Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isomonit Retard 60 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60.0 mg isosorbide mononitrate.

Excipient(s) with known effect:
Also contains lactose monohydrate, 25.7mg per tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Round, white, biplane tablet with one-sided score notch and facet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Route of Administration:

Oral.

Recommended Dosage Schedule:

Dosage

Isomonit Retard once daily, to be taken in the morning. The dose may be increased to 120mg 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 may be titrated to minimise the possibility of headache, by initiating treatment with a 30mg dose, for the first two to four days.

Whole Isomonit Retard, 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 Isomonit Retard 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 Isomonit Retard tablets 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 Isomonit Retard has been used in combination with beta-blockers.

The matrix of the tablets 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

Hypersensitivity to the active substance, to nitrates or to any of the excipients listed in section 6.1

Patients treated with Isomonit Retard must not be given Phosphodiesterase Type 5 (PDE-5) inhibitors e.g. sildenafil

Isomonit Retard tablets 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

Isomonit contains lactose monohydrate.
Patients with the rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Isomonit Retard.

Isosorbide mononitrate should be used with caution in patients suffering from hypothyroidism, hypothermia, malnutrition, severe renal or liver disease.

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 30mg dose.

Cardiac and vascular disorders
In cases of recent myocardial infarction or acute heart failure, isosorbide mononitrate should only be used cautiously under strict medical surveillance and/or hemodynamic monitoring. **More severe cases are contraindicated, see section 4.3.**

Other special warnings and precautions with Isosorbide mononitrate:
Hypertrophic obstructive cardiomyopathy, severe cerebral sclerosis.

Treatment discontinuation
When transferring the patient on long-term therapy to another form of medication, isosorbide mononitrate should be gradually withdrawn and overlapping treatment should be started to avoid the risk of angina pectoris.

The safety and efficacy of Isosorbide mononitrate has not been established in children.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a contraindication
Phosphodiesterase Type 5 Inhibitors (e.g. **sildenafil)**

Concomitant administration of isosorbide mononitrate and Phosphodiesterase Type 5 Inhibitors can potentiate the vasodilatory effect of isosorbide mononitrate with the potential results of serious side effects such as syncope or myocardial infarction. Therefore, Isomonit Retard and Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil) must not be given concomitantly.

Interactions to be considered
Some of the effects of alcohol and other vasodilators may be potentiated by this agent.

Antihypertensive drugs
Concurrent intake of other vasodilators, antihypertensives, ACE inhibitors, beta-blockers, calcium antagonists, and diuretics can increase the antihypertensive effect of Isomonit Retard.

Dihydroergotamine
Concurrent administration of isosorbide mononitrate with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitrates and may lead to coronary vasoconstriction.

Non-steroidal anti-inflammatory drugs (NSAIDs)
The possibility that acetylsalicylic acid and NSAIDs might diminish the therapeutic response to isosorbide mononitrate cannot be excluded.

4.6 Fertility, pregnancy and lactation

The safety and efficacy of Isomonit Retard during pregnancy or lactation has not been established.

Isomonit Retard tablets should not be used during pregnancy or lactation unless considered essential by the physician.

Pregnancy
There is a limited amount of data from the use of isosorbide-5-mononitrate in pregnant patients. Limited animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Isosorbide mononitrate should be given to a pregnant woman only if clearly needed and the benefit outweighs the risk.

Breast-feeding
It is not known whether isosorbide mononitrate is secreted in human milk. The benefits for the mother must be weighed against the risks for the child.

Fertility
There is no data available on the effect of isosorbide-5-mononitrate on fertility in humans.

4.7 Effects on ability to drive and use machines

Patients may develop dizziness when first using Isomonit Retard. Patients should be advised to determine how they react to Isomonit Retard 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 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 (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

Cardiac and vascular disorders

Common:	Hypotension, tachycardia

Gastrointestinal disorders

Common:	nausea
Uncommon:	vomiting, diarrhoea

Nervous system disorders
Common: headache, dizziness
Rare: fainting

Skin and subcutaneous tissue disorders
Rare: rash, pruritus

Musculosketal and connective tissue disorders
Very rare: myalgia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via; HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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.

Excessive dosage of all nitrates may, on rare occasions, provoke methemoglobinemia

Management
Overdosage should be treated symptomatically.

Induction of emesis, activated charcoal. In case of pronounced hypotension, the patients 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

ATC CODE: C01D A14
Pharmacotherapeutic group: Vasodilator used in cardiac diseases

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

Isosorbide Mononitrate is a prolonged release formulation. 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 0.6l/kg and total clearance around 115ml/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 isosorbide mononitrate prolonged release tablets is about 90% compared to immediate release tablets. Absorption is not significantly affected by food intake and there is no accumulation during steady state. Isosorbide mononitrate prolonged release tablets exhibits dose proportional kinetics up to 120mg. After repeated peroral administration with 60mg 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, isosorbide mononitrate 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).

Isosorbide mononitrate is effective as monotherapy as well as in combination with chronic beta-blocker therapy and 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 intervals. Isosorbide mononitrate prolonged release tablets, when administered once daily in the morning, produces a plasma profile of high levels during the day and low levels during the night. With isosorbide mononitrate prolonged release tablets 60mg or 120mg 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 isosorbide mononitrate prolonged release tablets.

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 form 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

Lactose monohydrate
Hypromellose
Colloidal anhydrous silica
Povidone 25000

Talc
Microcrystalline cellulose
Calcium hydrogen phosphate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium blister packs.
Pack size: 30 tablets.

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 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Newtown
Bantry
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th December 1998

Date of last renewal: 10th December 2008

10 DATE OF REVISION OF THE TEXT

October 2016