Isosorbide Dinitrate

Isoket®

PRODUCT DESCRIPTION
Each tablet of Isosorbide Dinitrate (Isoket®) 5 mg contains 5mg of Isosorbide Dinitrate.
Each tablet of Isosorbide Dinitrate (Isoket®) 10mg contains 10mg of Isosorbide Dinitrate.
Each sustained-release tablet of Isosorbide Dinitrate (Isoket®) 20mg contains 20mg of Isosorbide Dinitrate.
Each sustained-release tablet of Isosorbide Dinitrate (Isoket®) 40mg contains 40mg of Isosorbide Dinitrate.
Each ampoule of Isosorbide Dinitrate (Isoket®) 1mg/mL solution for infusion contains 10mg of isosorbide Dinitrate in 10mL sterile isotonic sodium chloride solution.

PHARMACOLOGIC PROPERTIES
Mechanism of Action
Like all organic nitrates, isosorbide dinitrate 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.

Pharmacodynamic effects
Isosorbide dinitrate causes a relaxation of vascular smooth muscle thereby inducing a vasodilatation.
Both peripheral arteries and veins are relaxed by isosorbide dinitrate. 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, isosorbide dinitrate 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. Nitrates-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 compliant 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 haemodynamics 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 dilation) 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, isosorbide dinitrate may be useful in selected patients who suffered a myocardial infarction.
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 muscles is reported as well.

Pharmacokinetics
Absorption
Isosorbide dinitrate is rapidly absorbed through the oral mucosa. Onset of activity 1 - 2 (- 5) min, maximal plasma levels occur within 6 - 10 (- 15) min. Gastrointestinal absorption is slower. Onset of activity 15 – 30 min, maximal plasma levels occur within 15 min up to 1-2 hours. The first pass effect is higher when given orally.
Metabolism and Elimination
Isosorbide dinitrate is metabolized to isosorbide 2-mononitrate and isosorbide 5-mononitrate having a half-life of 1.5 to 2 and 4 to 6 h, respectively. Both metabolites are pharmacologically active.
Isosorbide Dinitrate (Isoket®) 5mg and 10mg tablet:
The absolute bioavailability of the unchanged active substance is 20 – 30 % after oral use, 60 % after sublingual use. However, the resulting metabolites isosorbide 2-mononitrate and isosorbide 5-mononitrate are haemodynamically effective, analogous to isosorbide dinitrate.
Isosorbide Dinitrate (Isoket®) 20mg and 40mg sustained-release tablet:
The relative bioavailability of isosorbide dinitrate in comparison to the non-sustained-release tablet is more than 80 % after oral use.
Isosorbide Dinitrate (Isoket®) 1mg/mL solution for infusion:
The half-life of intravenously infused isosorbide dinitrate amounts to 10 min. Isosorbide dinitrate is metabolized to isosorbide 2-mononitrate and isosorbide 5-mononitrate having a half-life of 1.5 to 2 and 4 to 6 h, respectively. Both metabolites are pharmacologically active.
The bioavailability of isosorbide dinitrate solution is defined as 100 %, as for all intravenously administered drugs.

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 isosorbide dinitrate 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 isosorbide dinitrate was administered in doses as high as 480 and 90 mg/kg b.w. per day respectively.
Reproduction studies:
There is no evidence from animal studies suggesting a teratogenic effect of isosorbide dinitrate.
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.
INDICATIONS
Isosorbide Dinitrate (Isoket®) 5mg and 10mg - sublingual use:
• Treatment of acute angina pectoris
• Prophylaxis of acute angina pectoris
• Acute myocardial infarction
• Acute left ventricular failure
Isosorbide Dinitrate (Isoket®) 5mg and 10mg tablet and 20mg and 40mg sustained-release tablet - oral use:
• Long-term treatment of coronary artery disease
• Long-term treatment and prevention of angina pectoris (even after treated myocardial infarction)
• Long-term treatment of severe chronic heart failure in combination with cardiac glycosides, diuretics, ACE-inhibitors or arterial vasodilators
• Pulmonary hypertension

