

# New Zealand Datasheet

## Name of Medicine

ISMO<sup>®</sup> 20

Isosorbide-5-nitrate 20 mg tablet  
Organic nitrate, vasodilating medicine

## Presentation

Each tablet contains isosorbide-5-nitrate, 20 mg

ISMO 20 tablets for oral administration are white, round tablets, with bilateral scorelines at right angles to each other engraved with BM 3B.

## Uses

### Actions

The following main pharmacological properties characterise isosorbide-5-nitrate:

- direct relaxation of vascular smooth muscle
- dilation of capacity vessels ("venous pooling")
- decrease in blood return to the heart
- reduction of central venous pressure
- reduction of ventricular wall tension
- dilation of the large arteries leading to a reduction in systemic and pulmonary vascular resistance
- increase in compliance of the large arteries ("windkessel" effect)

Reduction of the ventricular wall tension leads to reduced workload of the myocardium and in turn to decreased oxygen consumption. Additionally, the extravascular component of coronary vessel resistance is reduced, thereby improving the blood flow in areas of the myocardium in which wall tension is the limiting factor for the blood flow; i.e. the subendocardial layers and, in stenosing coronary arteriosclerosis, the poststenotic myocardial areas.

The overall myocardial blood flow may be reduced as a result of decreased oxygen demand.

The regional myocardial blood flow on the other hand is directly improved, independently of the systemic effects of organic nitrates.

The efficacy of nitrates in coronary spasms is due to their relaxing effect on the large coronary vessels.

The observed increase in compliance of the large arteries may contribute to the antianginal effect. The effect of nitrates on resistance vessels has also been demonstrated at the high doses.

As a result of the above mentioned effects, a decrease in systolic blood pressure may be observed while the diastolic blood pressure remains essentially unchanged. The combination of these effects improves the oxygen balance of the heart.

At the molecular level nitrates act via the formation of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP), which is the mediator of relaxation.

## **Pharmacokinetics**

### **Absorption and Distribution**

*In vitro* medicine release from isosorbide-5-nitrate 20 mg tablets occurs within 5 minutes.

Absorption takes place in the small intestine and is almost complete. A first-pass effect is absent.

A maximum serum level of about 480 mg/mL is reached after approximately 1 hour. The onset of action can be seen after approximately 20 minutes.

The distribution volume is 0.62 L/kg.

### **Metabolism and Elimination**

Isosorbide-5-nitrate is mainly dinitrated in the liver to isosorbide. All its metabolites are pharmacologically inactive. Up to 20% of isosorbide-5-nitrate is renally excreted as glucuronide and 30% as isosorbide. The half-life is approximately 5 h. The dose does not have to be adjusted in the presence of renal failure or liver cirrhosis.

### **Bioavailability**

The absolute bioavailability of isosorbide-5-nitrate from 20 mg tablets is approximately 100%.

### **Indications**

- long-term treatment of coronary heart disease (CHD)
- prophylaxis of angina pectoris
- adjunctive therapy in chronic congestive heart failure which is concomitantly being treated with glycosides, diuretics, ACE inhibitors or arterial vasodilating medicines
- treatment of pulmonary hypertension

### **Dosage and Administration**

The standard dosage of ISMO 20 is one tablet twice daily, which might be increased to 1 tablet three times daily if the individual requirement is higher.

In order to prevent or minimise nitrate headache it is recommended that the dose is reduced to half a tablet twice daily for the first 2 days then increased to one tablet twice daily for the next 2 days.

Afterwards the treatment can be maintained at this level or increased, if necessary, to 1 tablet three times daily.

### **Duration of Treatment**

Treatment with ISMO 20 tablets is normally a long-term therapy.

### **Method of Administration**

The tablets should be swallowed unchewed with plenty of fluid. If required, 1 tablet can be taken shortly before going to sleep.

ISMO 20 tablets have score-lines and can thus be easily broken into 2 or 4 parts to enable dose adjustment.

### **Contraindications**

Isosorbide-5-nitrate must not be used in:

- marked hypotension (BP  $\leq$  90 mm Hg systolic)

- circulatory collapse, shock
- cardiogenic shock unless sufficient end-diastolic pressure is maintained e.g. by the use of positive inotropic medicines or intra-aortic balloon counterpulsation
- myocardial infarction with low ventricular filling pressure
- hypersensitivity to organic nitrates

Concomitant administration of ISMO 20 and phosphodiesterase 5 inhibitors including sildenafil (Viagra<sup>®</sup>) is contraindicated (see Warnings and Precautions and Interactions).

