

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Isosorbide Mononitrate 10 mg Tablets

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains diluted isosorbide mononitrate equivalent to isosorbide mononitrate 10 mg.

Excipient(s) with known effect:

Each tablet contains 32.25mg lactose monohydrate.

For the full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Tablet

Isosorbide mononitrate 10 mg Tablets are white to off white circular, biconvex uncoated tablets debossed with 'I' and '10' separated by break line on one side and plain on other side.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

For the prophylaxis and long term management of angina pectoris.

#### **4.2 Posology and method of administration**

For oral administration

Tablet should be swallowed whole with water.

Isosorbide mononitrate 10 mg Tablets: one tablet twice daily, or three times daily

Adults:

One tablet to be taken asymmetrically (to allow a nitrate low period) two or three times a day. The dosage may be increased up to 120mg per day.

Dosage regime should be designed according to the clinical response of the patient.

Tablets should be taken after meals, unchewed with water.

The lowest effective dose should be used.

In patients taking one tablet twice daily the second dose should be taken 8 hours after the first dosage. If the dose is one tablet three times daily, take one every 6 hours and ensure 12 hours treatment-free interval every 24 hours..

*Paediatric population:* The safety and efficacy of Isosorbide Mononitrate 10mg Tablets in children has not been established.

Elderly There is no evidence to suggest that an adjustment of the dosage is necessary.

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 4.4)

Method of administration

For oral administration

### **4.3 Contraindications**

Isosorbide mononitrate tablets should not be given to patients with a known sensitivity to isosorbide mononitrate, the listed ingredients or other nitrates.

Isosorbide mononitrate tablets should not be used in cases of acute myocardial infarction with low filling pressures, acute circulatory failure (shock, vascular collapse), or very low blood pressure (systolic blood pressure below 90 mmHg), hypertrophic obstructive cardiomyopathy (HOCM), 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.

Isosorbide mononitrate Tablets should not be used in patients with severe anaemia, severe hypotension, closed angle glaucoma or severe hypovolaemia.

Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil and 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 section 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**

Isosorbide mononitrate Tablets should be used with caution in patients who are suffering from hypothyroidism, hypothermia, malnutrition and severe liver or renal disease.

Isosorbide 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), or orthostatic dysfunction. Reducing systolic blood-pressure below 90 mmHg must be avoided.

Symptoms of circulatory collapse may arise after first dose, particularly in patients with labile circulation.

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.

Isosorbide mononitrate Tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

In the event of an acute angina attack, a sublingual treatment such as a GTN spray or tablet should be used instead of Isosorbide mononitrate Tablets. The onset of action of Isosorbide mononitrate Tablets is not sufficiently rapid to be useful to treat an acute anginal attack.

If the tablets are not taken as indicated (see section 4.2), tolerance to the medication could develop. The lowest effective dose should be used.

Treatment with Isosorbide mononitrate, 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 who undergo a maintenance treatment with Isosorbide mononitrate should be informed that they must not use phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil).

Isosorbide mononitrate 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 section 4.3 & 4.5).

#### Hypoxaemia

Caution should be exercised in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure.

As a potent vasodilator, isosorbide mononitrate could result in increased perfusion of poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen. During treatment with isosorbide mononitrate alcohol should be avoided as it may potentiate the hypotensive effect of isosorbide mononitrate (see section 4.5).

### **4.5 Interaction with other medicinal products and other forms of interaction**

Concurrent administration of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel blockers, vasodilators, alprostadil, aldesleukin, angiotensin II receptor antagonists etc. and/or alcohol may potentiate the hypotensive effects of Isosorbide mononitrate Tablets. This may occur with neuroleptics and tricyclic antidepressants.

The concurrent intake of ISMN with ACE-inhibitors or arterial vasodilators could be a desirable interaction, unless the antihypertensive effects are excessive in which case consider reducing the dose of one or both drugs.

Any blood pressure lowering effect of Isosorbide mononitrate tablets will be increased if used together with phosphodiesterase type-5- inhibitors, which are used for erectile dysfunction (see special warning and contraindications). This may lead to life threatening cardiovascular complications. Patients who are on Isosorbide mononitrate therapy therefore must not use phosphodiesterase type-5 inhibitors. (e.g. sildenafil, tadalafil, vardenafil).

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

Reports suggest that concomitant administration of Isosorbide mononitrate tablets may increase the blood levels of dihydroergotamine and its hypertensive effects.

Sapropterine (Tetrahydrobiopterine, BH<sub>4</sub>) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterine-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 (5-ISMN) and others).

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Safety in pregnancy has not been established for isosorbide mononitrate. There is data that nitrates are excreted in breast milk and may cause methemoglobinemia in infants.

Therefore Isosorbide mononitrate tablets should only be used in pregnancy and during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the hazards.

##### Breast-feeding

The extent of excretion of isosorbide mononitrate in human breast milk has not been determined. Therefore caution should be exercised when administered to nursing women.

##### Fertility

There is no data available on the effect of isosorbide mononitrate on fertility in humans.

