Isodur 50XL Capsules

Summary of Product Characteristics Updated 09-Apr-2024 | Galen Limited

▼ 1. Name of the medicinal product

Isodur 50XL Capsules

▼ 2. Qualitative and quantitative composition

Isosorbide-5-mononitrate 50mg per capsule.

Excipient(s) with known effect

Not more than 112mg of sucrose per capsule.

For the full list of excipients, see section 6.1.

▼ 3. Pharmaceutical form

Hard prolonged-release capsule.

Hard gelatin capsule (size 3) with a brown cap and a red body; the cap is marked in white ink with " ISM 50" .

▼ 4. Clinical particulars

▼ 4.1 Therapeutic indications

For the prophylactic treatment of angina pectoris.

Isodur 50XL Capsules are indicated in adults, including the elderly.

▼ 4.2 Posology and method of administration

Posology

Adults:

One capsule (50mg) once daily, to be taken in the morning. For patients with higher nitrate requirements, the dose may be increased to two capsules if required. The lowest effective dose should be used.

Attenuation of effect has occurred in some patients being treated with prolonged-release preparations. In such patients intermittent therapy may be more appropriate (see section 4.4).

Treatment with Isodur 50XL Capsules, as with any other nitrate, should not be stopped suddenly. Both dosage and frequency should be tapered gradually (see section 4.4).

Elderly population:

There is no evidence of a need for routine dosage adjustment in the elderly, but special care may be needed in those with increased susceptibility to hypotension.

Paediatric population:

This product is not recommended for use in children. The safety and efficacy of these capsules in children has not yet been established.

Method of administration

For oral use.

The capsules must be swallowed whole and can be taken with water. They must not be chewed or crushed (see section 5.2).

▼ 4.3 Contraindications

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

This product should not be used in cases of acute myocardial infarction with low filling pressure, acute circulatory failure, shock, vascular collapse or very low blood pressure, hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, cardiac tamponade, low cardiac filling pressures and aortic/mitral valve stenosis.

This product should not be used in patients with a known sensitivity to nitrates, marked anaemia, diseases associated with a raised intracranial pressure e.g. following a head trauma and including a cerebral haemorrhage.

This product should not be used in patients with closed angle glaucoma, severe hypotension or severe hypovolaemia. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) have been shown to potentiate the hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contraindicated (see sections 4.4 and 4.5).

During nitrate therapy, the soluble guanylate cyclase stimulator riociguat must not be used (see section 4.5).

▼ 4.4 Special warnings and precautions for use

The capsules should be used with caution in patients who have a recent history of myocardial infarction or low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure). Reducing systolic blood pressure below 90 mmHg must be avoided.

This product should be used with caution in patients who are predisposed to closed angle glaucoma, or who are suffering from hypothyroidism, hypothermia, malnutrition or severe liver or renal disease. Symptoms of circulatory collapse may arise after the first dose, particularly in patients with labile circulation. A headache may occur at the start of treatment, but this usually disappears with continued treatment.

This product may give rise to symptoms of postural hypotension and syncope in some patients. Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol.

Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina.

This product is not indicated for the relief of acute angina attacks. In the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets/sprays should be used instead.

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

If the capsules are not taken as indicated (see section 4.2) tolerance to the medication could develop. In some patients being treated with prolonged-release preparations, attenuation of effect is observed. In such patients, intermittent therapy may be more appropriate. The lowest effective dose should be used.

Treatment with Isodur 50XL Capsules, as with any other nitrate, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually (see section 4.2).

In patients with decreased gastrointestinal transit time, a decrease in release of the active ingredient may occur.

Patients on maintenance treatment with this product should be informed that they must not use phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil).

Isodur 50XL Capsules therapy should not be interrupted to take phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil), because the risk of inducing an attack of angina pectoris could increase by doing so (see sections 4.3 and 4.5).

▼ 4.5 Interaction with other medicinal products and other forms of interaction

Hypotensive agents e.g beta-blockers, calcium channel blockers, vasodilators, alprostadil, aldesleukin, angiotensin II receptor antagonists etc may potentiate the hypotensive effect of isosorbide-5-mononitrate. This may also occur with alcohol, neuroleptics and tricyclic antidepressants.

