


For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Controlled Release Tablets of
Isosorbide-5-mononitrate
ImdurTM  30mg/60mg

Composition

Each Controlled release film coated tablet contains:

Isosorbide-5-mononitrate 30mg

Colour: Red oxide of Iron.

Each Controlled release film coated tablet contains:

Isosorbide-5-mononitrate 60mg

Colour: Yellow oxide of Iron.

Pharmaceutical form

Imdur Durules 30 mg is pink, oval, biconvex tablet having embossed marked A/II, on one side & scoreline on the other 7 x 13 mm.

Imdur Durules 60 mg is yellow, oval, biconvex tablet scored, marked A/ID, on one side & scoreline on the other 7 x 13 mm.

The Durules formulation provides gradual release of the active ingredient over a long period of time. The plastic matrix in Imdur Durules is completely inert in the digestive juice but generally disintegrates under the influence of intestinal peristalsis when all active ingredient has been released.

Therapeutic Indications

Prophylactic treatment of angina pectoris.

Posology and method of administration

30 or 60 mg once daily to be taken in the morning. The dose may be increased to 120 mg daily, taken once daily in the morning. The dose can be titrated to minimize the possibility of headache by initiating treatment with 30 mg for the first 2-4 days. The tablets can be taken with or without food.

The 30 or 60 mg depotablets are scored and dividable. The whole tablets or if needed the divided halves, should not be chewed or crushed and should be swallowed together with half a glass of fluid. Imdur is not indicated for the relief of acute attacks. In these situations sublingual or buccal nitroglycerine tablets or spray formulations should be used.

The matrix of the tablet is insoluble but disintegrates when the active substance is released. Occasionally the matrix may pass through the gastrointestinal tract without disintegrating and may be visible in the stool but this does not indicate that the drug has had a reduced effect.

Contraindications

Hypersensitivity to the active substance or to any of the excipients, shock, hypotension, constrictive cardiomyopathy and pericarditis.

To an existing therapy with Imdur, sildenafil (Viagra) must not be given additionally.

Special warnings and precautions for use

Caution should be observed in patients with severe cerebral arteriosclerosis and hypotension.

Interactions

Concomitant administration of Imdur and sildenafil (Viagra) can potentiate the vasodilatory effect of Imdur with the potential results of serious side-effects as syncope or myocardial infarction. Therefore to an existing therapy with Imdur, sildenafil may not be given additionally.

The effect of food on the absorption of Imdur is not clinically significant.

Pregnancy and lactation

The safety and efficacy of Imdur during pregnancy or lactation have not been established.

Effects on ability to drive and use machines

Patients may develop dizziness when first using Imdur. Patients should be advised to determine how they react to Imdur before they drive or operate machinery.

Undesirable effects

Most of the adverse reactions are pharmacodynamically mediated and dose dependent. Headache may occur when treatment is initiated, but usually disappears during continued treatment. Hypotension, with symptoms such as dizziness and nausea with syncope in isolated cases, has occasionally been reported. These symptoms generally disappear during continued treatment.

The following definitions of frequencies are used: Very common (>10%), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0.09%) and very rare (<0.01%).

Cardiovascular system

Common: Hypotension, tachycardia.

Central nervous system

Common: Headache, dizziness.

Rare: Fainting.

Gastrointestinal

Common: Nausea

Uncommon: Vomiting, diarrhoea.

Musculoskeletal

Very rare: Myalgia

Skin

Rare: Rash, pruritus.

Overdose

Symptoms – Pulsing headache. More serious symptoms are excitation, flushing, cold perspiration, nausea, vomiting, vertigo, syncope, tachycardia and fall in blood pressure.

Management – Induction of emesis, activated charcoal. In case of pronounced hypotension the patient should first be placed in the supine position with legs raised. If necessary intravenous administration of fluid.

190 mm

150 mm

Pharmacodynamic properties

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 of 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 afterload.

Isosorbide-5-mononitrate may also have a direct dilating 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.

In placebo controlled studies, Imdur once daily has been shown effectively to control angina pectoris both in the terms of exercise capacity and symptoms and in reducing signs of myocardial ischaemia. The duration of the effects is at least 12 hours. At this point the plasma concentration is similar to the level 1 hour after dose intake – about 1300 nmol/l.

Imdur has been shown to be effective in monotherapy as well as in combination with beta-blockers and calcium antagonists.

The clinical effects of nitrates may be attenuated during repeated administration owing to high and even plasma levels. This can be avoided by allowing low plasma levels for a certain period of the dosage interval. Imdur when administered once daily in the morning, produce a plasma profile that provides high plasma levels during daytime and low night-time plasma levels. With Imdur 30 or 60 mg 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 Imdur.

Imdur is safe and well tolerated also when used in connection with acute myocardial infarction. The first dose was 30 mg and another 30 mg 12h later, thereafter 60 mg once daily. Plasma concentrations in patients with acute myocardial infarction were similar to what is seen in healthy volunteers. Occasionally, protracted absorption may occur possibly due to concomitant morphine administration.

Pharmacokinetic properties

Isosorbide-5-mononitrate is completely absorbed and is not metabolized 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 denitration and conjugation. The metabolites are excreted mainly via the kidneys. Only about 2% of the dose is excreted as unchanged drug via the kidneys.

Impaired liver function or kidney function have no major influence on the pharmacokinetic properties of Imdur.

Imdur is an prolonged release formulation (Durules) 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 Imdur is prolonged and the duration of effect is extended. The extent of bioavailability of Imdur is about 90% compared to immediate release tablets. Absorption is not significantly affected by food intake. After repeated peroral administration of 30 or 60 mg once daily, a maximal plasma concentration (around 3000 nmol/l) is achieved after around 4 hours. The plasma concentrations then gradually fall to around 500 nmol/l at the end of the dosage interval (24 hours after dose intake).

List of excipients

Imdur Durules 30 mg tablets : Sodium aluminium silicate, paraffin, hydroxypropylcellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, macrogol, red iron oxide (E172), titanium dioxide (E171).

Imdur Durules 60 mg tablets : Sodium aluminium silicate, paraffin, hydroxypropylcellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, macrogol, yellow iron oxide (E172), titanium dioxide (E171).

Special precautions for storage

Do not store above 30°C.

Shelf-life

Please see outer pack.

Presentation

Imdur 30mg - Strip of 10 tablets
Imdur 60mg - Strip of 10 tablets

Date of revision:

July 2002

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For further information:

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AstraZeneca 

34-169-57

190 mm

150 mm