New Zealand Datasheet

1 PRODUCT NAME
ISMO® 40 retard tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each prolonged-release tablet contains 40 mg isosorbide mononitrate.

Contains glucose syrup, lactose and sucrose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
ISMO 40 retard prolonged-release tablets for oral administration are white, round, coated tablets with a diameter of 6.5 – 7.0 mm and a thickness of 3.3 – 3.8 mm.

4 CLINICAL PARTICULARS
4.1 Therapeutic 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

4.2 Dose and method of administration
Unless otherwise prescribed one ISMO 40 retard is taken once daily (equivalent to 40 mg isosorbide-5-mononitrate).

For patients with greater nitrate requirements, the dose can be increased to one ISMO 40 retard tablet twice daily (equivalent to 80 mg isosorbide-5-mononitrate).

With a daily regimen of 2 x 1 prolonged-release tablets (equivalent to 80 mg isosorbide-5-mononitrate), in order for the product to reach its full effect, the second dose should be taken no later than 6 hours after the first dose.

Method and Duration of Administration:
The tablets should be taken whole (not chewed) with sufficient liquid (e.g. a glass of water).

Treatment should be initiated at a low dose and slowly titrated up to the required level.

Duration of use is decided by the treating physician. Any discontinuation of therapy with ISMO 40 retard should be gradual and not abrupt, as rebound phenomena cannot be excluded.

4.3 Contraindications
Isosorbide-5-mononitrate must not be used in cases of:
- hypersensitivity to isosorbide-5-mononitrate (the active substance), other nitrate compounds or to any of the excipients
- acute circulatory failure (shock, circulatory collapse)
- cardiogenic shock, unless a sufficiently high left-ventricular end-diastolic pressure is ensured by intra-aortic counterpulsation or positive inotropic medications
- marked hypotension (systolic blood pressure below 90 mmHg)

- severe anaemia
- severe hypovolaemia
- concomitant intake of phosphodiesterase-5 inhibitors, e.g. sildenafil, vardenafil and tadalafil as, in this case, a considerable hypotensive effect may occur.

4.4 Special warnings and precautions for use

ISMO 40 tablets should not be used after the expiry date specified on the pack.

Isosorbide-5-mononitrate may only be used with caution in the following cases:

- hypertrophic obstructive cardiomyopathy, constrictive pericarditis and pericardial tamponade
- low filling pressures, e.g. in cases of acute myocardial infarction, impaired left ventricular function (left-heart failure). Any fall in blood pressure below 90 mmHg systolic should be avoided
- aortic and/or mitral stenosis
- susceptibility to orthostatic circulatory dysregulation
- disorders associated with increased intracranial pressure (to date, any further increase in pressure has only been observed with high-dose IV administration of glyceryl trinitrate).

ISMO 40 retard is not suitable for the treatment of acute attacks of angina pectoris or acute myocardial infarction.

Due to their pharmacological effect (inhibition of cGMP degradation), phosphodiesterase-5 inhibitors - including sildenafil - potentiate the hypotensive effect of nitrates and other NO-donors, which can lead to serious and often therapy-resistant hypotension. Use of phosphodiesterase-5 inhibitors during treatment with ISMO 40 retard is therefore contraindicated. Patients must be informed about this potentially life-threatening interaction. If the phosphodiesterase-5 inhibitor has already been taken, intake of isosorbide-5-mononitrate within the next 24 hours is contraindicated.

Patients with rare hereditary problems of glucose-galactose malabsorption should not take ISMO 40 retard.

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take ISMO 40 retard.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take ISMO 40 retard.

Safety, effectiveness and dosage of isosorbide-5-nitrate in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

The following interactions of this medicinal product must be considered:

Concomitant intake of other vasodilators, antihypertensives, ACE inhibitors, beta-blockers, calcium antagonists, diuretics, neuroleptics or tricyclic antidepressants and alcohol can potentiate the antihypertensive effect of ISMO 40 retard.

This particularly applies to the concomitant use of phosphodiesterase-5 inhibitors, e.g. sildenafil, vardenafil and tadalafil (see Contraindications).

With concomitant use of dihydroergotamine, ISMO 40 retard can lead to a rise in the DHE level and thereby potentiate its hypertensive effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

For special precautionary reasons, ISMO 40 retard should only be taken during pregnancy on the express instructions of a doctor, as there are no adequate data on the use of ISMO 40 retard in pregnant women. Studies in animals have revealed no evidence of any embryofoetal damage (see section 5.3 Preclinical Safety Data).

Breast feeding

For special precautionary reasons, ISMO 40 retard should only be taken during lactation on the express instructions of a doctor, as there is insufficient experience with use in lactating women and it is not known whether ISMO 40 retard passes into breast milk. If ISMO 40 retard is taken during breast-feeding, vigilance is required for possible drug effects in the infant.

4.7 Effects on ability to drive and use machines

Even when used as directed, this medicinal product can alter responsiveness to such an extent that the ability to drive, use machines or perform dangerous tasks is impaired. This particularly applies at the start of treatment, whenever there is a dose increase or change in medication and in interaction with alcohol.

