SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ISIB 60 XL Prolonged Release Tablets
XISMOX 60 XL Prolonged Release Tablets
TARDISC XL 60 Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Isosorbide mononitrate 60 mg
Excipients with a known effect:
Each tablets contains approximately 98.5 mg of lactose
Each tablet contains approximately 43 mg of sucrose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged Release Tablets
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

The recommeded dose is one 60 mg 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 30mg (half a tablet) for the first 2-4 days.

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.

Paediatric population
The safety and efficacy of this medicine 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 the 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 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 the medicine must not be given Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil).
Severe cerebrovascular insufficiency or hypotension are relative contraindications to the use of the medicine.

4.4 Special warnings and precautions for use
The medicine is not indicated for relief of accute angina attacks; in the event of accute attack, sublingual or buccal glyceryl 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.

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
The tablets are not indicated for relief of acute angina attacks.

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 the tablets and Phosphodiesterase Type 5 Inhibitors can potentiate the vasodilatory effect of the tablets with the potential result of serious side effects such as syncope or myocardial infarction. Therefore, this medicine 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. The tablets 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 the tablets. Patients should be advised to determine how they react to the 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
Skin and subcutaneous tissue disorders	Rare	Rash, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Myalgia

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medical product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

In case of cyanosis as a result of methaemoglobinaemia, methyl thionine (methylene blue) 1-2mg/Kg, slow intravenous delivery). Expert advice should be sought.

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: C01D A14.

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.

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 completely absorbed and is not subject to first pass metabolism by the liver and its oral bioavailability is therefore close to 100%. 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 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 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). The tablets are divisible. 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**.** Neither renal nor hepatic disease influence the pharmacokinetic of isosorbide mononitrate.

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 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 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 monohydrate
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 Clear or Opaque PVC/ACLAR/PVC and Aluminium
and
Blister pack PVC/PE/PVDC and 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
UK

8. MARKETING AUTHORISATION NUMBER

PL 14017/0096

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/09/2010

10 DATE OF REVISION OF THE TEXT

29/12/2017