Isosorbide Dinitrate
Isoket® Spray
1.25mg / dose spray

PRODUCT DESCRIPTION
Each actuation (0.05mL) of Isosorbide Dinitrate (Isoket® Spray) spray contains 1.25 mg of Isosorbide Dinitrate. The 12.7g solution (15mL) contains 375mg of Isosorbide Dinitrate.

PHARMACOLOGIC PROPERTIES
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.

Mechanism of action:
Like all organic nitrates, Isosorbide Dinitrate (Isoket® Spray) spray 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.

Pharmacokinetics
After sprayed into the oral cavity, the active drug, Isosorbide Dinitrate (Isoket® Spray) spray 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. 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 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 pharmacologically active.

Bioavailability
Following oral use Isosorbide Dinitrate is subject to a marked first pass effect leading to a bioavailability of about 15-30 %. Isosorbide Dinitrate (Isoket® Spray) 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 metabolism in the liver. In this way a clearly marked higher bioavailability of 60-100 % is reached.

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 480mg / kg b.w. per day.

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
• Prophylaxis and treatment of angina pectoris
• Acute myocardial infarction
• Acute left ventricular failure

DOSEAGE AND ADMINISTRATION
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.

A 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.

**CONTRAINDICATIONS**

Isosorbide Dinitrate (Isoket® Spray) must not be used in:
- Hypersensitivity to Isosorbide Dinitrate, other nitro compounds or any of the excipients
- Acute circulatory failure (shock, collapse)
- Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures)
- Hypertrophic obstructive cardiomyopathy
- Constrictive pericarditis
- Cardiac tamponade
- Severe hypotension (systolic blood pressure less than 90 mmHg)
- During nitrate therapy, phosphodiesterase inhibitors (e.g. sildenafil) must not be used (see Drug Interactions)

**WARNINGS AND PRECAUTIONS**

Isosorbide Dinitrate (Isoket® Spray) spray 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 should be avoided.
- Aortic and/or mitral stenosis
- Orthostatic dysfunction
- Diseases associated with an increased intracranial pressure (however, until now, a further increase of intracranial pressure has only been observed following the administration of nitroglycerin i.v. in high dosages)

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.

Warning: The solution contains 85 volume % of ethanol!

Patients who undergo a maintenance treatment with Isosorbide Dinitrate (Isoket® Spray) spray should be informed that they must not use phosphodiesterase inhibitors-containing products (e.g. sildenafil). Isosorbide Dinitrate spray therapy should not be interrupted to take phosphodiesterase inhibitors-containing products (e.g. sildenafil), because the risk of inducing an attack of angina pectoris could increase by doing so (see Drug Interactions). In case of accidental extensive skin contact with the content of the Isosorbide Dinitrate (Isoket® Spray) 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 also Adverse Effects).

**DRUG INTERACTIONS**

Concurrent intake of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel antagonists, vasodilators etc. and/or alcohol may potentiate the hypotensive effect of Isosorbide Dinitrate (Isoket® Spray). This might also occur with neuroleptics and tricyclic antidepressants. A blood pressure lowering effect of Isosorbide Dinitrate spray will be increased, if used together with phosphodiesterase inhibitors (e.g. sildenafil) which is used for erectile dysfunction (see warnings and precautions).

This might lead to life-threatening cardiovascular complications. Patients who are on Isosorbide Dinitrate (Isoket® Spray) therapy therefore must not use phosphodiesterase inhibitors (e.g. sildenafil).

Reports suggest that, when administered concomitantly, Isosorbide Dinitrate spray may increase the blood level of dihydroergotamine and its hypertensive effect.

**PREGNANCY AND LACTATION**

Pregnancy Category: C

There is no evidence from animal studies suggesting teratogenic effects of Isosorbide Dinitrate.

Isosorbide Dinitrate spray should only be used during pregnancy if clearly needed and solely under the direction and continuous supervision of a physician.

It is not known whether Isosorbide Dinitrate is excreted in human milk. Because many drugs are excreted in this way, caution should be exercised when Isosorbide Dinitrate spray is administered to a nursing woman.

**ADVERSE EFFECTS**

Adverse effects frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) or very rare (<1/10,000).

During administration of Isosorbide Dinitrate spray, the following undesirable effects may be observed:

**Cardiac disorders:**
- common: reflex tachycardia
- uncommon: enhanced angina pectoris symptoms

**Gastrointestinal disorders:**
- uncommon: nausea, vomiting

**very rare:**
- heartburn

**General disorders and administration site conditions:**
- common: feeling of weakness, application site burning of the tongue

**Nervous system disorders:**
- very common: headache
- common: light headedness, dizziness, drowsiness.
Skin and subcutaneous tissue disorders:
- uncommon: allergic skin reactions (e.g. rash), flush
- very rare: angioedema, Stevens-Johnson-Syndrome
- in single cases: exfoliative dermatitis.

Vascular disorders:
- common: hypotension on standing
- uncommon: collapse (sometimes accompanied by bradycardia and syncope).

Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration.

Advice: During treatment with Isosorbide Dinitrate spray, a 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 a myocardial hypoxia.

OVERDOSAGE AND TREATMENT

Animal experience:
In mice, significant lethality (LD$_{50}$) at single intravenous doses of 33.4 mg/kg was observed.

Human experience:
Symptoms:
- Fall of blood pressure $\leq$ 90 mmHg
- Paleness
- Sweating
- Weak pulse
- Tachycardia
- Light-headedness on standing
- Headache
- Weakness
- Dizziness
- Nausea
- Vomiting
- Diarrhoea

Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During Isosorbide Dinitrate 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 delivery of the drug
- General procedures in the event of nitrate-related hypotension:
  - Patients should be kept horizontal with the head lowered and legs raised
  - Supply oxygen
  - Expand plasma volume
  - Specific shock treatment (admit patient to intensive care unit!)

Special procedure:
- Raising the blood pressure if the blood pressure is very low
- Additional administration of norepinephrine HCl or other vasoconstrictors. The use of epinephrine in this setting is likely to do more harm than good.
- Treatment of methaemoglobinemia
  - Reduction therapy of choice with vitamin C, methylene blue, or toluidine blue
  - Administer oxygen (if necessary)
  - Initiate artificial ventilation
  - Haemodialysis (if necessary)
- Resuscitation measures
  In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Store in the original package.

INSTRUCTIONS FOR USE/ HANDLING
The solution is to be sprayed into the mouth; it should not be inhaled!
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:
- Inhale deeply
  - Hold your breath
  - By pressing the dosing pump, spray the drug into the mouth (this may induce a light burning sensation on the tongue)
Then close your mouth and continue breathing solely through the nose for about 30 seconds.

Note:
The label of the spray bottle bears an error 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. At any rate, 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.

AVAILABILITY
One bottle contains not less than 300 squirts of 1.25 mg Isosorbide Dinitrate (pack size: 1 spray).

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

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GlaxoSmithKline Philippines Inc
2266 Chino Roces Avenue
1231 City of Makati
Tel. 892 0761

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