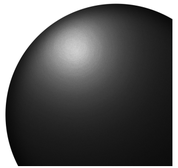
isoket® 0.1% solution

ISOSORBIDE DINITRATE



4007623 0607-0 10/501 1524

Patient information

isoket® 0.1% solution

Active ingredient: isosorbide dinitrate

COMPOSITION

The infusion solution contains per 1 ml:

pharmaceutically active ingredients:
isosorbide dinitrate 1 mg

Other ingredients:
sodium chloride, water for injection

PRESENTATION AND SIZES

Infusion solution

Packs of 10 ampoules (N2), each containing isosorbide dinitrate 10 mg in 10 ml of solution

Packs with 1 pierce-cap vial (N1) of isosorbide dinitrate 100 mg in 100 ml of solution

Hospital-size packs of 5 x 10 ampoules, each containing isosorbide dinitrate 10 mg in 10 ml of solution

Hospital-size packs with 1 pierce-cap vial of isosorbide dinitrate 50 mg in 50 ml of solution

SUBSTANCE OR INDICATION GROUP OR MODE OF ACTION

Drug to treat blood flow disorders of the coronary vessels

NAME AND ADDRESS OF THE PHARMACEUTICAL MANUFACTURER:

SCHWARZ PHARMA AG
Alfred-Nobel-Str. 10
D-40789 Monheim
Phone: 02173/48-0
Fax: 02173/48-1608

INDICATIONS

- severe angina pectoris (chest pain due to blood flow disorders of the coronary vessels): unstable and vasospastic forms;
- acute myocardial infarction;
- acute left ventricular failure (myocardial insufficiency with impaired function of the left ventricle).

CONTRAINDICATIONS

When must you not use isoket® 0.1 % solution?

Isosorbide dinitrate must not be used in cases of:

- allergy to nitrate-type drugs or to any other ingredient;
- acute circulatory failure (shock, circulatory collapse);
- cardiogenic shock (shock caused by heart failure), unless a sufficiently high filling pressure in the heart (left ventricular end-diastolic pressure) is ensured by appropriate measures;
- very low blood pressure (marked hypotension: systolic blood pressure less than 90 mm Hg).

isoket® 0.1 % solution and phosphodiesterase type 5 inhibitors such as Viagra® must not be used concomitantly, because this may result in a severe blood pressure lowering effect.

Warning:
isoket® 0.1 % solution must never be used in patients who have recently taken Viagra® even if acute angina occurs. *In which cases may you use isoket® 0.1 % solution only on certain conditions and observing particular caution?*

The following section describes the cases in which isoket® 0.1 % solution may be used only on certain conditions and observing particular caution. Please ask your doctor in such cases. This section is also relevant when the factors mentioned below applied to you at any time in the past.

Medical monitoring must be particularly careful in cases of:
myocardial disease with reduction of the myocardial cavities (hypertrophic obstructive cardiomyopathy), constrictive pericarditis and cardiac tamponade;

- low filling pressures, e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure). Decreasing the systolic blood pressure below 90 mm Hg should be avoided;
- narrowing of the aortic and/or mitral valve (aortic and/or mitral stenosis);
- tendency towards circulatory dysregulation due to low blood pressure (orthostatic dysfunction);
- diseases associated with an elevated intracranial pressure (further increases in pressure have so far been seen only after the i.v. administration of high doses of glyceryl trinitrate).

Adequate volume replacement is necessary in case a volume deficit is present at the beginning of therapy. *What do you have to observe during pregnancy and lactation?*

For reasons of particular caution, isosorbide dinitrate should be used only at a physician's special order during pregnancy and lactation, as there is no sufficient experience with its use in pregnant or nursing women. Animal experiments have not yielded any indication of fetal damage.

What has to be considered in children?

There are no reports so far concerning the treatment of children.

PRECAUTIONS OF USE AND WARNINGS

Which precautions have to be observed?

The solution is sterile, but has not been manufactured using preservative substances. The pierce-cap vial is not intended for multiple withdrawals.

isoket® 0.1 % solution should be used aseptically immediately after the container has been opened.

Materials of polyethylene (PE), polypropylene (PP) and polytetrafluoroethylene (PTFE) have proved suitable for being used for the infusion of isoket® 0.1 % solution. Infusion equipment of polyvinylchloride (PVC) or polyurethane (PU) results in losses of the drug substance by adsorption.

As isoket® 0.1 % solution is oversaturated with the drug substance, crystallization may sometimes be observed when the preparation is used undiluted. Although this will not impair its administration under normal conditions, it is advisable not to use the solution if crystal formation is detected.

The infusion tube should be changed any time the perfusor needle is changed.

NOTE ON REACTIVITY

Even when used in accordance with the instructions, this drug can alter the patient's reaction rate to an extent such as to impair his/her ability to drive a motor-vehicle or to operate machinery or to work in unsafe places. This is particularly true when the therapy is started, the dose is raised or the preparation is changed, or when the preparation interacts with alcohol.

INTERACTIONS WITH OTHER DRUGS

Which other drugs affect the effect of isoket® 0.1 % solution and how are the effects of other drugs affected by isoket® 0.1 % solution?

The concomitant use of other vasodilators, antihypertensives, beta blockers, calcium antagonists, neuroleptics or tricyclic antidepressants, and alcohol can enhance the hypotensive effect of isoket® 0.1 % solution.

This is true in particular for the concomitant use of phosphodiesterase type 5 inhibitors such as Viagra® (see „Contraindications").

When used together with dihydroergotamine (DHE), isoket® 0.1 % solution may lead to an increase in the DHE level and thus enhance the hypertensive effect of the latter.

Please note that this information may also apply to drugs you took a short time ago.

