SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Relosorb XL 60mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg of Isosorbide mononitrate.

For excipients see 6.1

3. PHARMACEUTICAL FORM

White tablet with score-line marked 'IM' on one side.
Prolonged release tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Prophylactic treatment of angina pectoris.

4.2 Posology and method of administration

Method of administration: Oral – the tablets must not be chewed or crushed. They should be swallowed whole with a half glass of water.
The lowest effective dose should be used

Adults: Relosorb XL 60mg Tablets (one tablet) once daily given in the morning. The dose may be increased to 120mg (two tablets) daily, both to be taken once daily in the morning. The dose can be titrated to minimise the possibility of headache, by initiating treatment with 30mg (half a tablet) for the first 2-4 days.

Paediatric population: The safety and efficacy of Relosorb XL 60mg tablets in children has not been established.

Elderly: No evidence of a need for routine dosage adjustment in the elderly has been found.

Caution may be needed in those with increased susceptibility to hypotension or marked hepatic or renal insufficiency.

The core of the tablet is insoluble in the digestive juices but disintegrates into small particles when all active substance has been released. Very occasionally the matrix may pass through the gastrointestinal tract without disintegrating and be found visible in the stool, but all active substance has been released.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Constrictive cardiomyopathy and pericarditis, aortic stenosis, cardiac tamponade, mitral stenosis and severe anaemia.

Patients treated with isosorbide mononitrate 60mg Tablets must not be given Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil).

Severe cerebrovascular insufficiency or hypotension are relative contraindications to the use of isosorbide mononitrate 60mg Tablets.

4.4 Special warnings and precautions for use

Isosorbide mononitrate modified release tablets are not indicated for relief of acute anginal attacks: in the event of an acute attack, sublingual or buccal glyceryl trinitrate should be used.

Relosorb XL 60mg tablets contain lactose, and therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

The safety of Relosorb XL 60mg Tablets during pregnancy or lactation has not been established.

4.7 Effects on ability to drive and use machines

Patients may develop dizziness when first using Relosorb XL. Patients should be advised to determine how they react to Isosorbide mononitrate modified release tablets 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 after 1-2 weeks of treatment. The dose can be titrated to minimise the possibility of headache, by initiating treatment with 30mg. 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) and very rare (<1/10,000).

System Organ Class	**Frequency**	**Reaction**
Nervous system disorders	Common	Headache, dizziness
	Rare	Fainting
Cardiac and vascular disorders	Common	Hypotension, tachycardia
Gastrointestinal disorders	Common	Nausea
	Uncommon	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Rare	Rash, pruritus
Musculoskeletal 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms and signs
Pulsing headache. More serious symptoms include 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 fluids should be administered intravenously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiovascular disease (organic nitrates). ATC Code: C01D A.

The principal metabolic 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 dilation resulting in peripheral pooling of blood, decreased venous return and reduction in the 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 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 administered 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 completely absorbed and is not subject to first pass metabolism by 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 have no major influence on the pharmacokinetic properties.

Relosorb XL 60mg Tablets are a prolonged release formulation. The active substance is released independently of pH over a 10-hour period. Compared to

ordinary tablets the absorption phase is prolonged and the duration of effect is extended.

The extent of bioavailability of Relosorb XL 60mg 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. Relosorb XL 60mg Tablets exhibit 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 500nmol/l at the end of the dosage interval (24 hours after dose intake). The tablets are divisible.

In placebo-controlled studies Relosorb XL 60mg 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 nmol/l).

Relosorb XL 60mg Tablets are effective as monotherapy as well as in combination with chronic-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. Relosorb XL 60mg, 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 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 mononitrate.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Magnesium stearate
Hydroxypropylmethylcellulose
Maize Starch

Glyceryl palmitostearate
Lactose monohydrate

6.2. Incompatibilities

None.

6.3. Shelf Life

3 years.

6.4. Special Precautions for Storage

Do not store above 30° C.

6.5. Nature and Contents of Container

Strips (250 µm transparent PVC and 20 µm hard temper aluminium foil, in a carton) containing 7, 14, 28 and 98 tablets.

6.6. Instruction for Use/Handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Relonchem Limited
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Gorsey Lane, Widnes, Cheshire
WA8 0RP, UK

8. MARKETING AUTHORISATION NUMBER

PL 20395/0039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

23rd December 2004

10 DATE OF REVISION OF THE TEXT

20/12/2016