SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ETIMONIS XL 50 mg Capsules
ZIOTAN XL 50 mg Capsules
IMO LA 50 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide Mononitrate 50 mg
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsules, hard
White capsules containing prolonged release microgranules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prophylaxis of angina pectoris.

4.2 Posology and method of administration

For oral administration

Posology

Adults:
One capsule to be taken in the morning. For patients with higher nitrate requirements the dose may be increased to two capsules taken simultaneously. The lowest effective dose should be used. The dose can be titrated to minimise the possibility of headache by initiating treatment with half a tablet (25 mg) for the first two to four days.
The tablets should not be chewed or crushed and should be swallowed with half a glass of fluid.
**Children:**
Safety and efficacy in children have not been established.

**Elderly:**
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 or marked hepatic or renal insufficiency.

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 IMO LA, as with any other nitrate, should not be stopped suddenly; abrupt discontinuation of therapy may lead to exacerbation of symptoms. When discontinuing long-term treatment both dosage and frequency should be tapered gradually (see section 4.4).

**4.3 Contraindications**

Isosorbide Mononitrate should not be used in patients with 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, aortic/mitral valve stenosis and diseases associated with a raised intra-cranial pressure e.g. following a head trauma and including cerebral haemorrhage.

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

IMO LA should not be used in patients with marked anaemia, closed angle glaucoma, severe cerebrovascular insufficiency severe hypotension or 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 4.5 Interaction with other medicinal products and other forms of interaction)

**4.4 Special warnings and precautions for use**

The lowest effective dose should be used.

Isosorbide Mononitrate should be used with caution in patients who have a recent history of myocardial infarction or who are suffering from hypothyroidism, hypothermia, malnutrition, and severe liver or renal disease.
Symptoms of circulatory collapse may arise after first dose, particularly in patients with labile circulation.

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

Isosorbide Mononitrate is not suitable for relief of acute angina attacks. In the event of an acute attack, sublingual or buccal glyceryl trinitrate (GTN) tablets/sprays should be used.

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.

IMO LA capsules contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption.

If the capsules are not taken as directed (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 of IMO LA, as with any other nitrate, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually (see section 4.2).

The administration of isosorbide mononitrate causes a decrease of effective renal plasma flow (eRPF) in cirrhotic patients and should be used with caution.

Oral nitrates should also be used with caution in patients with angina due to other causes, or pre-existing hyperdynamic conditions.

Since oral nitrates can cause venous dilatation, they should not be used in patients with increased intracranial pressure.

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 effect of IMO LA. This may also occur with neuroleptics and tricyclic antidepressants.

Any blood pressure lowering effect of IMO LA will be increased, if used together with phosphodiesterase type-5 inhibitors, which are used for erectile dysfunction (see section 4.3 Contraindications). This might lead to life-threatening cardiovascular complications. Patients who are on IMO LA therapy therefore must not use phosphodiesterase type-5 inhibitors.

Reports suggest that concomitant administration of IMO LA may increase the
blood level of dihydroergotamine and its hypertensive effect. Alcohol can attenuate cerebral ischaemia associated with postural hypotension. Isosorbide mononitrate can act as a physiological antagonist to noradrenaline, acetylcholine and histamine.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety and efficacy of isosorbide mononitrate tablets during pregnancy in humans has not been established. Animal studies have shown reproductive toxicity (see section 5.3). Isosorbide mononitrate should only be used in pregnancy if, in the opinion of the physician, the possible benefits of treatment outweigh the hazards.

Lactation
The safety and efficacy of isosorbide mononitrate during lactation has not been established. It is not known whether nitrates are excreted in human milk and therefore caution should be exercised when administered to nursing mothers. This product should therefore not be used during lactation unless considered essential by the physician and unless possible benefits outweigh the possible hazards.

4.7 Effects on ability to drive and use machines

Since postural hypotension with symptoms such as dizziness, tiredness or blurred vision have been reported at the start of the treatment patients should be advised to be careful when driving or operating machinery if they suffer from these symptoms. This effect may be increased by alcohol.

4.8 Undesirable effects

Most of the adverse reactions are pharmacodynamically mediated and dose dependent.

