SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Isosorbide Mononitrate Tablets 10 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of Isosorbide Mononitrate. Also contains lactose. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet for oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:
- In the prophylactic management of angina pectoris.
- As an adjunctive treatment in the management of severe acute or chronic congestive cardiac failure not responding to cardiac glycosides and/or diuretics.

4.2 Posology and method of administration

Posology:
It is recommended that the tablets should be swallowed whole with a little fluid after meals. Dosage should be reduced in patients with renal or hepatic impairment.

Adults (including elderly):
Angina: Usually 20mg, two or three times daily. Patients already accustomed to prophylactic nitrate therapy may normally be transferred directly to a therapeutic dose of isosorbide mononitrate. For patients not already receiving prophylactic nitrate therapy, it is recommended that the initial dosage should be 10mg twice daily. The maintenance dose in individual patients is usually between 20-120mg daily in divided doses. The lowest effective dose should be used.

Congestive cardiac failure: In severe congestive cardiac failure doses of 20mg, two or three times daily may be employed depending on individual requirements. The optimum dosage is best determined by continuous haemodynamic monitoring. The use of isosorbide mononitrate tablets in severe congestive cardiac failure should be regarded as an adjunctive therapy to more conventional treatment (eg cardiac glycosides, diuretics).
**Elderly:** Dosage requirements may be reduced especially when hepatic or renal function is impaired. Also, particular care should be taken due to susceptibility to hypotension.

**Children:** Not recommended. The safety and efficacy of Isosorbide Mononitrate Tablets has yet to be established in children.

Treatment with Isosorbide Mononitrate Tablets, as with any other nitrates, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually (see section 4.4)

**Method of Administration:** For oral administration

### 4.3 Contraindications

- Acute myocardial infarction with low filling pressure, acute circulatory failure (shock, vascular collapse) or very low blood pressure, constrictive pericarditis, cardiac tamponade, low cardiac filling pressures, aortic/mitral valve stenosis and diseases associated with a raised intra-cranial pressure e.g. following a head trauma and including cerebral haemorrhage
- The product should not be given to patients with a known sensitivity to nitrates (Isosorbide Mononitrate or dinitrate), to other nitrates or to any other excipients.
- The product should not be used in patients with severe anaemia, severe hypotension, closed angle glaucoma or hypovolemia.
- Angina caused by hypertrophic obstructive cardiomyopathy.
- Phosphodiesterase type -5 inhibitors (eg sildenafil, tadalafil or vardenafil) has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitrates or nitric oxide donors is therefore contra-indicated (see section 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

- Isosorbide Mononitrate may give rise to postural hypotension and syncope.
- Alcohol should be avoided as some of the effects of alcohol may be potentiated by this compound (drug reduction capacity may be reduced). Severe postural hypotension with light headedness and dizziness is frequently observed after the consumption of alcohol
- Symptoms of circulatory collapse may arise after the first dose in patients with labile circulation and patients already taking ACE inhibitors.
- Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina.
- The product should be used with caution in patients who have a recent history of myocardial infarction, 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. Patients who are pre-disposed to closed-angle glaucoma and in patients suffering from hypothyroidism, hypothermia, malnutrition, severe liver or renal disease.
• In the event of an acute angina attack, sublingual treatment such as a GTN spray or tablet should be used instead of isosorbide mononitrate tablets.
• If the tablets are not taken as indicated (see section 4.2) tolerance and cross tolerance to other nitrate may occur.
• This product contains lactose. Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose, which are very rare hereditary problems, should not take this medicine.
• Treatment with isosorbide mononitrate tablets, as with any other nitrate, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually (see section 4.2).
• Patients who undergo a maintenance treatment with Isosorbide Mononitrate Tablets should be informed that they must not use phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil).
• Isosorbide Mononitrate Tablets 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

• Nitrates can act as physiological antagonists to noradrenaline, acetylcholine and histamine and other agents.
• The hypotensive effects of nitrates are potentiated by concurrent administration of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel blockers, vasodilators, alprostadil, aldesleukin, angiotensin II receptor antagonist, ACE inhibitors etc. This may also occur with neuroleptics and tricyclic antidepressants.
• The hypotensive effects of nitrates are potentiated by concurrent administration of phosphodiesterase type-5 inhibitors (eg sildenafil, tadalafil and verdenafil) which are used for erectile dysfunction (see special warnings and contraindications). This might lead to life threatening cardiovascular complications. Patients who are on Isosorbide Mononitrate Tablets therapy therefore must not use phosphodiesterase type-5 inhibitors.
• Alcohol can accentuate cerebral ischaemia associated with postural hypotension.
• Beta-blocking drugs have a different pharmacological action in angina and may have a complimentary effect when co-administered with Isosorbide Mononitrate.
• Reports suggest that concomitant administration of Isosorbide Mononitrate Tablets may increase the blood level of dihydroergotamine and its hypertensive effect.
• Saproterine (Tetrahydropterine, BH4) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of saproterine-containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glycercyl trinitrate (GTN), isosorbide dinitrate (ISDN), isosorbide 5-mononitrate (5-ISMN) and others).
• The use of isosorbide 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
The product should not be used in pregnancy or by nursing mothers unless considered essential by the physician and the possible benefits of treatment outweigh the potential risks to the foetus.

**Pregnancy:**
There is inadequate evidence of safety of the drug in human pregnancy but nitrates have been used widely in the treatment of angina for many years without apparent ill consequence; animal studies have shown no hazards.

**Breastfeeding:**
It is not known whether nitrates are excreted in human milk and therefore caution should be exercised when administered to nursing women.