4.8 Undesirable effects

The following categories are used when stating the frequency of undesirable effects:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

Nervous system disorders

Very common: At the start of treatment, headache (“nitrate-induced headache”) may occur, which - based on experience - mostly resolves after a few days of continued intake.

Vascular disorders

Common: During initial use - but also upon dose escalation - a fall in blood pressure and/or orthostatic hypotension have been observed, which may be accompanied by a reflex increase in the pulse rate, stupor, as well as feelings of dizziness and weakness. Such symptoms generally recede during treatment.

Uncommon: a significant drop in blood pressure with exacerbation of angina pectoris symptoms has been observed, as well as states of collapse, sometimes with bradyarrhythmias and syncope.

Not known: Severe hypotensive responses including nausea, vomiting, restlessness, pallor, and hyperhidrosis have been reported for organic nitrates.

Skin and subcutaneous tissue disorders

Uncommon: transient erythema (flush) and allergic skin reactions have been observed. Very rare: exfoliative dermatitis may occur.

Blood and lymphatic system disorders
Methaemoglobin formation may occur, particularly in patients with methaemoglobin reductase deficiency or in patients with diaphorase deficiency and abnormal haemoglobin structure.

Gastrointestinal disorders Uncommon: nausea and/or vomiting have been observed.
Not known: heartburn

Tolerance development and occurrence of cross-tolerance with other nitrate compounds have been described. In order to avoid any attenuation or loss of the effect, high continuous dosing regimens should be avoided.

Note:
During administration of ISMO 40 retard, transient hypoxaemia may occur due to a relative redistribution of blood flow into hypoventilated alveolar areas, which may precipitate myocardial hypoxia in patients with coronary heart disease.

Dose escalation and/or changes in the dosing interval can lead to an attenuation or loss of the effect.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms
A fall in blood pressure with orthostatic dysregulation, reflex tachycardia and headache, asthenia, dizziness, stupor, flush, nausea, vomiting and diarrhoea may occur.

At high doses (more than 20 mg/kg body weight), methaemoglobin formation, cyanosis, dyspnoea and tachypnoea can be expected, as a result of the nitrite ion formed when ISMN is degraded.

At very high doses, increased intracranial pressure with cerebral symptoms may occur.

In cases of chronic overdose, increased methaemoglobin levels have been measured, the clinical relevance of which is debated.

Treatment
In addition to general procedures, such as gastric lavage and keeping the patient horizontal with the legs raised, vital parameters must be monitored under intensive care conditions and corrected where necessary.

In the event of marked hypotension and/or shock, volume replacement should be given; in exceptional cases, norepinephrine and/or dopamine can be infused as circulatory therapy. Administration of epinephrine and related substances is contraindicated.

For methaemoglobinaemia, the following antidotes are available, depending on the degree of severity:

1. Vitamin C:

1 g p.o. or, as sodium salt i.v.

2. Methylene blue:
   Up to 50 ml of a 1% methylene blue solution i.v.

3. Toluidine blue:
   Initially, 2 - 4 mg/kg body weight, strictly via the intravenous route; if required, administration of 2 mg/kg body weight can be repeated several times at 1-hourly intervals.

4. Oxygen therapy, haemodialysis, exchange transfusion.

The Poisons Information Centre, telephone number 0800 764 766 in New Zealand, should be contacted for advice on management.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: isosorbide-5-mononitrate, ATC code: C01D A14

Isosorbide-5-mononitrate has a directly relaxing effect on the vascular smooth muscles and leads to vasodilation.

In this respect, the post-capillary capacitance vessels and major arteries - particularly those sections of coronary arteries that are still responsive - are more affected than resistance vessels. Vasodilation in the blood stream leads to an increase in venous capacity (“pooling”), blood flow back to the heart is reduced and ventricular volumes and filling pressures are lowered (“preload” reduction).

The smaller ventricular radius and reduced systolic wall tension lower myocardial energy requirements and O_2 requirements.

The decrease in cardiac filling pressures promotes perfusion of subendocardial wall layers threatened by ischemia; regional wall movement and ejection fractions can be improved.

Dilation of the major pericardial arteries leads to a decrease in both systemic (“afterload” reduction) and pulmonary ejection resistance.

Isosorbide-5-mononitrate causes relaxation of the bronchial muscles, lower urinary tract and muscles of the gallbladder, biliary tract, oesophagus, small intestine and colon, including sphincter muscles.

