ISOKET 0,1 % SOLUTION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

ISOKET 0,1 % SOLUTION

Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

ISOKET 0,1 % SOLUTION is a concentrated solution of isosorbide dinitrate 1 mg/1 mL in sterile isotonic saline.

Sugar-free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

A clear colourless solution in 10 mL ampoules.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

- Severe angina pectoris (e.g. unstable or vasospastic angina).
- Acute myocardial infarction.
- Acute left ventricular failure.

4.2 Posology and method of administration:

Posology:

The dosage should be adjusted to suit the patient's needs and the response of the clinical and haemodynamic variables should be monitored.

Adults:

Initially, treatment is started with a dose of 1 to 2 mg per hour; then the dose can be adjusted to the individual requirements. The maximum dose does not normally exceed 12 mg/hour. However, patients suffering from heart failure may require higher doses of up to 20 mg per hour.

Children:

The safety and efficacy of ISOKET in children has not yet been established.

Elderly:

No dosage adjustment is necessary.

Renal and hepatic impairment:

ISOKET should be used with caution in patients with severely impaired renal or hepatic function (see section 4.4).

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. ISOKET can be administered as an intravenous admixture with a suitable vehicle such as 0,9 % sodium chloride injection or 5 % dextrose and water injection (also see section 6.6). When 0,9 % sodium chloride is given, the effect of sodium overload should be taken into consideration.

Prepared ISOKET admixtures are always given by intravenous infusion or with the aid of a syringe pump incorporating a glass or rigid plastic syringe, 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) should be completed using invasive haemodynamic measurements.

Example of admixture preparation:

Admixtures are prepared by exchanging the required volume of ISOKET with an equal volume of infusion vehicle.

For example, if a dose of 5 mg per hour is required, 50 mL of ISOKET (equivalent to 5 x 10 mL ampoules) should be added to 150 mL of the infusion vehicle to give a final volume of 200 mL. This admixture now contains 250 µg/mL (2,5 mg in 10 mL) and the required dosage can be obtained by giving 20 mL per hour, which is equivalent to a drip rate of 20 paediatric microdrops per minute, or 6-7 standard drops per minute. This drip rate provides enough solution for an infusion time of 10 hours.

When it is necessary to further reduce the fluid intake, a more concentrated solution may be obtained by using 100 mL (100 mg) of ISOKET made up to 200 mL with a suitable infusion vehicle. This admixture now contains 500 µg/mL (5 mg in 10 mL). With a concentration of 500 µg/mL, the patient requiring 5 mg ISOKET per hour would need a drip rate of 10 paediatric microdrops per minute (which is the same as 10 mL per hour) or 3-4 standard drops per minute. Likewise the same concentration may be obtained by adding equal volumes of ISOKET and infusion vehicle together.

Concentration 0,1 mg/mL (0,01 %):

50 mL ISOKET solution 0,1 % (5 ampoules of 10 mL each) made up to 500 mL of ready-for-use solution.

Concentration 0,2 mg/mL (0,02 %):

100 mL ISOKET solution 0,1 % (10 ampoules of 10 mL) made up to 500 mL of ready-for-use solution.

The use of PVC containers e.g. Viaflex should be avoided as a loss of activity of up to 40 % is possible on prolonged contact e.g. 8 hours.

4.3 Contraindications:

ISOKET must not be used in:

- hypersensitivity to ISOKET, to other nitrates or nitrites or to any of the other ingredients listed in section 6.1
- low left ventricular filling pressure (see section 4.4)
- hypertrophic obstructive cardiomyopathy (HOCM)
- cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures e.g. unless medicines with positive inotropic effect or intra-aortic balloon counterpulsation are simultaneously used)
- severe hypotension (systolic blood pressure less than 90 mmHg)
- marked anaemia
- head trauma
- cerebral haemorrhage
- hypovolaemia
- closed angle glaucoma
- diseases associated with an increased intracranial pressure
- constrictive pericarditis
- cardiac tamponade
- circulatory collapse

- aortic and/or mitral valve stenosis
- patients receiving phosphodiesterase-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) (see sections 4.4 and 4.5)
- patients receiving the soluble guanylate cyclase stimulator riociguat (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
- hypothermia
- malnutrition
- severe liver disease or renal disease
- orthostatic hypotension.

In patients with initial hypotension and low ventricular filling pressures, ISOKET for infusion should, when absolutely needed, be used simultaneously with either positive inotropic medicines or assisted circulation (balloon pump). Continuous haemodynamic monitoring is required during the infusion (see section 4.3).

Tolerance:

The development of tolerance and cross-tolerance towards other nitrate-type medicines 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 4.5).

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 4.3 and 4.5).

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).

Excipients:

As ISOKET contains 3,54 mg of sodium per mL, it should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction:

Phosphodiesterase-5 inhibitors:

Phosphodiesterase-5 inhibitors e.g. sildenafil, potentiate the hypotensive effects of ISOKET. This might lead to life-threatening cardiovascular complications. Therefore, ISOKET 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 4.3 and 4.4).

Blood pressure lowering medicines:

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

The concurrent intake of ISOKET 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 medicines.

