Name of Medicinal Product
Isoket® Spray
Isosorbide dinitrate, 1.25mg/dose, oromucosal spray

Qualitative and Quantitative Composition
Isosorbide dinitrate, 1.25 mg/ dose, oromucosal spray, 15 ml
Each isosorbide dinitrate oromucosal spray bottle contains 375 mg isosorbide dinitrate per 15 ml. One dose (0.05 ml) of isosorbide dinitrate oromucosal spray contains 1.25mg of isosorbide dinitrate.

Excipients
Alcohol 85%v/v, Polyethylene Glycol

PHARMACEUTICAL FORM
The solution is a clear colourless liquid.

Indications
For the treatment of:
• prophylaxis and treatment of angina pectoris
• acute myocardial infarction
• acute left ventricular failure

Dosage and Administration

Route of Administration
For oromucosal use.

Adults
The dosage should be adjusted to suit the patient's needs.
1–3 squirts at about 30 seconds intervals are sprayed into the mouth during an attack or shortly before physical and/or mental stress that may trigger an attack.
The single dose of 3 squirts applied to treat an acute angina attack should only be exceeded upon the physician’s express advice.
In acute myocardial infarction or acute heart failure one starts with 1–3 squirts. In the event of non-response within 5 minutes, an additional squirt may be given. In case there is no improvement within the subsequent 10 minutes, spray application may be repeated under close blood pressure monitoring.

Children
The safety and efficacy of isosorbide dinitrate has yet to be established in children.
Elderly

There is no evidence to suggest that dose adjustment in elderly patients is needed.

Renal impairment

There are no relevant data available.

Hepatic impairment

There are no relevant data available.

Contraindications

Isosorbide dinitrate oromucosal spray is contraindicated in:

- hypersensitivity to the active substance, to other nitro compounds or to any of the excipients
- acute circulatory failure (collapse, shock)
- cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures)
- hyperthrophic obstructive cardiomyopathy (HOCM)
- constrictive pericarditis
- pericardial effusion
- cardiac tamponade
- severe hypotension (systolic blood pressure less than 90mmHg)
- severe hypovolaemia
- severe anaemia
- during nitrate therapy, phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil) must not be used (see Sections: Warnings and Precautions; Interactions).

Warnings and Precautions

Use with particular caution and under medical supervision

Isosorbide dinitrate should be used only with particular caution and under medical supervision in:

- low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure). Reducing systolic blood-pressure below 90 mmHg must be avoided.
- aortic and/or mitral stenosis
- diseases associated with an increased intracranial pressure (however, until now, a further increase of intracranial pressure has only been observed following the administration of glyceryl trinitrate i.v. in high dosages).
- Tendency to circulatory failure
- Orthostatic dysfunction

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 should be avoided.

Maintenance and acute therapy
Patients who undergo a maintenance treatment or acute therapy with isosorbide dinitrate oromucosal spray should be informed that they 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).

**Hypoxia**
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.

**Alcohol content**
Isosorbide dinitrate oromucosal spray contains small amounts of ethanol (alcohol), less than 100 mg per dose.

**Excessive skin contact**
In case of accidental extensive skin contact with the content of the isosorbide dinitrate spray bottle the contaminated skin should be cleaned immediately. Otherwise the solution could be absorbed from the skin and this might cause severe undesirable effects (see Section Adverse Reactions).

**INTERACTIONS**

**Blood pressure lowering agents**
The concomitant use of drugs with blood pressure lowering properties, e.g. vasodilators, beta-blockers, diuretics, calcium channel antagonists, ACE inhibitors, neuroleptics or tricyclic antidepressants and alcohol may potentiate the antihypertensive effect of isosorbide dinitrate.

**Phosphodiesterase inhibitors**
A blood pressure lowering effect of isosorbide dinitrate will be increased, if used together with phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil) (see Sections: Warnings and Precautions, Contraindications). This might lead to life-threatening cardiovascular complications. Patients who are on isosorbide dinitrate therapy therefore must not use phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil). Patients who have recently taken phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil) therefore must not receive acute isosorbide dinitrate therapy.

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

**Sapropterine**
Sapropterine contains the API Tetrahydrobiopterine (BH4). BH4 is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterine-containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glycercyl trinitrate (GTN), isosorbide dinitrate (ISDN), isosorbide mononitrate and others).
Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

Isosorbide dinitrate should be used during pregnancy only if clearly needed and solely under the direction and continuous supervision of a physician, as animal studies are not always predictive of human response.