Isosorbide Dinitrate (Isoket®) 1mg/mL Solution for Infusion – intravenous or intracoronary use:
• Severe angina pectoris (e.g. unstable or vasospastic angina)
• Acute myocardial infarction
• Acute left ventricular failure
• To facilitate or prolong revascularization procedures and to prevent or relieve coronary spasm during percutaneous transluminal coronary angioplasty

DOSAGE AND ADMINISTRATION
Unless otherwise prescribed:
Isosorbide Dinitrate (Isoket®) 5mg tablet
Oral use:
1 tablet 3 to 4 times daily without chewing and with a sufficient amount of fluid for the initiation of therapy and for long-term low dose therapy with Isosorbide Dinitrate
Sublingual use:
1 tablet sublingual or buccal for treatment of acute angina pectoris or before physical or mental stress, which is expected to cause angina pectoris

The dose given after acute myocardial infarction or acute left ventricular failure must be assessed by the treating physician

Isosorbide Dinitrate (Isoket®) 10mg tablet
Oral use:
1 tablet 2 to 4 times daily without chewing and with a sufficient amount of fluid for the initiation of therapy and for long-term low dose therapy with Isosorbide Dinitrate
Sublingual use:
1/2 tablet sublingual or buccal for treatment of acute angina pectoris or before physical or mental stress, which is expected to cause angina pectoris

The dose given after acute myocardial infarction or acute left ventricular failure must be assessed by the treating physician

Isosorbide Dinitrate (Isoket®) sustained-release 20mg tablet
Oral use:
1 tablet 2 times daily without chewing and with a sufficient amount of fluid; second/subsequent dose should be given 6 to 8 hours after the first dose

For patients with higher nitrate requirement the dose may be increased to 1 tablet 3 times daily; last dose should be taken around 6 p.m.

Isosorbide Dinitrate (Isoket®) sustained-release 40 mg tablet
Oral use:
1 tablet once without chewing and with a sufficient amount of fluid; second/subsequent dose should be given 6 to 8 hours after the first dose

For patients with higher nitrate requirement the dose may be increased to 1 tablet 2 times daily; second/subsequent dose should be given 6 to 8 hours after the first dose,

Isosorbide Dinitrate (Isoket®) 1mg/mL Solution for Infusion
The posology must be adjusted to suit the patient’s needs and the response of the clinical and haemodynamic variables must be monitored.
Intravenous:
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.
Intracoronary:
The usual dose is 1 mg given as a bolus injection prior to balloon inflation. Further doses may be given not exceeding 5 mg within a 30 minute period.

Children
There are no relevant data available.
Elderly
No dose adjustment is necessary.
Renal and Hepatic impairment
Isosorbide dinitrate (Isoket®) should be used with caution in patients with severely impaired renal or hepatic function.

CONTRAINDICATIONS
Isosorbide Dinitrate (Isoket®) 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, shock
• aortic and/or mitral valve stenosis
• severe hypotension (systolic blood pressure less than 90mmHg)
• head trauma and cerebral haemorrhage
• diseases associated with an increased intracranial pressure,
• marked anaemia
• hypovolaemia
• closed angle glaucoma
• during nitrate therapy, phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil) must not be used (see Drug Interactions).

WARNINGS AND PRECAUTIONS
Isosorbide dinitrate (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.

Hypotension
This product may give rise to symptoms of postural hypotension and syncope in some patients. There have been reports of significant drop in blood pressure (especially in a standing position) and in patients predisposed to such drug action. Therefore caution is advised in patients with disturbances of circulatory regulation, orthostatic hypotension, hypotension of other origin (e.g. treated with diuretics) and/or with low systolic blood pressure.

Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina (see Adverse Effects).

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.

Hypoxia
During treatment with isosorbide dinitrate (Isoket®), 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. Patients who take isosorbide dinitrate (Isoket®) for the first time are advised to do so in a sitting position.

These medicinal products contain small amounts of ethanol (alcohol), less than 100mg per dose.

Tablets and sustained-release tablet
Due to the presence of lactose in tablets and prolonged released tablets, patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Solution for infusion
Blood pressure and pulse rate should always be monitored and the dose adjusted according to the patient’s response. As this medicinal product contains sodium, it should be taken into consideration by patients on a controlled sodium diet.