Dihydroergotamine:

ISOKET solution may increase the blood level of dihydroergotamine and its toxic effect.

Riociguat:

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

Sapropterin:

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).

4.6 Fertility, pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

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.

Breastfeeding:

Nitrates are excreted in breast milk and may cause methaemoglobinaemia in infants.

Fertility:

No data on effects of fertility are available.

4.7 Effects on ability to drive and use machines:

Patients receiving ISOKET should be warned not to drive or operate machinery if they experience dizziness of related symptoms. ISOKET 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:

Nervous system disorders:

Frequent: headache (the severity of headache usually diminishes gradually with time and continued use), light-headedness in upright position, dizziness, drowsiness

Cardiac disorders:

Frequent: reflex tachycardia

Less frequent: severe hypotension may lead to exacerbation of angina pectoris symptoms (see section 4.4). If severe hypotension occurs, administration should be stopped immediately. If the symptoms do not subside spontaneously, appropriate measures should be undertaken (e.g. raising legs, administration of volume expanding medicines)

Vascular disorders:

Frequent: hypotension on standing

Less frequent: circulatory collapse (sometimes accompanied by bradydysrhythmia and syncope) (see section 4.4).

Frequency unknown: hypotension.

Severe hypotensive responses have been reported for ISOKET and include nausea, vomiting, restlessness, pallor and excessive perspiration. Symptoms of cerebral ischaemia, marked blood pressure drop, cyanosis, methaemoglobinaemia, coldness of the skin, impairment of respiration and bradycardia. Patients may have no untoward effect while recumbent but may develop postural hypotension with faintness upon rising suddenly

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: hypoxia (see section 4.4).

During treatment with isosorbide dinitrate, 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 myocardial hypoxia

Gastrointestinal disorders:

Less frequent: nausea, vomiting, heartburn

Skin and subcutaneous disorders:

Less frequent: allergic skin reactions (e.g. rash), flushing, angioedema, Steven-Johnson syndrome

Frequency unknown: exfoliative dermatitis

General disorders and administration site conditions:

Frequent: feeling of weakness.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of ISOKET is important. It allows continued monitoring of the benefit/risk balance of ISOKET. Health care providers are asked to report any suspected adverse reactions to: SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms and signs:

The following symptoms were observed: tachycardia, headache, fall of blood pressure <90 mmHg, pallor, sweating, weak pulse, postural dizziness, asthenia, dizziness, nausea, vomiting, diarrhoea.

Methaemoglobinaemia has been reported in patients receiving organic nitrates. During ISOKET 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 increase. This might lead to cerebral symptoms. Overdosage may cause cyanosis and occasionally convulsions and respiratory paralysis. If symptoms of overdosage occur infusion should be stopped at once and therapeutic measures must be taken to the effect of raising the patient's blood pressure.

Treatment:

General procedure:

- stop delivery of the medicine.

General procedures in the event of nitrate-related hypotension:

- patient should be kept horizontal with the head lowered and legs raised
- supply oxygen
- expand volume
- specific shock treatment (admit patient to intensive care unit).

Special procedure:

- raising the blood pressure if the blood pressure is very low
- vasopressors should only be used 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
- exchange blood (if necessary).

Resuscitation measures:

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

Further management should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 7.1.4 Vasodilators – coronary and other medicines used in angina pectoris.

Isosorbide dinitrate (ISDN) causes a relaxation of vascular smooth muscle thereby inducing 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, reduces the systemic vascular resistance (afterload). This in turn reduces the cardiac work. This is probably the predominant effect in angina pectoris and cardiac failure.

The effects on both preload and afterload lead subsequently to a reduced oxygen consumption by 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. Coronary vasospasm can be relaxed by nitrates.

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 muscle is reported as well.

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-dependant 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 terminal half-life of ISDN administered intravenously amounts to 10 minutes. ISDN is metabolised 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium chloride

Water for injections

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment).

6.2 Incompatibilities:

Infusion material made of polyvinyl chloride (PVC) or polyurethane (PU) should not be used since significant losses of the active ingredient due to 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.

Materials made of polyethylene (PE), polypropylene (PP) or polytetrafluorethylene (PTFE) have proven to be suitable for infusing ISOKET solution.

ISOKET should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life:

Unopened ampoules:

60 months.

Once opened:

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

6.4 Special precautions for storage:

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

Discard any unused solution.

Keep out of reach of children.

6.5 Nature and contents of container:

ISOKET is filled into 10 mL colourless, OPC Type I glass ampoules.

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

6.6 Special precautions for disposal and other handling:

Due to the fact that ISOKET solution is supersaturated with the active substance, a deposit of crystals may be observed when ISOKET solution 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.

ISOKET is compatible with all commonly employed infusion solutions such as 5 – 30 % glucose infusion, sodium chloride solution 0,9 % (isotonic); Ringer's solution, solutions containing protein, heparin solution 5 000 U per mL.

ISOKET is compatible with glass infusion bottles. ISOKET solution does not contain propylene glycol, ethanol and potassium ions.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

W/7.1.4/0360

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

17 September 1991

10. DATE OF REVISION OF THE TEXT:

05 September 2021

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