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.

Lactation

Isosorbide dinitrate is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

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 methemoglobinemia in infants. The extent of excretion of isosorbide dinitrate and its metabolites in human breast milk has not been determined.

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

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

Clinical Trial Data and 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 ≥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 (the incidence of headache diminishes gradually with time and continued use)
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), flushing
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),
Very rare: angioedema, Stevens - Johnson syndrome
Not known: exfoliative dermatitis

General disorders and administration site conditions:
Common: asthenia, application site burning of the tongue

Overdosage
In mice, significant lethality (LD50) at single intravenous doses of 33.4 mg/kg were observed.

Symptoms and signs
The following symptoms may occur:
- fall in blood pressure ≤ 90 mmHg
• pallor
• sweating
• weak pulse
• tachycardia
• dizziness postural
• headache
• asthenia
• dizziness
• nausea
• vomiting
• diarrhoea

Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During isosorbide mononitrate 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 be increased. This might lead to cerebral symptoms.

**Treatment**

*General procedure*
- stop intake/use/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 (intravenous 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
  - hemodialysis (if necessary)
- resuscitation measures

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

**Clinical Pharmacology**

**Pharmacodynamics**

**Pharmacotherapeutic group**

Vasodilators used in cardiac diseases; organic nitrates
**ATC Code:**
C01DA08

**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. Nitrate-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 dilatation) 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**

Pharmacokinetic parameters of isosorbide dinitrate as oromucosal spray demonstrated superiority over other formulations of this medicinal product.
Absorption

After sprayed into the oral cavity, the active drug, isosorbide dinitrate is rapidly adsorbed by the mucosa. Pharmacological effects can be observed within 1-3 min after administration of isosorbide dinitrate spray with maximum plasma levels within 3-6 min.

Distribution

Following oral use isosorbide dinitrate is subject to a marked first pass effect leading to a bioavailability of about 15-30 %.

Metabolism

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 hours, respectively. Both metabolites are pharmaco-logically active.

Elimination

Elimination takes place with a half-life of 30-60 minutes. Within a period of 90-120 minutes plasma concentration drops to base-line values again.

Isosorbide dinitrate spray is exclusively designed for application into the oral cavity. By circumventing the gastro-intestinal tract, the active substance thus immediately reaches the systemic circulation and consequently circumvents rapid metabolisation in the liver. In this way a clearly marked higher bioavailability of 60-100 % is reached.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

Acute toxicity:

Investigations on the acute toxicity have not revealed any particular risks.

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 \textit{in vitro} and \textit{in vivo}.

\textit{Carcinogenicity:}
A long-term study in rats did not provide any evidence for carcinogenicity.

**PHARMACEUTICAL INFORMATION**

**Shelf-Life**

The shelf life is indicated on the packaging.

**Storage**

Store below 30°C

**Nature and Contents of Container**

Each pump spray contains 300 actuations

Brown transparent glass bottle with manging cap, dosing pump, white plastic spray head, and red protective cap.

Content: clear, colourless solution

**Incompatibilities**

There are no relevant data available.

**Use and Handling**

The solution is to be sprayed into the mouth; it should not be inhaled. Do not spray on a naked flame or incandescent materials; do not use when smoking.

Prior to the first application of the spray, the spray valve must be operated several times (light pumping), until an even mist escapes. Now the spray is ready for use.

If the spray has not been used for more than one day, the first squirt has to be released into the air in order to ensure complete subsequent dosing.

During application, the bottle is to be held in vertical position with the pump to upwards. The solution is sprayed into the mouth as follows:

1. Inhale deeply
2. Hold your breath
3. By pressing the dosing pump, spray the drug into the mouth (this may induce a light burning sensation on the tongue)
4. Then close your mouth and continue breathing solely through the nose for about 30 seconds.

Note:
The label of the spray bottle bears a mark at its lower margin. As soon as the fluid level in the bottle reaches this point, a new package of isosorbide dinitrate spray should be at hand for safety reasons. However, the open spray may further be used as long as - even on slightly tilting the spray bottle- the tip of the pump pipe is still immersed in the fluid.

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Manufactured by:
SCHWARZ PHARMA LTD
SHANNON INDUSTRIAL ESTATE
SHANNON COUNTY CLARE
IRELAND

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