

IMDUR® DURULES® PRODUCT INFORMATION

1 (8)

Date of TGA approval April 24, 1992

Addition of 120 mg strength December 9, 1996

Draft dated September 30, 1997

Draft dated January 8, 1998

IMDUR® DURULES® PRODUCT INFORMATION

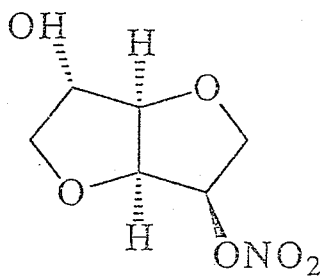
(isosorbide mononitrate)

DESCRIPTION


IMDUR DURULES contain isosorbide mononitrate (AAN) in a sustained release formulation.

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. CAS 16051-77-7.

The chemical structure of isosorbide mononitrate is:



IMDUR DURULES 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.


= 2 FEB 1998

PHARMACOLOGY

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 post-stenotic 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.

PHARMACOKINETICS

Isosorbide mononitrate has an elimination half-life of around five hours. IMDUR DURULES provide a sustained-release presentation of isosorbide mononitrate, with approximately 85% bioavailability. Administration of IMDUR DURULES 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 IMDUR DURULES has been shown not to be influenced by food intake.

After repeated once daily administration of IMDUR DURULES 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 IMDUR DURULES.

7
2 FEB 1998

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

In placebo-controlled studies, IMDUR DURULES 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 IMDUR DURULES produce a nitrate low period following once daily dosage. No development of tolerance with respect to antianginal effect has been detected when IMDUR DURULES 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 IMDUR is slower in some patients with acute myocardial infarction compared to healthy volunteers. At steady state absorption of IMDUR 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.


INDICATIONS

IMDUR DURULES are indicated for prophylactic treatment of angina pectoris.

IMDUR DURULES are not recommended for the management of acute attacks of angina pectoris (see PRECAUTIONS).

CONTRAINDICATIONS

Known hypersensitivity to nitrates.


- 2 FEB 1998

PRECAUTIONS

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 (eg. twice daily) of IMDUR DURULES are administered. It is therefore important that IMDUR DURULES 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.

Severe 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 sustained 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 DURULE presentation in patients with severe renal impairment, the possibility of accumulation should be borne in mind when administering IMDUR DURULES to such patients, in whom a reduced dosage may be appropriate.


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 INTERACTIONS, Propranolol).

Caution should also be observed if IMDUR DURULES are administered to patients with

- severe cerebral arteriosclerosis
- pronounced mitral stenosis
- hypertrophic cardiomyopathy
- hypotension
- cardiogenic shock

Acute angina. IMDUR DURULES 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 IMDUR DURULES, such withdrawal is not recommended because of the possibility of severe exacerbation of anginal symptoms.


- 2 FEB 1998

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 DURING 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.

USE IN CHILDREN

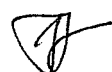
Due to lack of data, the use of IMDUR DURULES cannot be recommended in children.

USE IN ELDERLY

No dose reduction is necessary in the elderly unless they have severe renal impairment (see PRECAUTIONS).

INTERACTIONS

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 sustained-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.


= 2 FEB 1998

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 sustained 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.

ADVERSE REACTIONS

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

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

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


= 2 FEB 1998

DOSAGE AND ADMINISTRATION

One 60 mg IMDUR DURULE once daily. The dose may be increased to 120 mg once daily.

IMDUR DURULES 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.

IMDUR DURULES 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 sustained-release properties of IMDUR DURULES. The 120 mg tablet is not scored and should not be administered in half doses.

OVERDOSAGE

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 Induce emesis if possible, then 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.

PRESENTATION

Imdur 60 mg

Yellow, oval, biconvex tablets, scored on both sides, engraved A/ID containing isosorbide mononitrate 60 mg, in blister packs of 30.

Imdur 120 mg

White to off-white, oval, biconvex tablets, engraved A/IF containing isosorbide mononitrate 120 mg, in blister packs of 30.

2 FEB 1998

STORAGE

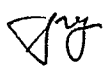
IMDUR DURULES have a shelf life of 3 years when stored below 30°C.

NAME AND ADDRESS OF MANUFACTURER/DISTRIBUTOR

Astra Pharmaceuticals Pty Ltd
A.C.N. 009 682 311
Alma Road,
North Ryde NSW 2113

® = Registered Trademark of AB Astra.
Astra Pharmaceuticals authorised user.

920424
imdurpi


2 FEB 1998