Australian Product Information – MONODUR® (isosorbide mononitrate)

1. NAME OF THE MEDICINE

Isosorbide mononitrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MONODUR modified release tablets containing isosorbide mononitrate 60 mg or 120 mg.

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

3. PHARMACEUTICAL FORM

MONODUR (modified release tablets) 60 mg: Yellow, oval, biconvex tablets, scored on both sides, engraved A/ID.

MONODUR (modified release tablets)120 mg: White to off-white, oval, biconvex tablets, engraved A/IF.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MONODUR are indicated for prophylactic treatment of angina pectoris.

MONODUR 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 60 mg MONODUR Durule once daily. The dose may be increased to 120 mg once daily.

MONODUR should not be administered twice daily.

If headache occurs, the initial dose may be reduced to half a 60 mg tablet daily until the headache disappears. Patients with severe renal impairment may require dosage reduction to half a tablet given once daily.

MONODUR should not be chewed or crushed, and should be swallowed whole with half a glass of fluid. If care is taken to avoid crushing or chewing the tablet, half doses of the 60 mg tablet may be administered without affecting the modified release properties of MONODUR. The 120 mg tablet is not scored and should not be administered in half doses.

4.3 CONTRAINDICATIONS

Known hypersensitivity to nitrates or to any of the components in MONODUR.

Shock (including cardiogenic shock), hypotension, obstructive hypertrophic cardiomyopathy and pericarditis.

Phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) must not be given concomitantly with MONODUR.

Co-administration with riociguat (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

PLEASE NOTE:

There is a risk of developing tolerance to haemodynamic and antianginal effects if higher doses (more than 120mg/day) and/or more frequent doses (e.g. twice daily) of MONODUR are administered. It is therefore important that MONODUR 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.

Caution should also be observed if MONODUR are administered to patients with

- severe cerebral arteriosclerosis
- pronounced mitral stenosis
- hypotension

Acute angina

MONODUR are not indicated for the relief of acute attacks of angina.

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.

Abrupt withdrawal

Although no clear-cut rebound phenomena were seen upon abrupt withdrawal of MONODUR, such withdrawal is not recommended because of the possibility of severe exacerbation of anginal symptoms.

Use in renal impairment

The elimination of isosorbide mononitrate following administration of an immediate release (IR) tablet has been investigated in patients with severe renal impairment, but not using the modified release Durule. Renal impairment makes no therapeutically important difference to the pharmacokinetics of isosorbide mononitrate administered as an IR 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 MONODUR Durule presentation in patients with severe renal impairment, the possibility of accumulation should be borne in mind when administering MONODUR to such patients, in whom a reduced dosage may be appropriate.

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).

Paediatric use

Due to lack of data, the use of MONODUR cannot be recommended in children.

Use in the elderly

No dose reduction is necessary in the elderly unless they have severe renal impairment (see Section 4.4 Special Warnings and Precautions for Use).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The use of isosorbide mononitrate with riociguat, a stimulator of soluble guanylate cyclase, is contra-indicated (see Section 4.3 Contraindications), since concomitant use can cause hypotension.

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 such (e.g. sildenafil, tadalafil, and vardenafil) should not be given to patients already receiving isosorbide mononitrate therapy.

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.

Sulfhydryl containing compounds

The metabolism of organic nitrates to nitric oxide is dependent on the presence of sulfhydryl groups in the muscle. The combination of oral N-acetylcysteine and a single dose of modified release isosorbide mononitrate 60mg 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 sulfhydryl 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 75mg, 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Category B2.

The safety of isosorbide mononitrate in pregnancy has not been established. In the absence of Segment I and III studies undertaken 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 breast feeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects associated with the vascular activity of the drug are common and as expected with all nitrate preparations. They occur mainly in the early stages of treatment. Headache predominates (up to 30%), but the incidence reduces rapidly as treatment continues. Only 2-3% of patients withdrew during clinical trials due to this adverse effect.

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

The following adverse reactions have been reported in studies with isosorbide mononitrate.

