

Data Sheet

DURIDE

Isosorbide-5-mononitrate

Presentation

DURIDE 60mg tablets contain 60mg isosorbide-5-mononitrate. 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 controlled-release preparation where the active substance is embedded in a porous, insoluble tablet matrix.

Uses

Actions

The principal pharmacological action of isosorbide-5-mononitrate, an active metabolite of isosorbide dinitrate, is relaxation of vascular smooth muscle, producing vasodilatation of both arteries and veins, with the latter effect predominating. The effect of the treatment is dependent on the dose. Low plasma concentrations lead to venous dilatation, resulting in peripheral pooling of blood, decreased venous return and reduction in left ventricular end-diastolic pressure (preload). High plasma concentrations also dilate the arteries, reducing systemic vascular resistance and arterial pressure, leading to a reduction in cardiac after load. Isosorbide-5-mononitrate may also have a direct dilatory effect on the coronary arteries. By reducing the end diastolic pressure and volume, the preparation lowers the intramural pressure, thereby leading to an improvement in the subendocardial blood flow. The net effect when administering isosorbide-5-mononitrate is therefore a reduced workload of the heart and an improved oxygen supply/demand balance in the myocardium.

Pharmacokinetics

Isosorbide-5-mononitrate is completely absorbed and is not metabolised during the first passage through the liver. This reduces the intra- and inter-individual variations in plasma levels and leads to predictable and reproducible clinical effects. The elimination half-life of isosorbide-5-mononitrate is around 5 hours. The volume of distribution for isosorbide-5-mononitrate is about 0.6 L/kg and total clearance around 115 mL/minute. Elimination takes place by de-nitration and conjugation. The metabolites are excreted mainly via the kidneys. Only about 2% of the dose given is excreted as unchanged medicine via the kidneys.

Impaired liver or kidney function has no major influence on the pharmacokinetic properties.

DURIDE is an extended release formulation of isosorbide-5-mononitrate. The active substance is released independently of pH, over a 10-hour period. Compared to ordinary tablets the absorption phase of Isosorbide-5-mononitrate controlled release tablets is prolonged and the duration of effect is extended. The extent of bioavailability of Isosorbide-5-mononitrate controlled release tablets is about 90% compared to immediate release tablets. Absorption is not significantly affected by food intake. After repeated peroral administration with 60mg once daily, a maximal plasma concentration (around 3000 nmol/L) is achieved after around 4 hours. The plasma concentration then gradually falls to around 500 nmol/L at the end of the dosage interval (24 hours after dose intake). The 60mg tablets are dividable.

In placebo controlled studies, Isosorbide-5-mononitrate controlled release tablet once daily has been shown to effectively control angina pectoris both in terms of exercise capacity and symptoms, and in reducing signs of myocardial ischaemia. The duration of the effects is at least 12 hours and at this point the plasma concentration is at the same level as at around 1 hour after dose intake (around 1300 nmol/L).

Isosorbide-5-mononitrate controlled release tablets have been shown to be effective in monotherapy as well as in combination with chronic β -blocker therapy. The clinical effects of nitrates may be

attenuated during repeated administration owing to high and/or even plasma levels. This can be avoided by allowing low plasma levels for a certain period of the dosage interval. Isosorbide-5-mononitrate controlled release tablet when administered once daily in the morning, produces a plasma profile that provides high plasma levels during daytime and low night-time plasma levels.

With Isosorbide-5-mononitrate controlled release 60mg or 120mg once daily, no development of tolerance with respect to antianginal effect has been observed. Rebound phenomenon between doses as described with intermittent nitrate patch therapy has not been seen with Isosorbide-5-mononitrate controlled release tablets.

Indications

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

Dosage and Administration

60mg 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. The dose can be titrated to minimise the possibility of headache by initiating treatment with 30mg for the first 2 – 4 days.

Twice daily dosing should not be used with Duride.

The 60mg DURIDE tablet is scored and dividable.

Neither the whole tablets nor the divided halves, should be chewed or crushed, but should be swallowed with half a glass of fluid.

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.

Contraindications

Known hypersensitivity to nitrates or to any of the other ingredients in Duride.

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

Concurrent administration with sildenafil.

Warnings and 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.

Severe cerebrovascular insufficiency and hypotension are relative contraindications to the use of DURIDE.

Caution should be observed if Duride sustained release tablets are administered to patients with severe cerebral arteriosclerosis 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.

Adverse Effects

Most of the adverse effects are pharmacodynamically mediated and dose dependent. They occur on 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 if Isosorbide mononitrate due to this adverse effect.

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

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.

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 angio-graphically 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 further improve when a calcium channel blocker of the verapamil type 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 changes in azygos blood flow. In patients whose portal pressure was not reduced by propranolol, the added effect of isosorbide mononitrate was particularly apparent.

Sildenafil.

Concomitant administration of isosorbide mononitrate and sildenafil can potentiate the vasodilatory effects of isosorbide mononitrate with the potential result of serious side effects such as syncope or myocardial infarction. Therefore, sildenafil should not be given to patients already receiving isosorbide mononitrate therapy.

Overdosage

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.

Management:

Induce emesis if possible, then 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.

Pharmaceutical Precautions

Store below 30°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Calendar packs of 30 or 90 tablets.

Further Information

Duride controlled 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, hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, iron oxide yellow, iron oxide black and iron oxide red.

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