NEW ZEALAND DATA SHEET

DURIDE

1. Product Name

DURIDE, 60 mg, modified release tablet.

2. Qualitative and Quantitative Composition

Each modified release tablet contains 60 mg of isosorbide-5-mononitrate.

Duride modified release tablets contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Duride tablets are pale yellow, film-coated, elliptical shaped, 13.1 mm x 7.1 mm, embossed IM breakline 60 on one side & plain with breakline on the other. Duride is a modified -release preparation where the active substance is embedded in a porous, insoluble tablet matrix.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

Prophylaxis of angina pectoris. Duride is not recommended for the management of acute attacks of angina pectoris.

4.2 Dose and method of administration

Dose

60 mg once daily, to be taken in the morning. The dose may be increased to 120 mg daily, with both tablets taken together once daily in the morning.

Duride tablets should not be administered twice daily.

If headache occurs, the initial dose may be reduced to 30 mg once daily until the headache disappears.

Patients with severe renal impairment may require dosage reduction to 30 mg once daily.

Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Note that Duride is not indicated for the relief of acute attacks; in these situations sublingual or buccal nitroglycerin tablets should be used.

Method of administration

The 60 mg Duride tablet is scored and dividable.

Duride modified release 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 other ingredients in Duride listed in section 6.1.

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

Note: If higher doses (more than 120 mg/day) and/or more frequent doses (e.g. twice daily) of Duride are administered, there is a risk of developing tolerance to haemodynamic and antianginal effects. To ensure that intervals with low nitrate concentrations are achieved each day and thus to reduce the risk of tolerance developing, it is important to give Duride modified release tablets once daily.

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 abrupt withdrawal is not recommended.

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 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.

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 isosorbide mononitrate modified release tablets are prescribed for such patients.

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).

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 Duride cannot be recommended in children.

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.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

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 further improve when a calcium channel blocker of the verapamil type (such as 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

Use in pregnancy (risk 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.

Breast-feeding

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.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients may develop dizziness (especially when first using Duride), vertigo or fainting when using Duride. Patients should be advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 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 2-3% 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 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 https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

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

Treatment

Administer activated charcoal. In case of pronounced hypotension the patient should first be placed in the supine position with legs elevated. If necessary, further symptomatic treatment, including intravenous fluids should be administered.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Organic nitrates, ATC code: C01DA14

Pharmacodynamic effects

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 post-stenotic 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

Duride tablets are a modified release preparation of isosorbide mononitrate. Administration of Duride 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 Duride.

In a bioequivalence study comparing Duride modified 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.

After repeated once daily administration of isosorbide mononitrate modified release 60mg, the maximum plasma level (about 3000 nanomol/L) of isosorbide mononitrate is achieved at about 4 hours. The plasma concentration remains above 1400-1500 nanomol/L for approximately 10 hours, dropping to under 500 nmol/L by the end of the dosage interval (24 hours after dose).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 and excretion

Isosorbide mononitrate has an elimination half-life of around 5 hours with approximately 85% bioavailability.

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

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 administration. However, the pharmacokinetic characteristics of Duride 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 or 120 mg once daily (one or two tablets). Twice daily dosing with Duride is not recommended.

Pharmacokinetics studies suggest that absorption of isosorbide mononitrate 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).

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 isosorbide mononitrate embedded in a porous inert matrix.

List of excipients:

- microcrystalline cellulose,
- aluminium silicate,
- magnesium stearate,
- colloidal silicon dioxide,
- paraffin wax blend,
- hypromellose,
- titanium dioxide,
- lactose monohydrate,
- polyethylene glycol,
- iron oxide yellow,
- iron oxide black,
- and iron oxide red.

Contains lactose and sulfites.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Duride are available in Al/PVC/PVdC blister packs containing 30 or 90 modified release tablets, or HDPE bottles with PP cap containing 100 or 500 modified release tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

09 April 1998

10. Date of Revision of the Text

27 June 2022

Section	Summary of new information
Header	Updated sponsor logo.
5.3	Added preclinical safety data information.
6.1	Removed gluten free statement. Added allergen statement, “Contains lactose and sulfites.”
8	Sponsor contact number updated.
10	Update date of text revision.