

AUSTRALIAN PRODUCT INFORMATION – ISOBIDE MR (ISOSORBIDE MONONITRATE) MODIFIED RELEASE TABLETS

1 NAME OF THE MEDICINE

Isosorbide mononitrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ISOBIDE MR 60 mg tablets contain 60 mg isosorbide mononitrate,

Isosorbide mononitrate is a white to pale yellow, crystalline, odourless powder that is freely soluble in water.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets 60 mg. A cream, film-coated oval tablet of 13 mm length scored on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prophylactic treatment of angina pectoris. ISOBIDE MR 60 mg Modified release tablets are not recommended for the management of acute attacks of angina pectoris (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.2 DOSE AND METHOD OF ADMINISTRATION

One (1) tablet once daily. That dose may be increased to two (2) tablets daily, both tablets taken at the same time. ISOBIDE MR 60 mg Modified release tablets should not be administered twice daily.

There is insufficient evidence to show that one halved tablet of ISOBIDE MR delivers exactly half the dose of one full tablet, or whether the rate of release is the same. *In-vitro* dissolution testing showed that dissolution was slightly faster with halved isosorbide mononitrate modified release tablets than with whole tablets.

ISOBIDE MR 60 mg Modified release tablets should not be chewed or crushed, and should be swallowed whole with half a glass of fluid.

4.3 CONTRAINDICATIONS

Known hypersensitivity to nitrates or to any of the components in ISOBIDE MR 60 mg Modified release tablets, shock (including cardiogenic shock), hypotension, obstructive hypertrophic cardiomyopathy and pericarditis.

Phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) are contraindicated and must not be given to patients already receiving isosorbide mononitrate therapy.

Concomitant administration of isosorbide mononitrate and Phosphodiesterase type 5 inhibitors

can potentiate the vasodilatory effect of isosorbide mononitrate with the potential result of serious side effects such as syncope or myocardial infarction.

Acute Angina: ISOBIDE MR 60 mg Modified release tablets are not indicated for the relief of acute attacks of angina.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Note: There is a risk of developing tolerance to haemodynamic and antianginal effects if higher doses (more than 120 mg/day) and/or more frequent doses (eg. twice daily) of ISOBIDE MR 60 mg Modified release tablets are administered. It is therefore important that ISOBIDE MR 60 mg Modified release tablets are administered once a day in order to ensure that intervals with low nitrate concentrations are achieved each day, reducing the risk of the development of tolerance.

Acute Myocardial Infarction & Congestive Cardiac Failure:

The benefits of isosorbide mononitrate in patients with acute myocardial infarction or congestive cardiac failure have not been established. Because the effects of isosorbide mononitrate are difficult to terminate rapidly, the medicine is not recommended in these settings. If isosorbide mononitrate is used in these conditions, careful clinical and haemodynamic monitoring is necessary to avoid the hazards of hypotension and tachycardia.

Hypotension:

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide mononitrate. Hypotension and lightheadedness on standing may be more frequent in patients who have consumed alcohol. The drug should be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Industrial workers:

Tolerance develops in industrial workers who have had long-term exposure to high doses of organic nitrates. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Check the following before use.

Caution should be observed if ISOBIDE MR 60 mg Modified release tablets are administered to patients with: severe cerebral arteriosclerosis, pronounced mitral stenosis, hypertrophic cardiomyopathy, hypotension or cardiogenic shock.

Abrupt Withdrawal: Although no clear cut rebound phenomena were seen upon abrupt withdrawal of isosorbide mononitrate modified release tablets, such withdrawal is not recommended because of the possibility of severe exacerbation of anginal symptoms.

Use with caution in the following circumstances.

Use in hepatic impairment

Isosorbide mononitrate has been shown to cause a significant decrease in portal pressure in patients with cirrhosis and portal hypertension during long-term therapy (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Propranolol).

Use in renal impairment

The elimination of isosorbide mononitrate following administration of an immediate release tablet has been investigated in patients with severe renal impairment, but not using the modified release tablet. Renal impairment makes no therapeutically important difference to the pharmacokinetics of isosorbide mononitrate administered as an immediate release tablet, although two single dose studies did indicate a prolonged half-life in these patients with severe renal impairment. One of these studies also showed a higher plasma concentration. In view of the lack of data regarding the use of the tablet presentation in patients with severe renal impairment, the possibility of accumulation should be borne in mind when administering ISOBIDE MR 60 mg Modified release tablets to such patients, in whom a reduced dosage may be appropriate.