## **Warnings and Precautions**

ISMO 20 tablets should not be used after the expiry date specified on the pack.

In acute myocardial infarction isosorbide-5-nitrate may only be given under strict medical supervision; reduction of the systolic blood pressure to below 90 mm Hg should be avoided.

Isosorbide-5-nitrate should be used with caution in the presence of hypertrophic obstructive cardiomyopathy, constrictive pericarditis, cardiac tamponade, aortic and/or mitral stenosis, orthostatic disorders of circulatory regulation and increased intracranial pressure.

Isosorbide-5-nitrate is not suitable for the treatment of acute angina pectoris attacks. Safety, effectiveness and dosage of isosorbide-5-nitrate in children have not been established.

Since a rebound phenomenon cannot be excluded, therapy with isosorbide-5-nitrate should be terminated gradually rather than stopping the medicine abruptly.

The development of tolerance or cross-tolerance, i.e. a decrease in efficacy despite unchanged dosage, has been observed at constant and/or high nitrate levels. The tolerance disappears within 24 hours of discontinuing therapy.

The development of tolerance can be avoided by the use of an intermittent dosage regimen.

Because of their pharmacological action (inhibition of cGMP breakdown), phosphodiesterase 5 inhibitors including sildenafil (Viagra<sup>®</sup>) potentiate the blood pressure-lowering effect of nitrates and other nitric oxide (NO) donors, which may lead to serious and often treatment-resistant hypotension. Use of phosphodiesterase 5 inhibitors during treatment with ISMO 20 is therefore contraindicated. Patients must be informed about this potentially life-threatening interaction.

## **Use in Pregnancy and Lactation**

Animal reproduction studies have revealed no evidence of a teratogenic potential for isosorbide-5-nitrate.

Isosorbide-5-nitrate was foetotoxic at maternally toxic doses in the rat.

There are no adequate and well-controlled studies in pregnant women.

It is not known whether isosorbide-5-nitrate is excreted in human milk.

Isosorbide-5-nitrate should be used during pregnancy and lactation only if the potential benefit justifies the potential risk to the foetus or infant.

### **Effects on Ability to Drive and Use Machines**

Individually varying reactions can impair alertness (e.g. a patient's ability to drive vehicles or to operate machinery). This applies particularly when beginning treatment, switching from another medicine or starting a new co-medication and in conjunction with alcohol.

### **Adverse Effects**

#### **Central Nervous System**

- Frequently, particularly at the start of treatment, a transient "nitrate headache" may occur which normally subsides after some days of continued treatment.
- Occasionally, particularly when first used, slight states of dizziness or feeling of weakness may occur which normally improve during treatment.

#### **Cardiovascular System**

- Occasionally, especially at the beginning of treatment, postural hypotension, tachycardia or flush, which normally improve on continuation of therapy.
- Rarely collapse, in some instances accompanied by bradyarrhythmias and syncope.
- In rare cases where there is a significant drop in blood pressure the symptoms of angina pectoris may be intensified.
- Administration of isosorbide-5-nitrate may produce transient hypoxaemia as a result of redistribution of blood flow with a relative increase in perfusion of poorly ventilated areas of the lung. This may cause ischaemia in patients with coronary heart disease.

#### **Gastro-intestinal System**

- Occasionally, especially when first used, gastro-intestinal symptoms, e.g. nausea and/or vomiting may occur.

#### **Haematology**

- Formation of methaemoglobin might occur, in particular in patients with methaemoglobin reductase deficiency or in patients with diaphorase deficiency of abnormal haemoglobin structure.

#### **Skin**

- Rarely allergic skin reactions.

### **Interactions**

When isosorbide-5-nitrate is used at the same time as other medicines the following interactions must be taken into account:

- Isosorbide-5-nitrate may intensify the effect of other concomitantly administered medicines that are antihypertensive in action or have hypotension as part of their adverse effect profile (e.g. other vasodilating medicines, antihypertensives,  $\beta$ -blockers, calcium-channel blockers, ACE inhibitors, diuretics, neuroleptic medicines, tricyclic antidepressants, alcohol).
- Isosorbide-5-nitrate can enhance the hypertensive effect of dihydroergotamine (i.e. increase standing systolic blood pressure) by increasing its oral bioavailability.

