Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isomel SR 60 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Isosorbide mononitrate 60 mg.

Excipients with known effect:
Each tablet contains approximately 98.5 mg/tablet lactose and approximately 43 mg/tablet sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release Tablet
Light yellow, biconvex, oval-shaped, scored on both sides and marked "DX 31" on one side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylactic treatment of angina pectoris.

4.2 Posology and method of administration

Posology
Adults*:*
Isomel SR 60mg Tablets(one tablet) once daily given in the morning. The dose may be increased to 120 mg (two tablets) daily, both to be taken once daily 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 minimize the possibility of headache, by initiating treatment with 30 mg (half tablet) for the first 2-4 days.

Paediatric population
The safety and efficacy of Isomel SR 60mg Tablets in children has not yet 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.

There is a risk of tolerance developing when nitrate therapy is given. For this reason it is important that Isomel SR 60mg tablets are taken once a day to achieve an interval with low nitrate concentration, thereby reducing the risk of tolerance development.

When necessary the product may be used in combination with beta-adrenoreceptor blockers and calcium antagonists. Dose adjustments of either class of agent may be necessary.

Method of administration

Isomel SR 60mg Tablets must not be chewed or crushed. They should be swallowed with half a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Acute myocardial infarction with low filling pressure, head trauma, cerebral haemorrhage, severe hypotension or hypovolaemia
Constrictive cardiomyophaty and pericarditis, aortic stenosis, cardiac temponade, mitral stenosis and severe anaemia.
Patients treated with Isomel SR 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 Isomel SR 60mg Tablets.

4.4 Special warnings and precautions for use

Isomel SR 60mg Tablets is not indicated for relief of accute angina attacks; in the event of accute attack, sublingual or buccal glyceril trinitrate tablets should be used.

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.

Other special warnings and precautions with Isosorbide mononitrate:

Hypoxaemia, Hypothyroidism, Hypothermia, Malnutrition, severe liver or renal disease.

Patients with rare hereditary problems of fructose intolerance or galactose intolerance, total lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Isosorbide mononitrate may act as a physiological antagonist to noradrenaline, acetylcholine, histamine and many other agents. The effect of anti-hypertensive drugs may be enhanced. Alcohol may enhance the hypotensive effects of isosorbide mononitrate.

Concomitant administration of Isomel SR 60mg Tablets and Phosphodiesterase Type 5 Inhibitors can potentiate the vasodilatory effect of Isomel SR 60mg Tablets with the potential result of serious side effects such as syncope or myocardial infacrction. Therefore, Isomel SR 60mg Tablets and Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil) must not be given concomitantly.

4.6 Fertility, pregnancy and lactation

The safety and efficacy of Isosorbide Mononitrate Tablets during pregnancy or lactation
has not been established. Isomel SR 60mg should not be used during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Patients may develop headache or dizziness when first using Isomel SR 60mg Tablets. Patients should be advised to determine how they react to Isomel SR 60mg Tablets before they drive or use 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 minimize 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).

Adverse drug reactions by frequency and system organ class (SOC)

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 side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
or search for MHRA Yellow card in the Google Play or Apple App Store.

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

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. Very large doses may give rise to methaemoglobinaemia (Very rare).

Treatment: In cases of cyanosis as a result of methaemoglobinaemia, methyl thionine (methylene blue) 1-2mg/Kg, slow intravenous delivery.

Management
Induction of emesis, activated charcoal. In case of pronounced hypothension the patient should first be placed in the supine position with legs raised. If necessary fluids should be administrated intravenously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Organic nitrates, ATC code: C01DA A14.

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.

Isosorbide mononitrate is an effective antianginal agent because it improves exertional angina by reducing myocardial oxygen demand, secondary to reduced preload and afterload. Organic nitrates release nitric oxide (NO), which induces protein phosphorylations, finally resulting in vascular smooth muscle relaxation.

In comparison to an immediate release product taken on a multiple dose basis, this prolonged release product has the advantage of both lowering the incidence of tolerance and increasing patient compliance.

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 6.5 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. The active substance is released independently of pH. Compared to ordinary tablets the absorption phase is prolonged and the duration of effect is extended.

The extent of bioavailability of the medicine is about 90% compared to immediate release tablets. Absorption is not significantly affected by food intake and there is no accumulation during steady state. The medicine 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). The tablets are divisible.

In placebo-controlled studies, The medicine 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).

The medicine is effective as monotherapy as well as in combination with chronic β-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. The medicine, when administered once daily in the morning, produces a plasma profile of high levels during the day and low levels during the night. With the medicine 60 mg or 120 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 the medicine.

5.3 Preclinical safety data

Isosorbide mononitrate is a well-established drug for which there is adequate published 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

Hydroxypropyl methylcellulose 2208
Lactose Compressible Sugar (composed of Sucrose and Maltodextrin)
Magnesium stearate
Silica colloidal anhydrous
Ferric oxide yellow E-172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister pack PVDC-or ACLAR-coated-PVC/Aluminium
28, 30 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dexcel Pharma GmbH
Carl-Zeiss-Strasse 2
63755 Alzenau
Germany

8 MARKETING AUTHORISATION NUMBER

PA2261/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 1998

Date of last renewal: 1st September 2007

10 DATE OF REVISION OF THE TEXT

August 2018