The hypotensive effects of nitrates are potentiated by concurrent administration of phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) (see sections 4.3 and 4.4). This might lead to life threatening cardiovascular complications. Patients who are on Isodur 50XL Capsules therapy therefore must not use phosphodiesterase type-5 inhibitors.

Reports suggest that concomitant administration of isosorbide-5-mononitrate may increase the blood level of dihydroergotamine and its hypertensive effect.

Sapropterin (Tetrahydrobiopterin, BH4) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterin-containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glyceryl trinitrate (GTN)), isosorbide dinitrate (ISDN), isosorbide-5-mononitrate (ISMN) and others).

The use of isosorbide-5-mononitrate with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (see section 4.3) since concomitant use can cause hypotension.

▼ 4.6 Fertility, pregnancy and lactation

Pregnancy

Nitrates have been used widely in the treatment of angina for many years without apparent ill consequence and animal studies have shown no hazard. However, safety in human pregnancy has not been established. This drug should therefore not be used in pregnancy and lactation unless considered essential by the physician.

Breast-feeding

It is unknown whether nitrates are excreted in human milk and therefore caution should be exercised when administered to nursing women.

Fertility

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

▼ 4.7 Effects on ability to drive and use machines

Symptoms such as dizziness, tiredness or blurred vision have been reported at the start of treatment with isosorbide-5-mononitrate. Patients should be advised that if affected, they should not drive or operate machinery. This effect may be increased by alcohol.

▼ 4.8 Undesirable effects

Undesirable effects frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10,000 <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

During the administration of Isodur 50XL Capsules the following undesirable effects may be observed:

Nervous system disorders	
Very common	Headache
Common	Dizziness (including dizziness postural), somnolence
Cardiac disorders	
Common	Tachycardia
Uncommon	Angina pectoris aggravated
Not known	Palpitations
Vascular disorders	
Common	Postural hypotension
Uncommon	Circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope)
Not known	Hypotension
Gastrointestinal disorders	
Uncommon	Nausea, vomiting
Very rare	Heartburn
Not known	Abdominal discomfort
Skin and subcutaneous tissue disorders	
Uncommon	Allergic skin reactions (e.g. rash), flushing
Not known	Dermatitis exfoliative
Immune system disorders	
Not known	Angioedema

General disorders and administration site conditions	
Common	Asthenia
Not known	Fatigue

Headache may be minimised by starting with the lower dose and gradually increasing the dose.

Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration.

Temporary hypoxaemia may occur during treatment with isosorbide-5-mononitrate due to a relative redistribution of blood flow in hypoventilated alveolar areas. This may lead to myocardial hypoxia, particularly in patients with coronary artery disease.

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 website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

▼ 4.9 Overdose

Animal experience:

In rats and mice, significant lethality at oral doses of 1965 mg/kg and 2581 mg/kg, respectively, was observed.

Human experience:

Symptoms:

• Fall of blood pressure ≤ 90 mmHg

• Paleness

• Sweating

• Weak pulse

• Tachycardia

• Light-headedness on standing

• Headache

• Weakness

• Dizziness

• Nausea

• Vomiting

• Diarrhoea

Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During isosorbide-5-mononitrate biotransformation nitrite ions are released, which may induce methaemoglobinaemia and cyanosis with subsequent tachypnoea, anxiety, loss of consciousness and cardiac arrest. It cannot be excluded that an overdose of isosorbide-5-mononitrate may cause this adverse reaction.

In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

General procedure:

• Stop intake of the drug

• General procedures in the event of nitrate-related hypotension

- Patients should be kept horizontal with the head lowered and legs raised

- Supply oxygen

- Expand plasma volume (i.v. fluids)

- Specific treatment for shock (admit patient to intensive care unit)

Special procedure:

• Raising the blood pressure if the blood pressure is very low

• Treatment of methaemoglobinaemia

- To include reduction therapy with methylene-blue, administration of oxygen, initiation of artificial ventilation and haemodialysis, as necessary

• Resuscitation measures

In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

▼ 5. Pharmacological properties

▼ 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: CARDIAC THERAPY; organic nitrates.