Use in the elderly

No dose reduction is necessary in elderly patients unless they have severe renal impairment.

Paediatric use

Due to lack of data, the use of ISOBIDE MR 60 mg Modified release tablets cannot be recommended in children.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Phosphodiesterase type 5 inhibitors: Concomitant administration of isosorbide mononitrate and Phosphodiesterase type 5 inhibitors can potentiate the vasodilatory effect of isosorbide mononitrate with the potential result of serious side effects such as syncope or myocardial infarction. Therefore, Phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) should not be given to patients already receiving isosorbide mononitrate therapy.

Sulphydryl Containing Compounds: The metabolism of organic nitrates to nitric oxide is dependent on the presence of sulphydryl groups in the muscle. The combination of oral N-acetylcysteine and a single dose of modified release isosorbide mononitrate 60 mg significantly prolonged the total exercise time in patients with angina pectoris and angiographically proven significant coronary artery disease, when compared with isosorbide mononitrate alone. Concomitant administration of other exogenous sources of sulphydryl groups such as methionine and captopril may produce a similar interaction.

Phenylalkylamine Calcium Antagonists: The addition of a calcium channel blocker of the verapamil type, such as gallopamil 75 mg, has been shown to further improve left ventricular functional parameters when given in combination with isosorbide mononitrate in a modified release formulation.

Propranolol: The addition of isosorbide mononitrate to propranolol treatment in patients with cirrhosis and portal hypertension caused a marked fall in portal pressure, a reduction in hepatic blood flow, cardiac output and mean arterial blood pressure, but no additional change in azygos blood flow. The additional effect of isosorbide mononitrate was especially evident in patients whose portal pressure was not reduced by propranolol.

Calcium Antagonists (general): Marked symptomatic orthostatic hypotension has been reported when calcium antagonists and organic nitrates were used in combination. Dose adjustments of either class of agent may be necessary.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category B2

The safety of isosorbide mononitrate in pregnancy has not been established. In the absence of Segment I and III studies with isosorbide mononitrate, the drug should only be administered to pregnant women if, in the opinion of the physician, the clinical benefits outweigh the potential risks.

Use in lactation.

At present there is no documentation about the passage of isosorbide mononitrate into breast milk, therefore its use in women who are breastfeeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients may develop dizziness when first using isosorbide mononitrate. Patients should be advised to determine how they react before they drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse effects which follow have been reported in studies with isosorbide mononitrate.

Very Common: Headache (up to 30%) necessitating withdrawal of 2 - 3 % of patients.

Common: Tiredness, sleep disturbances (6%) and gastrointestinal disturbances (6%) have been reported during clinical trials with isosorbide mononitrate modified release tablets, but at a frequency no greater than for placebo. Hypotension (4 to 5%), poor appetite (2.5%), nausea (1%).

Adverse effects associated with the clinical use of the drug are as expected with all nitrate preparations. They occur mainly in the early stages of treatment.

Very Common: Headache predominates (up to 30%), but the incidence reduces rapidly as treatment continues.

Common: Hypotension (4%) with symptoms such as dizziness and nausea have been reported. These symptoms generally disappear during long-term treatment.

Other reactions that have been reported with isosorbide mononitrate modified release tablets include: tachycardia, vomiting, diarrhoea, vertigo & heartburn.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms: The most common symptom of overdose is a pulsing headache. More serious symptoms are excitation, flushing, cold sweats, nausea, vomiting, vertigo, syncope, tachycardia and a fall in blood pressure.

Treatment: Administer activated charcoal. In patients with severe hypotension, place patient in supine position with the legs raised. If necessary, further symptomatic treatment should be given, including intravenous fluid administration.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Isosorbide mononitrate is an active metabolite of isosorbide dinitrate and exerts qualitatively similar effects. Isosorbide mononitrate reduces the workload of the heart by producing venous and arterial dilatation. By reducing the end diastolic pressure and volume, isosorbide mononitrate lowers intramural pressure, hence leading to an improvement in the subendocardial blood flow. The net effect when administering isosorbide mononitrate is therefore a reduced workload for the heart and an improvement in the oxygen supply/demand balance of myocardium.