Cardiovascular: hypotension (4-5%), tachycardia

Central nervous system: headache, vertigo, fainting

Gastrointestinal: poor appetite (2.5%), nausea (1%), vomiting, diarrhoea, heartburn.

Skin: rash, pruritus

Tiredness, sleep disturbances (6%), and gastro-intestinal disturbances (6%) have been reported during clinical trials with MONODUR but at a frequency no greater than for placebo.

The following adverse events have been observed in the post-marketing period (definitions of frequency: common 1 - 9.9%; uncommon 0.1 - 0.9%; rare 0.01 - 0.09%; very rare < 0.01%).

Central nervous system	Common: dizziness
Musculoskeletal	Very rare: Myalgia

Reporting suspected adverse reactions

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 https://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.

Management

Administer activated charcoal. In patients with severe hypotension, first place in the 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 the 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 the 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 (NO). Organic nitrates are metabolised to NO 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

Absorption

Administration of MONODUR 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. Drug particles close to the tablet surface are released relatively rapidly but those incorporated more deeply are released more slowly. The absorption of MONODUR has been shown not to be influenced by food intake.

After repeated once daily administration of MONODUR 60mg, the maximum plasma level (about 3000 nmol/L) of isosorbide mononitrate is achieved at about 4 hours. The plasma concentration remains above 1400-1500 nmol/L for approximately 10 hours, dropping to under 500 nmol/L by the end of the dosage interval (24 hours after dose). This nitrate low period minimises the possibility of nitrate tolerance developing during prolonged treatment with MONODUR.

Distribution

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.

Metabolism and excretion

Isosorbide mononitrate has an elimination half-life of around five hours. MONODUR provide a sustained release presentation of isosorbide mononitrate, with approximately 85% bioavailability.

Elimination takes place predominantly by denitrification and conjugation in the liver. The metabolites are excreted mainly via the kidneys, with only about 2% of the dose being excreted intact.

Special populations

In placebo-controlled studies, MONODUR 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 beta-blocker therapy.

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

Pharmacokinetic studies suggest that absorption of MONODUR is slower in some patients with acute myocardial infarction compared to healthy volunteers. At steady state absorption of MONODUR is similar in patients with acute myocardial infarction and in healthy volunteers. The steady state elimination half-life is longer in patients with acute myocardial infarction compared to healthy volunteers (see Section 4.4 Special Warnings and Precautions for Use, Acute Myocardial Infarction & Congestive Cardiac Failure).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

MONODUR contain the active drug embedded in a porous inert matrix consisting of paraffin-synthetic, aluminium sodium silicate, magnesium stearate, hydroxypropylcellulose and silica - colloidal anhydrous. In addition the tablet coating contains hypromellose, macrogol, titanium dioxide, hydrogen peroxide, paraffin-synthetic and water-purified.

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

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

MONODUR 60 mg: blister packs of 7^, 10^, 15^, 30.

MONODUR 120 mg: blister packs of 7^, 30.

^ currently not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

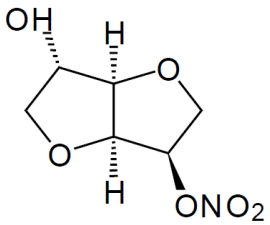
6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name is 1,4:3,6-Dianhydro-D-glucitol 5-nitrate. Molecular formula $C_6H_9NO_6$; m.w. 191.14.

Isosorbide mononitrate is a white to pale yellow crystalline powder and is freely soluble in water.

Chemical Structure

The chemical structure of isosorbide mononitrate is:



CAS Number

CAS 16051-77-7.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Clinect Pty Ltd,

120-132 Atlantic Drive,

Keysborough, VIC 3173,

Australia

Free Call Australia: 1800 899 005

9. DATE OF FIRST APPROVAL

7 July 1997

10. DATE OF REVISION

02 November 2026

Summary table of changes

Section changed	Summary of new information
4.3, 4.5	Safety update to include contraindication for concomitant use with riociguat