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

Dizziness, tiredness or blurred vision might occur at the start of the treatment.

The patient should therefore be advised that if affected, they should not drive or operate machinery. This effect may be increased by alcohol.

#### **4.8 Undesirable effects**

Frequency categories are defined according to the following convention:

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  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

During administration of Isosorbide Mononitrate Tablets 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

Vascular disorders:

- common: orthostatic hypotension
- uncommon: circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope)
- not known: hypotension

Gastrointestinal disorders:

- uncommon: nausea, vomiting
- very rare: heartburn

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.

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 Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or by searching 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  $\leq 90$  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 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 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
  - Reduction therapy of choice with vitamin C, methylene-blue or toluidine-blue
  - Administer oxygen (if necessary)
  - Initiate artificial ventilation
  - Hemodialysis (if necessary)
- Resuscitation measures

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

ATC code: C01D A14 Vasodilator used in cardiac diseases

Isosorbide mononitrate is an organic nitrate, which, in common with other cardioactive nitrates, is a vasodilator. It produces decreased left and right ventricular end-diastolic pressures to a greater extent than the decrease in systemic arterial pressure, thereby reducing after load and especially the preload of the heart.

Isosorbide mononitrate influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions by selective dilation of large epicardial vessels.

It reduces the requirements of the myocardium for oxygen by increasing venous capacitance, causing a pooling of blood in peripheral veins, thereby reducing ventricular volume and heart wall distension.

Mechanism of action:

Like all organic nitrates, isosorbide mononitrate acts as a donor of nitric oxide (NO). NO causes a relaxation of vascular smooth muscle via the stimulation of guanylyl cyclase and the subsequent increase of intracellular cyclic guanosine monophosphate (cGMP) concentration. A cGMP-dependent protein kinase is thus stimulated, with resultant alteration of the phosphorylation of various proteins in the smooth muscle cell. This eventually leads to the dephosphorylation of the light chain of myosin and the lowering of smooth muscle tone.

### **5.2 Pharmacokinetic properties**

Isosorbide-5-mononitrate is rapidly absorbed and peak plasma levels occur approx. 1 hour following oral dosing.

Isosorbide-5-mononitrate is completely bioavailable after oral doses and is not subject to pre-systemic elimination processes.

Isosorbide-5-mononitrate is eliminated from the plasma with a half-life of about 5.1 hours. It is metabolised to Isosorbide-5-mn-2-glucuronide, which has a half-life of approximately 2.5 hours. As well as being excreted unchanged in the urine.



After multiple oral dosing plasma concentrations are similar to those that can be predicted from single dose kinetic parameters.

**Characteristics in patients:**

Evidence was provided that the plasma profiles in healthy volunteers and patients suffering from chronic stable angina are similar.

Isosorbide mononitrate is dialysable.

### **5.3 Preclinical safety data**

**Acute toxicity:**

Studies on acute toxicity in mice and rats with different routes of administration indicate a low acute toxicity (LD50 oral approximately 2,000 - 2,500 mg/kg b.w.).

**Chronic toxicity:**

Long term toxicity has been tested in rats for 78 weeks and in dogs for 52 weeks. First toxic reactions occurred in dosages of 90 mg/kg (dog) and 405 mg/kg (rat), respectively. Thus taking into account the recommended dosage of 20 to 30 mg/d in humans, the therapeutic index can be stated as high.

**Reproduction studies:**

These studies included a fertility and breeding study over two generations in rats; teratology studies in rats and rabbits; and a rat peri-postnatal study. The dosage levels used were generally high and produced maternal toxic effects at the highest dose. No teratogenic effects of isosorbide mononitrate were observed.

**Mutagenicity:**

Isosorbide mononitrate was tested in different studies both in vitro and in vivo (Ames test, Human peripheral lymphocytes, Bone marrow of rats and hamsters, V 79 test, SCE test) on possible mutagenic effects. As all tests were negative the mutagenic risk in humans is considered low.

**Carcinogenicity:**

Neither the long term toxicity studies in rats and dogs nor a special carcinogenicity study, performed in rats over 125 weeks (males) and 138 weeks (females), indicated neoplastic properties of isosorbide mononitrate. Therefore, it can be concluded that the carcinogenic risk in humans is low.

## **6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Microcrystalline cellulose (E460),  
Lactose monohydrate,  
Colloidal silicon dioxide (E551),  
Talc  
Stearic acid

**6.2 Incompatibilities**

Not Applicable.

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Child resistant Aluminium-PVC blister pack of 56s tablets.

**6.6 Special precautions for disposal**

Not Applicable.

**7 MARKETING AUTHORISATION HOLDER**

Flamingo Pharma UK Ltd.  
1<sup>st</sup> floor, Kirkland House,  
11-15 Peterborough Road,  
Harrow, Middlesex,  
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**8 MARKETING AUTHORISATION NUMBER(S)**

PL 43461/0014

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

15/06/2017

**10 DATE OF REVISION OF THE TEXT**

06/11/2018