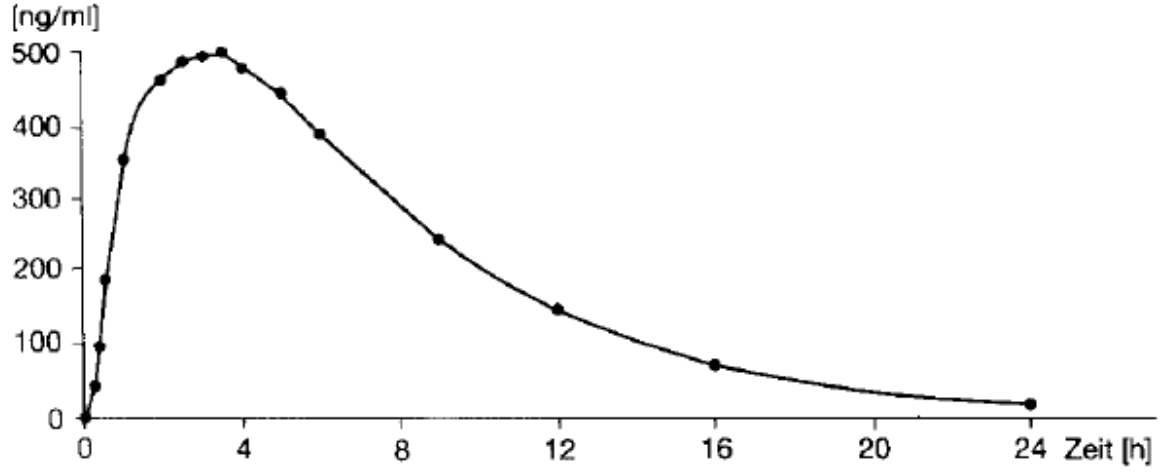
On a molecular level, nitrates most probably act on the formation of nitrogen (NO) and cyclic guanosine monophosphate (cGMP), which is considered to be a mediator of relaxation.

5.2 Pharmacokinetic properties

Following oral administration, isosorbide-5-mononitrate is rapidly and completely absorbed. Systemic availability is 90 – 100%. Isosorbide mononitrate is almost completely metabolised in the liver. The metabolites formed are inactive.
The plasma half-life is 4 – 5 hours. Isosorbide mononitrate is almost exclusively excreted in the form of its metabolites via the kidneys. Only approximately 2% is renally eliminated in unchanged form.
Bioavailability
Bioavailability studies (performed in 1981 and 1989) on 12 subjects yielded the following pharmacokinetic characteristics (mean values ± standard deviation):

Parameters	Ismo retard 40 mg ISMN n = 12
Peak plasma concentration (C_{max}) [ng/ml]	510.0 ± 70.0
Time to peak plasma concentration (t_{max}) [h]	3.6 ± 0.57
Area under the concentration-time curve (AUC) [ng/ml h]	4954 ± 776

Serum concentration of ISMN following intake of 1 Ismo retard prolonged-release tablet (40 mg ISMN); n = 12



[*Zeit* = time]

Tolerance
Despite a constant dosage at constant nitrate levels, a decrease in efficacy has been observed. Any existing tolerance resolves within 24 hours upon discontinuation of therapy.

No tolerance development was observed with analogous intermittent administration.

5.3 Preclinical safety data

Chronic toxicity
Chronic toxicity studies on rats revealed no evidence of any toxic effects. Following daily oral administration of 191 mg/kg isosorbide-5-mononitrate over a 43-day period, a 2.6 % rise above baseline in the methaemoglobin level was measured in dogs. After 191 mg/kg isosorbide-5-mononitrate per os, the serum nitrite concentration was at the limit of detection (less than 0.02 mg/l); alkaline phosphatase and GPT did not change.

These findings may be clinically relevant for patients with methaemoglobin reductase deficiency, as well as in patients with diaphorase deficiency and abnormal haemoglobin structure.

Mutagenic and tumorigenic potential
Long-term studies on rats revealed no evidence of any tumorigenic potential for isosorbide-5-mononitrate.

Studies in several mutagenicity tests (*in vitro* and *in vivo*) were negative.

Reproductive toxicity
No evidence of any teratogenic effect was revealed for isosorbide-5-mononitrate in animal studies.

In peri/postnatal toxicity studies, foetotoxic effects were only seen after very high doses within the maternally toxic range.

There is insufficient human experience with use during pregnancy and lactation. When administering to breast-feeding women, it is recommended that infants be observed for any pharmacological effects of isosorbide-5-mononitrate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose syrup, lactose, macrogol 35,000, magnesium stearate (Ph.Eur.), montanglycol wax, povidone K25, poly[butyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate] (1:2:1), sucrose, highly dispersed silica, talc, kaolin and titanium dioxide (E171).

6.2 Incompatibilities

None are known.

6.3 Shelf life

3 years (36 months).

6.4 Special precautions for storage

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

Store below 30ºC.

6.5 Nature and contents of container

ISMO 40 retard is supplied in blister packs of 30 tablets.

6.6 Special precautions for disposal

No special precautions required.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
AUCKLAND
Telephone: (09) 918 5100
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9 DATE OF FIRST APPROVAL

2 December 2010

10 DATE OF REVISION OF THE TEXT

30 October 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Update to SPC format
4.3	Addition of severe anaemia and severe hypovolaemia
4.8	Additional adverse effects added
4.9	Poison centre contact added
5.2	Updated section