Phosphodiesterase 5 inhibitors including sildenafil (Viagra<sup>®</sup>) increases the blood pressure-lowering effect of acutely and chronically administered nitrates and other nitric oxide (NO) donors. Use of phosphodiesterase 5 inhibitors including sildenafil

(Viagra®) during treatment with ISMO 20 is therefore contraindicated. If sildenafil has nevertheless been taken, use of ISMO 20 within 24 hours after taking sildenafil (Viagra®) is contraindicated.

## **Overdosage**

### **Symptoms**

The primary symptoms of intoxication are headache, a fall in blood pressure with orthostatic hypotension and reflex tachycardia.

High doses may cause methaemoglobinemia with cyanosis, dyspnoea and tachypnea, due to the formation of nitrite ions.

Very high doses of isosorbide-5-nitrate may lead to increased intracranial pressure with cerebral symptoms.

### **Treatment**

Therapeutic measures should aim at the normalization of blood pressure, which may be achieved in mild cases by keeping the patient recumbent in the shock position.

In the case of severe intoxication the general guidelines for treatment of poisoning and shock should be followed. Volume substitution may be necessary in the case of severe hypotension. Sympathomimetic medicines (e.g. noradrenaline, dopamine) may be used in exceptional cases; adrenaline is ineffective in reversing the severe hypotensive events associated with isosorbide-5-nitrate overdosage and should therefore not be used.

If methaemoglobinemia is present, the following antidotes are recommended, depending on the severity of intoxication:

- Vitamin C, 1 g orally or i.v. as the sodium salt
- Methylene blue (i.v. only): up to 50 mL of a 1% methylene blue solution
- Toluidine blue (i.v. only): initially 2 - 4 mg/kg body weight, repeated hourly administrations of 2mg/kg body weight, if necessary

Oxygen should be administered, if necessary, as well as haemodialysis or exchange transfusion.

## **Pharmaceutical Precautions**

Do not use after the expiry date shown on the pack.

Store below 25°C.

## **Medicine Classification**

Prescription Medicine

## **Package Quantities**

ISMO 20 is supplied in blister packs of 100.

## **Further Information**

### **Inactive Ingredients**

Lactose (anhydrous), colloidal silicon dioxide, magnesium stearate.

### **Toxicology**

#### ***Acute toxicity***

Mouse, female LD50 > 500 mg/kg ip.

|             |      |                                   |
|-------------|------|-----------------------------------|
|             |      | >1000 mg/kg po                    |
| Mouse, male | LD50 | > 500 mg/kg ip.<br>>1000 mg/kg po |
| Rat, female | LD50 | > 500 mg/kg ip.<br>>1000 mg/kg po |
| Rat, male   | LD50 | > 500 mg/kg ip.<br>>1000 mg/kg po |

### **Subchronic and Chronic Toxicity**

In the dog oral dosing with 191 mg/kg/day isosorbide-5-nitrate for a period of 43 days elicited a slight increase in serum methaemoglobin of about 3% above baseline. Under the same conditions, serum nitrite concentrations were below the limit of detection ( $\leq 0.02$  mg/L). Serum AP, ALAT (GPT) and ASAT (GOT) did not change.

These results may be important for patients with methaemoglobin reductase deficiency, as well as for patients with diaphorase deficiency or abnormal haemoglobin structure.

Chronic toxicity experiments in rats and dogs did not show any results that are relevant for therapy.

### **Oncogenicity and Mutagenicity**

An oncogenicity study in rats revealed no tumorigenic potential.

No indication of mutagenic potential of isosorbide-5-nitrate was found in the *in vivo* and *in vitro* experiments that have been carried out.

### **Reproduction Toxicity**

Isosorbide-5-nitrate has been shown to be associated with stillbirths and neonatal death in rats receiving 500 mg/kg/day. At 250 mg/kg/day, no adverse effects on reproduction and development were reported. In rats and rabbits receiving isosorbide-5-nitrate at up to 250 mg/kg/day, no developmental abnormalities, foetal abnormalities, or other effects upon reproductive performance were detected. In rats receiving 500 mg/kg/day, there were small but statistically significant increases in the rates of prolonged gestation, prolonged parturition, stillbirth, and neonatal death; and there were small but statistically significant decreases in birth weight, live litter size, and pup survival.

### **Name and Address**

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics  
58 Richard Pearse Drive  
Airport Oaks  
Mangere  
AUCKLAND  
Telephone: (09) 918 5100  
Fax: (09) 918 5101

### **Date of Preparation**

1 April 2009

Reference: International Data Sheet v 1.2, 27 April 2005.