Effects on ability to drive and use machines
Dizziness, tiredness or headaches may occur. The patient should therefore be advised that if affected, they should not drive or operate machinery. This effect may be increased by alcohol.

DRUG INTERACTIONS
Phosphodiesterase inhibitors
Phosphodiesterase inhibitors potentiate the anti-hypertensive effect of nitrates and other nitric oxide (NO) donors that can lead to severe refractory hypotension. Therefore the administration of sildenafil, tadalafil or vardenafil is contraindicated during treatment with isosorbide dinitrate (Isoket®) (see Contraindications). The patient must be informed of this potential life-threatening interaction.

If phosphodiesterase inhibitors have been administered, the use of isosorbide dinitrate (Isoket®) is contraindicated within 24 hours of taking phosphodiesterase inhibitors.

Blood pressure lowering drugs
Isosorbide dinitrate (Isoket®) may increase the effect of medicinal products lowering blood pressure. The concomitant administration of antihypertensives, vasodilators, β-blockers, calcium antagonists, tricyclic antidepressants, antipsychotics and alcohol may potentiate the hypotensive effect of isosorbide dinitrate (Isoket®). Symptoms of circulatory collapse can arise in patients already taking ACE inhibitors.

Dihydroergotamine
Isosorbide dinitrate (Isoket®) used in combination with dihydroergotamine may lead to higher blood concentration of dihydroergotamine and thus increase the effect of this medicinal product.

PREGNANCY AND LACTATION
Fertility
There are no relevant data available.

Pregnancy
Isosorbide dinitrate should only be used in pregnancy if, in the opinion of the physician, the possible benefits of treatment outweigh the possible hazards.

No data have been reported which would indicate the possibility of adverse effects resulting from the use of isosorbide dinitrate in pregnancy. Safety in pregnancy, however, has not been established.

Lactation
Isosorbide dinitrate should only be used in during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the possible hazards.

ADVERSE EFFECTS
Post Marketing Data
Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon $\geq 1/1000$ to $<1/100$
Rare $\geq 1/10000$ to $<1/1000$
Very rare $<1/10000$
Not known (cannot be estimated from the available data).

**Nervous system disorders:**
- **Very common:** headache (the incidence of headache diminishes gradually with time and continued use)
- **Common:** dizziness, light headedness in upright position, drowsiness

**Cardiac disorders:**
- **Common:** reflex tachycardia
- **Uncommon:** severe hypotension may lead to exacerbation of angina pectoris symptoms (see Warnings and Precautions)

**Vascular disorders:**
- **Common:** hypotension on standing
- **Uncommon:** flushing, collapse (sometimes accompanied by bradycardia and syncope) (see Warnings and Precautions)
Severe hypotensive responses have been reported for organic nitrates including nausea, vomiting, restlessness, pallor, and excessive perspiration.

**Respiratory, thoracic and mediastinal disorders**
- **Not known:** hypoxia (see Section Warnings and Precautions)

**Gastrointestinal disorders:**
- **Uncommon:** nausea, vomiting
- **Very rare:** heartburn

**Skin and subcutaneous tissue disorders:**
- **Uncommon:** allergic skin reaction (e.g. rash), angioedema, Stevens-Johnson syndrome
- **Very rare:** exfoliative dermatitis

**General disorders and administration site conditions:**
- **Common:** feeling of weakness

### OVERDOSAGE AND TREATMENT

**Symptoms and signs**
The severity of overdose symptoms depends on the size of the dose. The principal symptoms of overdose are headache, tachycardia and fall in blood pressure with a tendency to collapse. At very high doses the (reversible) formation of methaemoglobin, cyanosis and tachypnoea is additionally possible; intracranial pressure may be increased and this might lead to cerebral symptoms. Other symptoms which may be result of an overdose include: persistent dizziness, sudden loss of consciousness, disorders of heart conductivity, bradycardia, vision disorders, nausea, vomiting, diarrhoea, flushing, dyspnoea, apnoea, paleness, sweating, light-headedness on standing, weakness and weak pulse.

