

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Isomel SR 60 mg Prolonged-Release Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide mononitrate 60 mg.  
Also includes 98.5 mg/tablet lactose and 42.3 mg/tablet sucrose.  
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-Release Tablet  
Light yellow, biconvex, oval-shaped, prolonged release tablet, scored on both sides and marked “DX 31” on one side.

The tablet can be divided into equal halves.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Isomel SR 60 mg is indicated for the prophylaxis of angina pectoris.

### 4.2 Posology and method of administration

#### Posology

*Adults:* The recommended dose of Isomel SR 60 tablets is one Isomel SR 60 mg tablet once daily to be taken 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, by initiating treatment with 30 mg (half tablet) for the first 2-4 days to minimize the possibility of headache.

Note that isosorbide mononitrate 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 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.

There is a risk of tolerance developing when nitrate therapy is given. For this reason it is important that Isomel SR 60 mg 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

The tablets must not be chewed or crushed. They should be swallowed with half a glass of water.

### 4.3 Contraindications

Hypersensitivity to isosorbide mononitrate, or to any of the excipients listed in section 6.1. Sildenafil has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitrates or nitric oxide donors is therefore contra-indicated.

Isosorbide mononitrate 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 30mg dose.

The safety and efficacy in children has not been established.

Use with extreme caution in hypotension with or without other signs of shock and in cases of cerebrovascular insufficiency.

Other special warnings and precautions with Isosorbide mononitrate:

Significant aortic or mitral valve stenosis.

Hypertrophic obstructive cardiomyopathy.

Anaemia. Hypoxaemia, Hypothyroidism, Hypothermia, Malnutrition, Severe liver or Renal disease.

Isomel SR 60mg is not indicated for relief of acute angina attacks.

Patients with rare hereditary problems of fructose or galactose intolerance, the Lapp 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 isosorbide mononitrate and Phosphodiesterase Type 5 Inhibitors can potentiate the vasodilatory effect of the product 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

Isomel SR 60 mg should not be used during pregnancy and lactation.

## 4.7 Effects on ability to drive and use machines

Patients experiencing headache or dizziness following initial treatment with Isomel SR 60 mg should become stabilised on treatment before driving or using machines.

## 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 long-term treatment.

The following definitions of frequencies are used: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).

### Cardiac and vascular disorders

Common: Hypotension, tachycardia.

### Nervous system disorders

Common: Headache, dizziness.

Rare: Fainting.

### Gastrointestinal disorders

Common: Nausea.

Uncommon: Vomiting, diarrhoea.

### Musculoskeletal and connective tissue disorders

Very rare: Myalgia.

### Skin and subcutaneous tissue disorders

Rare: Rash, pruritus.

## 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: <http://www.hpra.ie/>; E-mail: [medsafety@hpra.ie](mailto: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. Very large doses may give rise to methaemoglobinaemia (Very rare).

*Treatment:* 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, fluid should be administered intravenously. (In cases of cyanosis as a result of methaemoglobinaemia, methyl thionine (methylene blue) 1-2mg/Kg, slow intravenous delivery). Expert advice should be sought.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Organic nitrates, ATC code: C01D A14

Isosorbide mononitrate is an organic nitrate, the major active metabolite of isosorbide dinitrate and an active vasodilator in its own right. The mechanism of action of isosorbide mononitrate, like other organic nitrates, is believed to involve peripheral vasodilation, both venous and arterial. Maximal venous dilatation is usually achieved with lower doses of the nitrate, while higher doses cause progressive dilatation of the arterial vasculature. Nitrates thus lead to pooling of blood in the veins and reduced left ventricular and diastolic pressure. As arterial vascular resistance is also decreased, arterial blood pressure is reduced. 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 after oral administration. The absorption is not affected by simultaneous food intake. Contrary to many other nitrates, Isosorbide mononitrate is not subject to first pass metabolism and its oral bioavailability is therefore close to 100%. This feature probably contributes to the relatively small intersubject variability in plasma levels that are achieved following ingestion of the drug. Peak plasma concentrations of Isosorbide mononitrate after oral ingestion of a prolonged release tablet usually occur within 3.1-4.5 hours. Isosorbide mononitrate's volume of distribution is about 0.6 litres/kg, and its plasma protein binding is negligible (about 4%). Isosorbide mononitrate is metabolised to form several inactive compounds. Elimination is primarily by denitration and conjugation in the liver. The metabolites are excreted mainly via the kidneys. About 2% of the dose is excreted intact via the kidneys. The half-life of Isosorbide mononitrate in the plasma of healthy volunteers as well as in most patients is about 6.5 hours after administration of prolonged release tablets. Neither renal nor hepatic disease influence the pharmacokinetic of isosorbide mononitrate. Isomel SR 60 mg is a prolonged release formulation. The active substance is released independently of pH.

## 5.3 Preclinical safety data

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Hypromellose 2208  
Lactose monohydrate  
Compressible sugar (composed of Sucrose and Maltodextrin)  
Magnesium stearate  
Colloidal anhydrous silica  
Iron oxide yellow

## 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 Ltd.  
7 Sopwith Way  
Drayton Fields  
Daventry  
Northamptonshire NN11 8PB  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER**

PA 895/1/1

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 14<sup>th</sup> August 1998

Date of last renewal: 1<sup>st</sup> September 2007

**10 DATE OF REVISION OF THE TEXT**

August 2014