### 4.7 Effects on ability to drive and use machines

- Isosorbide mononitrate may, owing to side effects (e.g. dizziness, tiredness or blurred vision) at the start of treatment, affect the ability to drive and operate machines. The patients should therefore be advised that if affected, they should not drive or operate machinery.
- This action is potentiated by intake of alcohol.

### 4.8 Undesirable effects

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

During administration of Isosorbide Mononitrate Tablets 10 the following undesirable effects may be observed:

**Nervous system disorders:**
Very common: headache. Headaches may occur as a side effect and usually subside after a few days. Nitrate headache may be relieved by simple analgesics. In majority of patients, nitrate headache diminishes or disappears after 1-3 weeks and optimum dosage of Isosorbide Mononitrate may be achieved.
Common: dizziness (including dizziness postural), somnolence.

**Cardiac disorders:**
Common: tachycardia and paroxysmal bradycardia
Uncommon: angina pectoris aggravated.

**Vascular disorders:**
Common: orthostatic hypotension.
At the start of therapy or when the dosage is increased, hypotension and/or light headedness in the upright position are observed. These symptoms may be associated with cutaneous vasodilatation with flushing, dizziness, drowsiness, reflex tachycardia and occasionally unexplained bradycardia, a feeling of weakness and other signs of cerebral ischemia.
Uncommon: circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope).
Not known: hypotension.

Gastrointestinal disorders:
Uncommon: nausea, vomiting,
Very rare: heartburn most likely due to a nitrate induced sphincter relaxation.

Skin and subcutaneous tissue disorders:
Uncommon: allergic skin reactions (e.g. rash), flushing
Not known: dermatitis exfoliative.

Immune system disorders:
Not known: angioedema

Endocrine disorders:
Not known: Nitrate induced pituitary apoplexy has been reported in patients with undiagnosed pituitary tumours.

General disorders and administration site conditions:
Common: asthenia.
Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration.

During treatment with Isosorbide Mononitrate Tablets, a temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas. Particularly in patients with coronary artery disease, this may lead to a myocardial hypoxia.

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:
- Pulsing headache, excitation, restlessness, flushing, warm flushed skin, blurred vision, cold perspiration, sweating, nausea, vomiting, vertigo, syncope, tachycardia and a fall in blood pressure.
- A rise in intracranial pressure with confusion and neurological deficits can sometimes occur. Methaemoglobinemia (cyanosis, hypoxaemia, restlessness, respiratory depression, convulsions, cardiac arrhythmias, circulatory failure, raised intracranial pressure) occurs rarely.

Treatment:
- Induction of emesis, consider oral activated charcoal if ingestion of a potentially toxic amount has occurred within 1 hour. Observe for at least 12 hours after the overdose. Monitor blood pressure and pulse.
Gastric lavage is indicated in severe cases, otherwise treatment is symptomatic. Further measures to support the circulation are recommended e.g., elevating the legs and/or treatment with hypertensive agents. If methaemoglobinaemia (symptoms or > 30% methaemoglobin), IV administration of methylene blue 1-2 mg/kg body weight. If therapy fails with second dose after 1 hour or contraindicated, consider red blood cell concentrates or exchange transfusion. In case of cerebral convulsions, diazepam or clonazepam IV, or if therapy fails, phenobarbital, phenytoin or propofol anaesthesia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C01D A14 Vasodilators used in cardiovascular diseases.

- Vasodilator producing vasodilation by action on vascular smooth muscle reducing venous return and improving myocardial perfusion with a reduction of work performed by the heart and hence oxygen demand.
- Isosorbide 5-mononitrate is an active metabolite of isosorbide dinitrate and from an oral dose exerts qualitatively similar effects. However, unlike the dinitrate which is subject to considerable hepatic first-pass metabolism, it has virtually complete systemic availability from an oral dose hence it achieves predictable and sustained blood levels. Onset of pharmacological effects occurs within 20 minutes of an oral dose and is maintained for more than 8 hours.

5.2 Pharmacokinetic Properties:
- Absorption: Absorption is rapid and extensive with peak blood levels of approximately 400 micrograms / litre achieved within 30 minutes to one hour of oral administration of a 20mg dose. C_{max} is dose proportional with peak levels of approximately 200 micrograms / litre achieved within 30 minutes to one hour of oral administration of a 10 mg dose.
- Mean Elimination Half Life: 4.9 hours.
- Absolute Systemic Availability: 100% - indicating no first pass metabolism.
- Volume of Distribution: 48 litres – indicating distribution mainly in total body water.
- Systemic Clearance: 0.13 litres / minutes
- Metabolism: Metabolism is via denitration to Isosorbide and glucuronide conjugation.
- Excretion: 2% of Isosorbide Mononitrate excreted unchanged through urine.

5.3 Preclinical Safety Data

Isosorbide-5-mononitrate is a well documented long established ingredient and toxicological data have therefore not been included.

6 PHARMACEUTICAL PARTICULARS
6.1 List of Excipients

- Lactose Anhydrous Ph. Eur.
- Magnesium Stearate Ph. Eur.
- Colloidal Silicon dioxide USNF

6.2 Incompatibilities

None known

6.3 Shelf Life

Three years

6.4 Special Precautions for Storage

The product should be stored below 25°C, in a dry place.

6.5 Nature and contents of container

- Blister composed of 250 micron medical grade PVC film, sealed onto 20 micron hard tempered aluminium foil.
- Opaque plastic containers composed of polypropylene tubs, fitted with polyethylene made tamper- evident closures.
- In pack sizes of 28, 30, 56, 60 and 100 tablets.
- Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

Pharmavit Ltd
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8. MARKETING AUTHORIZATION NUMBER
PL 04556/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/01/2009

10 DATE OF REVISION OF THE TEXT

04/02/2016