

# Duride

isorbide mononitrate

ATTACHMENT 1



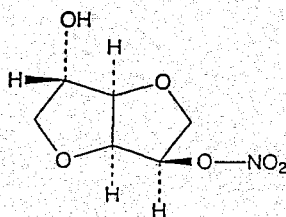
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## PRODUCT INFORMATION

### Name of the Drug

The active ingredient in Duride is isosorbide mononitrate (sustained release).

The chemical name of isosorbide mononitrate is 1,4:3,6-dianhydro-D-glucitol 5-nitrate. Its structural formula is:



$C_6H_9NO_6$

Molecular weight: 191.14

CAS Registry No: 16051-77-7

### Description

Isosorbide mononitrate is a white crystalline powder and is freely soluble in water. Duride sustained release tablets contain the active drug embedded in a porous inert matrix consisting mainly of hard paraffin, synthetic paraffin, aluminium silicate, magnesium stearate and microcrystalline cellulose. The tablets also contain colloidal anhydrous silica, hypromellose, iron oxide yellow CI 77492, iron oxide red CI 77491, iron oxide black CI 77499, lactose, macrogol 4000 and titanium dioxide.

### Pharmacology

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.

### Pharmacokinetics

Isosorbide mononitrate has an elimination half-life of around 5 hours. Duride tablets are a sustained 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 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.

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

In placebo controlled studies, isosorbide mononitrate sustained 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  $\beta$ -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 Duride sustained release tablets produce a nitrate low period following once daily dosage. No development of tolerance with respect to antia nginal effect has been detected when isosorbide mononitrate sustained release tablets are given at a dose 60 or 120 mg once daily (one to two tablets). Twice daily dosing with Duride is not recommended.

## Indications

Prophylactic treatment of angina pectoris. Duride are not recommended for the management of acute attacks of angina pectoris (see Precautions).

## Contraindications

Known hypersensitivity to nitrates.

## Precautions

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 sustained release tablets once daily.

Caution should be observed if Duride sustained release tablets are administered to patients with severe cerebral arteriosclerosis, cardiogenic shock, hypertrophic cardiomyopathy, hypotension or pronounced mitral stenosis.

*Acute angina.* Duride sustained release tablets are 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 sustained release tablets, because of the possibility of severe exacerbation of anginal symptoms such abrupt withdrawal is not recommended.

**Impaired renal function.** The elimination of isosorbide mononitrate following administration of an immediate release tablet, but not a sustained release tablet, has been investigated in patients with severe renal impairment. Renal impairment makes no therapeutically meaningful 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 sustained 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.

**Impaired hepatic function.** 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 **Interactions, Propranolol**).

### 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.

**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.

**Use in the Elderly.** No dose reduction is necessary in elderly patients unless they have severe renal impairment.

**Use in Children.** Due to lack of data, the use of Duride cannot be recommended in children.

**Interactions. 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 angiographically proven significant coronary artery disease, the combination of oral N-acetylcysteine with a single dose of sustained 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 (eg. gallopamil) is added to therapy with sustained 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 change in azygos blood flow. In patients whose portal pressure was not reduced by propranolol, the added effect of isosorbide mononitrate was particularly apparent.

## Adverse Reactions

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.

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

*Cardiovascular.* Hypotension (4 to 5%), tachycardia.

*Central nervous system.* Headache, vertigo

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

Tiredness, sleep disturbances (6%) and gastrointestinal disturbances (6%) have been reported during clinical trials with isosorbide mononitrate sustained release tablets, but at a frequency no greater than for placebo.

## Dosage and Administration

1 tablet once daily. The dose may be increased to 2 tablets daily. Both tablets should be taken at the same time.

Twice daily dosing should not be used with Duride.

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 sustained 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 sustained release properties of Duride, if care is taken not to crush or chew the tablets.

## Overdosage

**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.** Induce emesis if possible, then 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.

## Presentation

**Duride** isosorbide mononitrate 60 mg sustained release tablet: yellow, oval, marked  $\alpha$ |I on one side and scored on both sides; 30's

## Poison Schedule

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ACN 002 359 739

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Approved by the Therapeutic Goods Administration on .....

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