

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it.

## Prescribing Information

### ISOKET 0.1%

ampoules

bottles

**DRUGS-ABOUT.COM**

### 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

#### SUBSTANCE OR INDICATION GROUP OR MODE OF ACTION

Drug to treat blood flow disorders of the coronary vessels

#### 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.

#### CONTRAINDICATIONS

. - 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®, Cialis 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® or Cialis even if acute angina occurs.

### **Special warnings and special precautions for use**

Isoket should be used with caution in patients who are suffering from hypothyroidism, malnutrition, severe liver or renal disease or hypothermia.

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 intra-cranial 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.

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 polytetrafluoro-ethylene (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 medicaments and other forms of interaction**

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® or Cialis. (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.

### **Pregnancy & 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.

### **Adverse effects**

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 dis-turbed blood flow in the coronary vessels (coronary heart disease).

isoket® 0.1 % solution must not be taken again once first signs of allergy start.

## **DOSAGE, MODE AND DURATION OF ADMINISTRATION**

The dosage must always be adapted to the individual clinical and haemodynamic pre-treatment 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.

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

*Dosage table for diluted solutions:*

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

### *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.

## **Symptoms of overdose**

Depending on the extent of overdose, 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 overdose, 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.

## Notes and shelf-life information

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.

## PRESENTATION AND SIZES

Infusion solution

Packs of 10 ampoules (N2), 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

## Manufacturer

Schwarz Pharma AG, D-40789, Monheim, Germany

## Importer

Pharma Medis Ltd., Holon

02.2004

**DRUGS-ABOUT.COM**

9.2.99 8.1.04	תאריך עדכון אחרון של העלון לרופא
23.5.99, 02.04	תאריך אישור משרד-הבריאות
Code 48106	תאריך קוד יצרן
	תאריך עלון קודם

V1 – עלון מאושר ע"י משה"ב – 23.5.99  
 V2 – גירסא לא מאושרת, מיועדת להגשה למשה"ב  
 V4 – גירסת **International patient leaflet** – להגשה לאישור משה"ב  
 (8.1.04)

V5 – עלון מאושר ע"י משה"ב – פברואר 2004