ATC code: C01DA14

Organic nitrates (including GTN, ISDN and ISMN) are potent relaxers of smooth muscle. They have a powerful effect on vascular smooth muscle with less effect on bronchiolar, gastrointestinal, ureteral and uterine smooth muscle. Low concentrations dilate both arteries and veins.

Venous dilation pools blood in the periphery leading to a decrease in venous return, central blood volume, and ventricular filling volumes and pressures.

Cardiac output may remain unchanged, or it may decline as a result of the decrease in venous return. Arterial blood pressure usually declines secondary to a decrease in cardiac output or arteriolar vasodilation, or both. A modest reflex increase in heart rate results from the decrease in arterial blood pressure. Nitrates can dilate epicardial coronary arteries including atherosclerotic stenoses.

The cellular mechanism of nitrate-induced smooth muscle relaxation has become apparent in recent years. Nitrates enter the smooth muscle cell and are cleaved to inorganic nitrate and eventually to nitric oxide. This cleavage requires the presence of sulphydryl groups, which apparently come from the amino acid cysteine. Nitric oxide undergoes further reduction to nitrosothiol by further interaction with sulphydryl groups. Nitrosothiol activates guanylate cyclase in the vascular smooth muscle cells, thereby generating cyclic guanosine monophosphate (cGMP). It is this latter compound, cGMP, that produces smooth muscle relaxation by accelerating the release of calcium from these cells.

▼ 5.2 Pharmacokinetic properties

The rationale for the product is based on the drug reaching relatively high plasma concentrations (≈ 500ng.ml^{-1}) rapidly, sustaining the concentration for a period of 12-16 hours, then concentrations falling to give relatively low drug concentration for the remaining period before the next dose. This profile is achieved by the use of immediate and prolonged-release drug within the formulation, which is then taken once a day.

Absorption

Isosorbide-5-mononitrate is readily absorbed from the gastro-intestinal tract, and absorption is essentially complete with bioavailability approaching 100%. The rate of absorption is slowed by food but overall bioavailability is unchanged.

Distribution

The determination of volume of distribution suggests that isosorbide-5-mononitrate is distributed in a volume which approximates to that of total body water.

Biotransformation

Isosorbide-5-mononitrate does not undergo first-pass hepatic metabolism. Metabolism occurs primarily in the liver by denitration to isosorbide and by glucuronidation in the kidney and the liver to the 2-glucuronide.

Elimination

ISMN is metabolised to inactive metabolites with a half life of approximately 7 hours. Only 2% of ISMN is excreted unchanged in the urine. An elimination half life of about 4-5 hours has been reported.

▼ 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology,

repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

▼ 6. Pharmaceutical particulars

▼ 6.1 List of excipients

Sucrose

Maize starch

Sugar spheres

Shellac

Povidone

Ethylcellulose

Talc

Capsule Shell Constituents:

Gelatin

Titanium dioxide (E171)

Yellow iron oxide (E172)

Red iron oxide (E172)

Black iron oxide (E172)

Erythrosine (E127)

Printing Ink Constituents:

Shellac

Propylene glycol

Strong ammonia solution

Povidone

Sodium hydroxide

Potassium hydroxide

Titanium dioxide (E171)

▼ 6.2 Incompatibilities

Not applicable.

▼ 6.3 Shelf life

36 months.

▼ 6.4 Special precautions for storage

Store below 25° C.

▼ 6.5 Nature and contents of container

Calendar/Blister packs comprising of heat sealable PVC/PVdC and aluminium. Each pack consists of 28 capsules.

▼ 6.6 Special precautions for disposal and other handling

No special requirements.

▼ 7. Marketing authorisation holder

Galen Limited

Seagoe Industrial Estate

Craigavon

BT63 5UA

UK.

▼ 8. Marketing authorisation number(s)

PL 27827/0022.

▼ 9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 15 January 1999

Date of latest renewal: 07 October 2005

▼ 10. Date of revision of the text

20 March 2024

Company Contact Details

Galen Limited

Address

Seagoe Industrial Estate, Craigavon, BT63 5UA, UK

Medical Information e-mail

customer.services@galen-pharma.com

Telephone

+44 (0)28 3833 4974

WWW

www.galen-pharma.com