Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imdur 60 mg Prolonged-release Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Isosorbide monoitrate 60 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated prolonged-release tablet.

Product imported from Greece:
A yellow, oval, bi-convex, film-coated, prolonged-release tablet, scored on both sides, engraved 'A/ID' on side, and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylactic management of angina pectoris. Imdur is not indicated in the management of acute attacks of angina pectoris.

4.2 Posology and method of administration

Dosage
Imdur 60 mg once daily, to be taken in the morning. The dose may be increased to 120 mg daily, the whole dose to be given together in the morning. This will produce effective nitrate blood levels during the day with low blood levels at night to prevent the development of tolerance.
The dose can be titrated to minimise the possibility of headache, by initiating treatment with a 30 mg dose, for the first two to four days.
Whole Imdur tablets, or if needed, the divided halves, must not be chewed or crushed. They should be swallowed together with half a glass of water.
Note that Imdur is not indicated for the relief of acute attacks, in the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets should be used
Children
The safety and efficacy of Imdur in children has not been established.
Elderly
No evidence of a need for routine dosage adjustment in the elderly has been found, but special care may be needed in those with increased susceptibility to hypotension or marked hepatic or renal insufficiency.
An additional anti-anginal effect has been achieved when Imdur has been used in combination with beta-blockers.
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 a reduced effect.

4.3 Contraindications

Imdur should not be given to patients with known sensitivity to nitrates.
Hypersensitivity to any of the components.
Patients treated with Imdur must not be given Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil).
Imdur should not be used in patients with acute myocardial infarction with low filling pressure, marked anaemia, head trauma, cerebral haemorrhage, severe hypotension or hypovolaemia, constrictive cardiomyopathy and pericarditis.
Use in patients with severe cerebrovascular insufficiency is contraindicated.

4.4 Special warnings and precautions for use

Nitrates may give rise to symptoms of collapse after the first dose in patients with labile circulation. These symptoms can largely be avoided if the treatment is started with a 30 mg dose.
The safety and efficacy of Imdur has not been established in children.
Imdur should be used with caution in patients suffering from hypothyroidism, hypothermia, malnutrition, severe liver or renal disease.

4.5 Interaction with other medicinal products and other forms of interaction

Some of the effects of alcohol and other vasodilators may be potentiated by this agent.
Concomitant administration of Imdur and Phosphodiesterase Type 5 Inhibitors can potentiate the vasodilatory effect of Imdur with the potential result of serious side effects such as syncope or myocardial infarction. Therefore, Imdur and Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil) must not be given concomitantly.

4.6 Fertility, pregnancy and lactation

The safety and efficacy of Imdur during pregnancy or lactation has not been established. Imdur should not be used during pregnancy or lactation unless considered essential by the physician.
Use during lactation
It is not known whether isosorbide mononitrate is secreted in human milk.

4.7 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.

4.8 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 has occasionally been reported. These symptoms generally disappear during continued treatment. Rash and pruritus have been reported rarely. Myalgia has been reported very rarely.

4.9 Overdose

Symptoms
Pulsing headache. More serious symptoms are excitation, flushing, cold perspiration, nausea, vomiting, vertigo, syncope, tachycardia and a 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 fluids should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The principal pharmacological action of isosorbide mononitrate, an active metabolite of isosorbide dinitrate, is relaxation of vascular smooth muscle, producing vasodilation 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 afterload. Isosorbide 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 mononitrate is, therefore, a reduced workload of the heart and an improved oxygen supply/demand balance in the myocardium.

5.2 Pharmacokinetic properties

Imdur is a prolonged-release formulation (Durules). The active substance is released independently of pH over a ten hour period. Compared to ordinary tablets the absorption phase is prolonged and the duration of effect is extended. Isosorbide 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 mononitrate is around 5 hours. The plasma protein binding is less than 5%. The volume of distribution for isosorbide mononitrate is about 0.6 l/kg and total clearance around 115 ml/minute. Elimination is primarily by denitration and conjugation in the liver. The metabolites are excreted mainly via the kidneys. Only about 2% of the dose given is excreted intact via the kidneys.
Impaired liver or kidney function has no major influence on the pharmacokinetic properties.
The extent of bioavailability of Imdur is about 90% compared to immediate release tablets. Absorption is not significantly affected by food intake and there is no accumulation during steady state. Imdur exhibits dose proportional kinetics up to 120 mg. After repeated peroral administration with 60 mg once daily, maximal plasma concentration (around 3000 nmol/l) is achieved after around 4 hours. The plasma concentration then gradually falls to under 500 nmol/l at the end of the dosage interval (24 hours after dose intake).
In placebo-controlled studies, Imdur once daily has been shown to effectively control angina pectoris both in terms of exercise capacity and symptoms, and also in reducing signs of myocardial ischaemia. The duration of the effect is at least 12 hours, at this point the plasma concentration is at the same level as at around 1 hour after dose intake (around 1300 mmol/l).
Imdur is effective as monotherapy as well as in combination with chronic beta-blocker therapyand calcium antagonists.
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. Imdur, when administered once daily in the morning, produces a plasma profile of high levels during the day and low levels during the night. With Imdur 60 mg or 120 mg once daily, no development of tolerance with respect to anti-anginal effect has been observed. Rebound phenomenon, between doses as described with intermittent nitrate patch therapy, has not been seen with Imdur.

5.3 Preclinical safety data

The accessible data indicate that isosorbide mononitrate has expected pharmacodynamic properties of an organic nitrate ester, has simple pharmacokinetic properties and is devoid of toxic, mutagenic or oncogenic effects. This indicates that the substance can be used clinically with sufficient safety, and this conclusion is supported by the data from the clinical use of isosorbide mononitrate which has shown that the substance is well tolerated in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium aluminium silicate
Paraffin special
Hyprolose
Magnesium stearate
Colloidal anhydrous silica

Coating layer:
Hypromellose
Macrogol 6000
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Paraffin special

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of 28 tablets contained in an over labelled outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Limited,
Ballymurray,
Co. Roscommon,
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 11th July 2007

10 DATE OF REVISION OF THE TEXT