**Treatment**
Therapeutic counter-measures are primarily aimed at raising the blood pressure again, and in milder cases placing the patient in a horizontal position with the legs raised generally results in resolution of the symptoms.
As there is no specific antidote, in cases of severe poisoning patient should be taken immediately to hospital and general guidelines for the treatment of poisoning and shock should be used.
In case of methaemoglobinemia patient may be, if necessary, treated with reduction therapy of choice with vitamin C, methylene-blue, or toluidine-blue. Haemodialysis may be performed if necessary.

### INCOMPATIBILITITES

**Solution for infusion and injection**
Isosorbide dinitrate intravenous. 0,1mg/ml is compatible with all infusion solutions usually administered in hospital such as physiological sodium chloride solution, 5 - 30% glucose solution, Ringer's solution, solutions containing albumin. Isosorbide dinitrate intravenous. 0,1mg/ml does not contain propylenglycol, ethanol, and potassium ions. Incompatibilities have not been reported.

**USE AND HANDLING**

**Solution for infusion and injection**
Materials made of polyethylene (PE), polypropylene (PP) or polytetrafluorethylene (PTFE) have proven to be suitable for infusing isosorbide dinitrate intravenous. 1mg/ml. However, infusion material made of polyyvinyl chloride (PVC) or polyurethane (PU) has been shown to induce a loss of the active substance due to adsorption. If these materials are used the dose must be adjusted to suit patient's needs.
Due to the fact that isosorbide dinitrate intravenous. 0,1mg/ml are supersaturated with the active substance, a deposit of crystals may be observed when isosorbide dinitrate intravenous. 0,1mg/ml are used in undiluted form. If crystals are observed, it is safer not to use the solution, although under normal conditions, efficacy is not impaired.

**Intravenous:**
Isosorbide dinitrate intravenous. 0,1mg/ml may be administered either diluted in a continuous intravenous infusion by means of an automatic infusion device, or undiluted using a syringe pump, 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) must be completed using invasive haemodynamic measurements. Isosorbide dinitrate intravenous. 0,1mg/ml must be diluted under aseptic conditions immediately after opening. The diluted solution is to be used immediately.
Concentration 0.1 mg/ml (0.01 %);
50 ml isosorbide dinitrate intravenous. 0.1mg/ml (5 ampoules of 10 ml each or 1 bottle of 50 ml or ½ bottle of 100 ml) made up to 500 ml of ready-for-use solution
Concentration 0.2 mg/ml (0.02 %):
100 ml isosorbide dinitrate intravenous. 0.1mg/ml (10 ampoules of 10 ml or 2 bottles of 50 ml each, or 1 bottle of 100 ml, respectively) made up to 500 ml of ready-for-use solution
Isosorbide dinitrate intravenous. 0.1mg/ml can also be used in undiluted form.
1 ml of this solution contains 1 mg isosorbide dinitrate.

Intracoronary:
Isosorbide dinitrate intravenous. 0.1mg/ml can be injected directly by this route according to the proposed schedule

STORAGE CONDITIONS
Isosorbide Dinitrate (Isoket®) 5mg tablet, 10mg tablet, 20mg sustained-release tablet and 40mg sustained-release tablet: Store at temperatures not exceeding 30°C.

Isosorbide Dinitrate (Isoket®) 1mg/mL Solution for Infusion: Store at temperatures not exceeding 25°C.

AVAILABILITY
*Isosorbide Dinitrate (Isoket®) 5mg tablet: 10 tablets per blister (box of 50’s)
*Isosorbide Dinitrate (Isoket®) 10mg tablet: 10 tablets per blister (box of 50’s)
**Isosorbide Dinitrate (Isoket®) 20mg sustained-release tablet: 10 tablets per blister (box of 50’s)
**Isosorbide Dinitrate (Isoket®) 40mg sustained-release tablet: 10 tablets per blister (box of 50’s)
*Isosorbide Dinitrate (Isoket®) 1mg/mL solution for infusion: 10mL ampoules (Box of 10’s)

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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NCDS. Isosorbide Dinitrate.
Version #: 2       Revision Date: 12 December 2011

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Packed by:
Zhuhai Schwarz Pharma Co. Ltd.
Zhuhai, China

* Manufactured by:
  Schwarz Pharma AG
  Monheim, Germany

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  Sifa Ltd.
  Claire, Ireland
  For: Schwarz Pharma AG
  Monheim, Germany