DOSAGE, MODE AND DURATION OF ADMINISTRATION

The dosage must always be adapted to the individual clinical and haemodynamic pretreatment values.

The clinical treatment starts at a dose of 1–2 mg/h and is then adapted to the individual demand. The maximum doses are usually 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. The mean dose is about 7.5 mg/h.

In patients having received a prior therapy with organic nitro compounds, e.g. isosorbide dinitrate, isosorbide-5-mononitrate, a higher dosage of isoket® 0.1 % solution may be necessary to achieve the desired haemodynamic effect.

Dosage table for diluted solutions:

100 µg/ml 5 ampoules of 10 ml or 1 vial of 50 ml topped up to produce 500 ml			**200 µg/ml** 10 ampoules of 10 ml or 2 vials of 50 ml or 1 vial of 100 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

MODE OF ADMINISTRATION

isoket® 0.1 % solution can be used both diluted and undiluted as i.v. continuous infusion by automated equipment in a hospital; 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 kind and severity of the clinical picture, invasive haemodynamic measurements are indicated to supplement the usual controls (symptoms, blood pressure, heart rate, urine output).

Product Name	Isoket 0,1%	
Identification No.	4007623 0607-0	
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Colours	schwarz	
Operators Name	woytke	
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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 vial 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 vials 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. Depending on the clinical picture, the haemodynamics and the ECG, the treatment may be continued for up to 3 days or longer.

FAULTY USE AND OVERDOSAGE (EMERGENCY MEASURES, SYMPTOMS AND ANTIDOTES)

What has to be done, if too much isoket® 0.1 % solution has been used (intentional or accidental overdosage)?
If overdosage with major quantities of isoket® 0.1 % solution is suspected, a doctor has to be called immediately.

SYMPTOMS OF OVERDOSAGE

Depending on the extent of overdosage, a marked reduction of blood pressure (hypotension) accompanied by a reflex increase in heart rate, a feeling of weakness, vertigo and dizziness, and headache, skin reddening, nausea, vomiting and diarrhoea can occur.
After high doses (more than 20 mg/kg body weight), nitrite ions as are formed during the decomposition of isosorbide dinitrate are not unlikely to induce methaemoglobinaemia, cyanosis, dyspnoea and tachypnoea.
Very high doses can lead to an increase in intracranial pressure and cerebral symptoms.
Elevated methaemoglobin concentrations were measured in cases of chronic overdosage, but are debated as to their clinical relevance.

THERAPY IN CASES OF OVER-DOSAGE

Besides general measures such as horizontal position of the patient with elevation of the legs, monitoring and – if necessary – adjustment of the vital parameters under intensive care is required.
In cases of marked hypotension and/or shock, volume expansion should be performed; norepinephrine and/or dopamine may be infused in exceptional cases to support the circulation.
The administration of epinephrine or of related substances is contraindicated.
According to severity, the following antidotes can be used to treat methaemoglobinaemia:

1. vitamin C: 1 g orally or i.v. as sodium salt
2. methylene blue: up to 50 ml i.v. of a 1 % solution of methylene-blue
3. toluidine blue: initially 2 - 4 ml/kg BW, strictly i.v.; several subsequent administrations of 2 ml/kg BW at one-hour intervals are possible, if necessary
4. administration of oxygen, haemodialysis, exchange transfusion.

SIDE EFFECTS

Which side effects can appear during the use of isoket® 0.1 % solution?
On the first use, but also when the dose is raised, a decrease in blood pressure and/or orthostatic hypotension (circulatory dysregulation on changes of position) is occasionally observed; these symptoms can be accompanied by a reflex increase in heart rate, dizziness, and feelings of vertigo and weakness. The infusion has to be stopped, when there is a major fall in blood pressure. 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.
Headache („nitrate headache") commonly occurs when the treatment begins; experience has shown it to subside in most cases as the use is continued.
Nausea, vomiting, temporary skin reddening (flushing), and allergic skin reactions are rare.
Infrequently a marked decrease in blood pressure may lead to an exacerbation of the anginal symptoms.
States of collapse, sometimes associated with cardiac arrhythmias accompanied by a reduction of heart rate (bradycardic arrhythmias) and sudden loss of consciousness (syncopes), are seldom seen.
Exfoliative dermatitis (inflammatory skin disease) may occur in isolated cases.
The development of tolerance (decrease in efficacy) as well as cross-tolerance towards other nitro substances (decrease in effect in case of a prior therapy with another nitrate drug) have been described. For a decrease in, or loss of, effect to be prevented, continuously high dosages should be avoided.
Note
Due to a relative redistribution of blood flow into hypoventilated alveolar areas of the lungs, the use of isoket® 0.1 % solution can result in temporary reductions of the content of oxygen in the arterial blood (hypoxaemia) and may lower the supply to the heart (ischaemia) in patients suffering from disturbed blood flow in the coronary vessels (coronary heart disease).
Please inform your doctor or pharmacist of any side effects not listed in this package insert. Which countermeasures have to be taken in case of side-effects?
If you observe any of the above-mentioned side-effects, inform your doctor so he can evaluate their seriousness and decide on any additional measures that may be necessary.
isoket® 0.1 % solution must not be taken again once first signs of allergy start.

NOTES AND SHELF-LIFE INFORMATION

The expiry date of this pack is printed on the container and the folding box. Do not use the pack after this date!
Use the ready-made solution within 24 hours of preparation.
The solution is sterile, but has not been manufactured using preservative substances. The pierce-cap bottle is not intended for multiple withdrawals. isoket® 0.1 % solution should be used aseptically immediately after the container has been opened.

DATE OF INFORMATION

May 1999
Store drugs out of the reach of children.

This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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