NON-CENTRAL DATA SHEET (NCDS)

ISOKET 0,1 % SOLUTION

Isosorbide dinitrate (solution for infusion or injection)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of isosorbide dinitrate 1mg/ml contains 10 mg isosorbide dinitrate in 10 ml sterile isotonic sodium chloride solution.

Excipients

Sodium chloride, water for injections, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment).

PHARMACEUTICAL FORM

The solution is clear, colourless liquid.

CLINICAL INFORMATION

Indications

Intravenous route:

For the treatment of:

- unresponsive left ventricular failure secondary to acute myocardial infarction,
- unresponsive left ventricular failure of various aetiology,
- severe or unstable angina pectoris.

Dosage and Administration

This medicinal product is a concentrated solution and must be diluted prior use. The diluted solution should never be injected directly in the form of a bolus.
Isosorbide dinitrate solution for infusion or injection, can be administered as an intravenous admixture with a suitable vehicle *(see Section Use and Handling).*
Prepared isosorbide dinitrate 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.

Route of Administration

For intravenous use.

Adults

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.

Children

The safety and efficacy of isosorbide dinitrate solution for infusion has not yet been established in children.

Elderly

No dose adjustment is necessary.

Renal and Hepatic impairment

Isosorbide dinitrate should be used with caution in patients with severely impaired renal or hepatic function *(see Section Warnings and Precautions)*.

Contraindications

Isosorbide dinitrate is contraindicated in:

- known hypersensitivity to the active substance, to any of the excipients, or to other nitrates or nitrites,
- low filling pressure,
- hypertrophic obstructive cardiomyopathy (HOCM),
- constrictive pericarditis,
- cardiac tamponade,
- cardiogenic shock (unless some means of maintaining an adequate diastolic pressure is undertaken),
- circulatory collapse,
- aortic and/or mitral valve stenosis,
- severe hypotension (systolic blood pressure less than 90 mmHg),
- head trauma,
- cerebral haemorrhage,
- diseases associated with an increased intracranial pressure,
- marked anaemia,
- hypovolaemia,
- closed angle glaucoma,
- patients receiving phosphodiesterase-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) (*see Sections: Warnings and Precautions; Interactions)*,
- patients receiving the soluble guanylate cyclase stimulator riociguat (*see Section Interactions)*.

Warnings and Precautions

Medical supervision required

Isosorbide dinitrate should be used with caution and under medical supervision in patients who are suffering from:

- hypothyroidism,
- hypothermia,
- malnutrition,
- severe liver disease or renal disease,
- orthostatic syndrome.

Tolerance

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 monitoring

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

Hypoxaemia

Caution should be exercised in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure. As a potent vasodilator, isosorbide dinitrate 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.

Alcohol

During treatment with isosorbide dinitrate alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of isosorbide dinitrate (*see Section Interactions*).

Phosphodiesterase inhibitors containing products

Patients who undergo a maintenance treatment with isosorbide dinitrate 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: Contraindications; Interactions)*.

Acute therapy with isosorbide dinitrate 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). Patients who receive isosorbide dinitrate as acute therapy must be warned not to take phosphodiesterase inhibitors containing products (e. g. sildenafil, vardenafil, tadalafil).

Interactions

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors e.g. sildenafil, potentiate the hypotensive effects of isosorbide dinitrate. This might lead to life-threatening cardiovascular complications. Therefore, isosorbide dinitrate must not be given to patients receiving phosphodiesterase-5-inhibitors.

Patients who have recently taken phosphodiesterase inhibitors (e.g., sildenafil, vardenafil, tadalafil) must not receive acute isosorbide dinitrate therapy within the next 24 hours for sildenafil and vardenafil, or within the next 48 hours for tadalafil *(see Sections: Contraindications; Warnings and Precautions).*

Blood pressure lowering drugs

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

The concurrent intake of isosorbide dinitrate 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.

Dihydroergotamine

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

Riociguat

The use of isosorbide dinitrate (ISDN) with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (*see Section Contraindications*) since concomitant use can cause hypotension.

Sapropterine

Sapropterin (tetrahydrobiopterine, BH4) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterin-containing medicine with any active substance 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).

Pregnancy and Lactation

Fertility

There are no relevant data available.

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 isosorbide dinitrate. 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.

Lactation

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 methaemoglobinemia 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.

Ability to perform tasks that require judgement, motor or cognitive skills

As for other drugs which produce changes in blood pressure, patients taking isosorbide dinitrate 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.

Adverse Reactions

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.
Frequencies are defined as:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

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)

Not known: hypotension

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

Respiratory, thoracic and mediastinal disorders

Not known: hypoxaemia *(see Section Warning and Precautions)*

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.

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: exfoliative dermatitis

General disorders and administration site conditions:

Common: asthenia

Overdosage

Symptoms and signs

The following symptoms were observed: 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 increase. This might lead to cerebral symptoms.

Treatment

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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group

Vasodilators used in cardiac diseases; organic nitrates

ATC Code:

C01DA08

Mechanism of Action and Pharmacodynamic effects

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.

Pharmacokinetics

Metabolism and Elimination

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 2.5h) 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.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

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
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.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date is indicated on the packaging.

Open ampoules should be used immediately and any unused drug discarded.

Once diluted, chemical and physical in-use stability for 24 hours at 2-8°C has been demonstrated.

From a microbiological point of view, the product must be used immediately once opened/diluted. 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 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Storage

Store at or below 30 °C, protected from light.

Discard any unused solution.

Keep out of reach of children.

Nature and Contents of Container

Each pack contains 10 x 10 ml ampoules (10 mg/10 ml).

Incompatibilities

Polyvinyl chloride (PVC) or polyurethane (PU) giving sets and containers should not be used since significant losses of the active ingredient by adsorption occur and it has not been verified how the dose can be adjusted to suit the patient's needs to account for this

adsorption. This medicinal product must not be mixed with other medicinal products except those mentioned in section Use and Handling.

Use and Handling

Isosorbide dinitrate 1mg/ml solution for infusion is oversaturated with the active substance, therefore, crystallisation may occur in undiluted form. If crystals are observed, it is safer not to use the solution, although under normal conditions, efficacy is not impaired.

Isosorbide dinitrate 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.

This medicinal product contains isosorbide dinitrate in isotonic solution and is compatible with commonly employed infusion fluids, such as sodium chloride solution, dextrose solution, 5-30% glucose solution, Ringer's solution and solutions containing albumin. No incompatibilities have so far been demonstrated.

This product is compatible with glass infusion bottles and infusion packs made from polyethylene (PE), polypropylene (PP) or polytetrafluoroethylene (PTFE). Isosorbide dinitrate may be infused slowly using a syringe pump with glass or plastic syringe.

Example of admixture preparation

To obtain a dose of 6 mg per hour, add 50 ml of isosorbide dinitrate solution for infusion or injection 1 mg/ml to 450 ml of a suitable vehicle, under aseptic conditions. The resultant admixture (500 ml) contains 100 µg/ml (1 mg/10ml) 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 isosorbide dinitrate solution for infusion 1 mg/ml may be diluted to 500 ml using a suitable vehicle. The resultant solution now contains 200 µg/ml (2 mg/10ml) 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 dose of 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.

Name and address of the holder of the certificate of registration

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