AUSTRALIAN PRODUCT INFORMATION

DURIDE

isosorbide mononitrate modified-release tablet

1 NAME OF THE MEDICINE

Isosorbide mononitrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 60 mg of isosorbide mononitrate as the active ingredient.

Excipients of known effect: sulfites.

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

3 PHARMACEUTICAL FORM

DURIDE tablets are yellow, oval, marked IM | 60 on one side and scored on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DURIDE is indicated for the prophylactic treatment of angina pectoris.

DURIDE is 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 tablet once daily. The dose may be increased to 120 mg once daily. Both tablets should be taken at the same time.

DURIDE should not be administered twice daily.

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

DURIDE tablets should be swallowed whole with half a glass of fluid.

The tablets should not be crushed or chewed.

Half tablet doses may be administered without affecting the modified-release properties of DURIDE, if care is taken not to crush or chew the tablets.

4.3 CONTRAINDICATIONS

Known hypersensitivity to nitrates or to any of the ingredients in DURIDE.

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 DURIDE.

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 120 mg/day) and/or more frequent doses (e.g. twice daily) of DURIDE are administered,. It is important to give

DURIDE modified- release tablets once daily to ensure that intervals with low nitrate concentrations are achieved each day, reducing the risk of tolerance developing,

Caution should also be observed if DURIDE modified-release tablets are administered to patients with:

- severe cerebral arteriosclerosis
- pronounced mitral stenosis
- hypotension

Acute Angina
DURIDE is not indicated for the relief of acute attacks of angina.

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

Acute Myocardial Infarction and 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 light headedness 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.

Use in Hepatic Impairment
In patients with cirrhosis and portal hypertension isosorbide mononitrate has been shown to cause a significant decrease in portal pressure 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, but not a modified-release tablet, has been investigated in patients with severe renal impairment. 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 modified-release tablets in patients with severe renal impairment, the possibility of accumulation should be borne in mind. A reduced dosage may be appropriate when DURIDE is prescribed for such patients.

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

Paediatric Use
Due to lack of data, the use of DURIDE 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.

Sulfhydryl Containing Compounds
The metabolism of organic nitrates to nitric oxide is dependent on the presence of sulfhydryl groups in the muscle. In patients with angina pectoris and angio-graphically proven significant coronary artery disease, the combination of oral N-acetylcysteine with a single dose of modified-release isosorbide mononitrate 60 mg prolonged total exercise time significantly, compared with isosorbide mononitrate alone. Other exogenous sources of sulfhydryl groups such as methionine and captopril may produce a similar interaction when administered together with DURIDE.

Phenylalkylamine Calcium Antagonists
Left ventricular functional parameters have been shown to be further improved when a calcium channel blocker of the verapamil type (e.g. gallopamil) is added to therapy with modified-release isosorbide mononitrate tablets.

Propranolol
Adding isosorbide mononitrate to propranolol treatment in patients with cirrhosis and portal hypertension led to a marked fall in portal pressure, a reduction in hepatic blood flow, cardiac output and mean arterial blood pressure. There were no additional changes in azygos blood flow. In patients whose portal pressure was not reduced by propranolol, the added effect of isosorbide mononitrate was particularly apparent.

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 agents 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 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 breastfeeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients may develop dizziness when first using DURIDE. 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 isosorbide mononitrate are common and as expected with all nitrate preparations. They occur mainly in the early stages of treatment. Headache predominates (up to 30%). However, the incidence of headache reduces rapidly as treatment continues. Only 2 to 3% of patients withdrew from clinical trials of isosorbide mononitrate 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 to 5%), tachycardia.

Central nervous system. Headache, vertigo, fainting.

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

Skin. Rash, pruritis.

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.

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 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 a fall in blood pressure, cold sweats, excitation, flushing, nausea and vomiting, syncope, tachycardia and vertigo.

Treatment

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

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. It has qualitatively similar effects. Isosorbide mononitrate reduces the workload of the heart by producing venous and arterial dilatation. It lowers intramural pressure by reducing the end diastolic pressure and volume. This leads to an improvement in the subendocardial blood flow. When isosorbide mononitrate is administered, the net effect 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 in pre- and poststenotic vessels and also in eccentric lesions. Vascular relaxation is thought to be initiated naturally by endothelium derived relaxing factor (EDRF). EDRF has both the clinical and biological characteristics of nitric oxide. In muscle cells, organic nitrates are metabolised to nitric oxide via a sulfhydryl dependent mechanism. Organic nitrates are therefore thought to act as a physiological substitute for EDRF.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Administration of isosorbide mononitrate results in a gradual, non-pH dependent release of the active substance, which is completed after approximately 10 hours. The absorption phase is extended and the duration of effect is lengthened when compared to immediate-release tablets. The intake of food has been shown not to influence the absorption of isosorbide mononitrate.

In a bioequivalence study comparing DURIDE sustained release tablets with the Australian brand leader, repeated once daily administration of 60 mg of both brands resulted in maximum plasma levels of isosorbide mononitrate of about 400 ng/mL, which were reached at around 3 hours. The plasma concentrations remained above 200 ng/mL for approximately 10 hours, dropping to under 100 ng/mL by the end of the dosage interval (24 hours after dose) for both brands.

The possibility of nitrate tolerance developing during prolonged treatment with DURIDE is minimised by the nitrate low period that occurs within each dosing interval.

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 distributed mainly into total body water.

Metabolism

Isosorbide mononitrate has an elimination half-life of around 5 hours. DURIDE tablets are a modified-release preparation of isosorbide mononitrate.

Excretion

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

Pharmacokinetics in Special Populations

In placebo-controlled studies, isosorbide mononitrate modified-release tablets have been shown to significantly increase exercise capacity in patients with angina pectoris. This effect was seen both in patients not taking any other chronic treatment and in those taking β-blocker therapy concomitantly.

It is known that the clinical effects of nitrates may be diminished during repeated administration with high and/ or frequent doses. However, the pharmacokinetic characteristics of isosorbide mononitrate 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 60 mg or 120 mg once daily (one to two tablets). Twice daily dosing with DURIDE is not recommended.

Pharmacokinetics studies suggest that absorption of isosorbide mononitrate modified-release tablets is slower in some patients with acute myocardial infarction compared to healthy volunteers. At steady state, absorption of isosorbide mononitrate 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 and Congestive Cardiac Failure).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

DURIDE modified-release tablets contain the following inactive ingredients: aluminium silicate, colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, Opadry Yellow OY-LS-22814 (Proprietary Ingredient Number: 2828) and Paraflint Med 851 (Proprietary Ingredient Number: 2858).

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 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack

Pack size: 30

Some strengths, pack sizes and/or pack types may not be marketed.

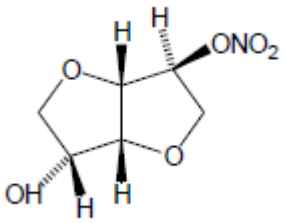
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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



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

Molecular formula: $C_6H_9NO_6$

Molecular weight: 191.14

CAS Number

16051-77-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

21/10/1997

10 DATE OF REVISION

16/08/2019

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat

2; 4.1; 4.2; 4.3; 4.4; 4.5; 4.6; 4.7; 4.8; 4.9; 5.2; 6.1; 6.5; 9	Editorial changes
6.5	Removed bottle pack as no longer registered

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