legs raised
 - Supply oxygen
 - Expand plasma volume
 - Specific shock treatment (admit patient to intensive care unit!).

Special procedure:

- Raising the blood pressure if the blood pressure is very low
- Additional administration of a sympathomimetic, e.g. epinephrine HCl or norepinephrine HCl.
- 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: vasodilators used in cardiac diseases

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 dosages arteriolar vessels, reduce 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 complaint 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 organic 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.

Pharmacokinetic properties

After sprayed into the mouth cavity, the active drug, isosorbide dinitrate (ISDN) is rapidly adsorbed by the mucosa. Pharmacological effects can be observed within 1-3 min after administration of Isoket[®] spray with maximum plasma levels within 3-6 min. Elimination takes place with a half-life of 30-60 minutes. Within a period of 90-120 minutes plasma concentration drops to base-line values again. ISDN is metabolized to isosorbide-2-mononitrate and isosorbide-5-mononitrate having a terminal half-life of 1.5 to 2 and 4 to 6 hours, respectively. Both metabolites are pharmacologically active.

Bioavailability

Following peroral administration isosorbide dinitrate is subject to a marked first pass effect leading to a bioavailability of about 15-30%.

Isoket[®] spray is exclusively designed for application into the oral cavity. By circumventing the gastro-intestinal tract, the active substance thus immediately

reaches the systemic circulation and consequently circumvents rapid metabolism in the liver. In this way a clearly marked higher bioavailability of 60-100% is reached.

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 Isoket 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 mg/kg b.w. per day.

Reproduction studies:

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

Mutagenicity:

No evidence for mutagenic effects were 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.

List of excipients

- Ethanol
- Macrogol 400

Shelf-life

Shelf-life in the product as packaged for sale: 5 years.

The drug should not be used after the expiry date.

Special precautions for storage

No special precautions for storage are necessary to protect the pharmaceutical quality of the product.

Nature and contents of container

One bottle contains not less than 300 squirts of 1.25 mg isosorbide dinitrate.

Instructions for use/handling

Please note!

The solution is to be sprayed into the mouth; it should not be inhaled!

Prior to the first application of the spray, the spray valve must be operated several times (light pumping), until an even mist escapes. Now the spray is ready for use.

If the spray has not been used for more than one day, the first squirt has to be released into the air in order to ensure complete subsequent dosing.

During application, the bottle is to be held in a vertical position with the pump facing upwards.

The solution is sprayed into the mouth as follows:

- Inhale deeply
- Hold your breath
- By pressing the dosing pump, spray the drug into the mouth (this may induce a light burning sensation on the tongue)
- Then close your mouth and continue breathing solely through the nose for about 30 seconds.

Note:

The label of the spray bottle bears an error mark at its lower margin. As soon as the fluid level in the bottle reaches this point, a new package of Isoket[®] spray should be at hand for safety reasons. At any rate, the open spray may further be used as long as – even on slightly tilting the spray bottle – the tip of the pump pipe is still immersed in the fluid.

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