Nitrates are highly effective in the prophylaxis of symptomatic and asymptomatic myocardial ischaemia. Nitrates dilate coronary arteries not only in pre- and poststenotic vessels, but also in eccentric lesions. The natural initiator of vascular relaxation is thought to be endothelium derived relaxing factor (EDRF), which has both the clinical and biological characteristics of nitric oxide. Organic nitrates are metabolised to nitric oxide in the muscle cell via a sulfhydryl dependent mechanism. They are therefore thought to be the physiological substitute for EDRF.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Isosorbide mononitrate has an elimination half-life of around 5 hours. ISOBIDE MR 60 mg modified release tablets provide a modified release presentation of isosorbide mononitrate, with approximately 85% bioavailability. The release mechanism in ISOBIDE MR comprises active drug distributed within a hydrophobic cellulose matrix with release occurring by diffusion. Drug particles close to the tablet surface are released relatively rapidly, but those incorporated more deeply are released more slowly. Administration of ISOBIDE MR 60 mg Modified release tablets results in a gradual, non-pH dependent release of the active substance, which is completed after approximately 10 hours. Compared to ordinary tablets, the absorption phase is prolonged and the duration of effect is extended. The absorption of ISOBIDE MR 60 mg Modified release tablets has been shown not to be influenced by food intake.

After repeated once daily administration of ISOBIDE MR 60 mg Modified release tablets, the maximum plasma level (about 3,000 nanomol/L) of isosorbide mononitrate is achieved at about 4 hours. The plasma concentration remains above 1,400 to 1,500 nanomol/L for approximately 10 hours, dropping to under 500 nanomol/L by the end of the dosage interval (24 hours after dose). This nitrate low period minimises the possibility of nitrate tolerances developing during prolonged treatment with ISOBIDE MR 60 mg Modified release tablets.

Isosorbide mononitrate is less than 5% plasma protein bound. The distribution volume of isosorbide mononitrate is about 0.6 L/kg, indicating that it is mainly distributed into total body water. Elimination takes place predominantly by hydrolysis of the nitrate and conjugation in the liver. The metabolites are excreted mainly via the kidneys, with only about 2% of the dose being excreted intact.

In placebo controlled studies, isosorbide mononitrate modified release tablets have been shown to significantly increase exercise capacity in patients with angina pectoris taking no other chronic treatment, as well as in patients taking concomitant β -blocker therapy.

It is known that the clinical effects may be attenuated during repeated administration with nitrates in high doses and/or frequent administration. However, the pharmacokinetic characteristics of ISOBIDE MR 60 mg Modified release tablets produce a nitrate low period following once daily dosage. No development of tolerance with respect to antianginal effect has been detected when isosorbide mononitrate modified release tablets are given at a dose of one or two tablets (60 or 120 mg) once daily. The drug is not recommended for twice daily administration.

There is insufficient evidence to show that one halved tablet of ISOBIDE MR delivers exactly half the dose of one full tablet, or whether the rate of release is the same. *In-vitro* dissolution testing showed that dissolution was slightly faster with halved isosorbide mononitrate modified release tablets than with whole tablets.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Other ingredients are hypromellose, carnauba wax, stearic acid, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, purified talc, titanium dioxide, iron oxide yellow and macrogol 4000.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light and moisture.

Blisters: Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

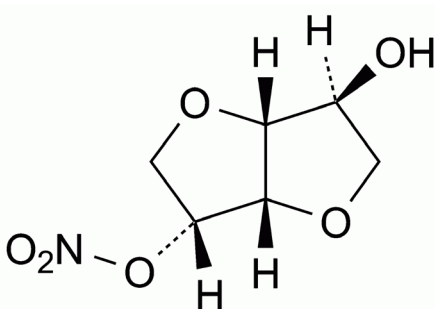
Available in PVDC/PVC/Al blisters of 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: 1,4:3,6-dianhydro-D-glucitol 5-nitrate

Molecular Formula: C₆H₉NO₆

Molecular Weight: 191.14

CAS number

[16051-77-7]

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription only Medicine)

8 SPONSOR

Amneal Pharma Australia Pty Ltd
12 River Street
South Yarra
VIC 3141
Australia

www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

05 April 2012

10 DATE OF REVISION

6 February 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
all	Trade name
All	Dosage form name
6.7	Chemical structure