Nervous system disorders:
A very common (10% of patients) adverse reaction to IMO LA is throbbing headache. This may occur at the onset of treatment but may be minimised by commencing with low doses and gradually increasing the dose. The incidence of headache diminishes after 1-2 week of treatment. Restlessness, somnolence, pituitary haemorrhage

Immune system disorders:
Allergic dermatitis, exfoliative dermatitis
Vascular disorders:
At the start of therapy or when the dosage is increased, hypotension and/or light-headedness in the upright position (orthostatic hypotension) are commonly observed (i.e. in 1-10% of patients). These symptoms may be associated with flushing dizziness, drowsiness, reflex tachycardia and a feeling of weakness. Severe hypotensive responses have been reported for organic nitrates and including nausea, vomiting, restlessness pallor and excessive perspiration. Uncommonly collapse may occur (sometimes accompanied by bradyarrhythmia, bradycardia and syncope). Uncommonly severe hypotension may lead to enhanced angina pectoris symptoms.

Respiratory, thoracic and mediastinal disorders:
Hypoxia

Gastrointestinal disorders:
Uncommon (i.e. in less than 1% of patients): nausea and vomiting
A few reports of heartburn most likely due to a nitrate-induced sphincter relaxation have been reported.
Not known: diarrhoea

Skin and subcutaneous tissue disorders:
Hyperhidrosis, pruritus and allergic skin reaction (e.g. rash) may occur, sometimes severely. In single cases exfoliative dermatitis may occur.

Musculoskeletal and connective tissue disorders:
Myalgia

General disorders and administrative site conditions:
Asthenia
Cardiac disorders:
Tachycardia and paroxysmal bradycardia have been reported- these symptoms generally disappear during long-term treatment.

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).

4.9 Overdose

Symptoms and signs:
Headache hypotension, nausea, vomiting, sweating, tachycardia, vertigo, warm flushed skin, blurred vision, excitation, cold perspiration and syncope. A rise in intracranial pressure with confusion and neurological deficits can sometimes occur. Methemoglobinemia (cyanosis, hypoxaemia, restlessness, respiratory depression, convulsions, change in mental status, cardiac arrhythmias, circulatory failure,
raised intracranial pressure) occurs rarely.

**Management:**
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. Correct hypotension by raising the foot of the bed and/or by expanding the intravascular volume. Other measures as indicated by the patient’s clinical condition. If severe hypotension persists despite the above measures consider the use of inotropes.

If Methemoglobinaemia occurs (symptoms or >30% methaemoglobin) treat with supplemental oxygen or IV administration of methylene blue 1-2mg/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.

**5.1 Pharmacodynamic properties**

ATC Code: C01D A14 Vasodilator used in cardiac diseases

**Mechanism of action**
Isosorbide Mononitrate is an organic nitrate, which, in common with other cardioactive nitrates, is a vasodilator. Nitrate compounds relax smooth muscle causing dilatation of the veins and arteries. It produces decreased left and right ventricular end-diastolic pressures to a greater extent than the decrease in systemic arterial pressure. The result is a very marked reduction of after load and especially preload of the heart. 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.

Isosorbide mononitrate influences the oxygen supply to the 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 requirement 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. Venous dilatation 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 vasodilatation, 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.

**Pharmacodynamic effects**
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 sulphhydryl groups, which apparently come from the amino acid cysteine. Nitric oxide undergoes further reduction to nitrosothiol by further interaction with sulphhydryl 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

Absorption
Isosorbide Mononitrate is a vasodilator and is absorbed from the gastro-intestinal tract completely and rapidly following oral administration.

Distribution
This product has all the pharmacokinetic characteristics of a true modified release dosage form. Compared with an immediate-release dosage form, the bioavailability is approximately 84 (±7)%. There is no effect of food on bioavailability.
The capsules are formulated to release 30% of the dose immediately and 70% of the dose is released slowly.
Time to peak plasma levels (T_max) is 5.0 (±3) hours; with a half-life (T½) of 5.02 (±0.68) hours.
Following oral administration of conventional tablets, peak plasma levels are reached in about 1 hour. Unlike isosorbide dinitrate, isosorbide mononitrate does not undergo first pass hepatic metabolism and bioavailability is 100%. Isosorbide mononitrate has a volume of distribution of about 40 litres and is not significantly protein bound.

Elimination
Isosorbide mononitrate is extensively metabolised to nitric oxide (NO-which is the active ingredient) and isosorbide (inactive). In patients with cirrhotic disease or cardiac failure or renal failure, parameters were similar to those obtained in healthy volunteers. Only 20% of isosorbide mononitrate is excreted unchanged in the urine. An elimination half-life of about 4-5 hours has been reported.

5.3 Preclinical safety data

High concentrations of isosorbide mononitrate in rats is associated with prolonged gestation and parturition, stillbirths and deaths.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents:
Lactose monohydrate,
Sucrose and maize starch microgranules
Bleached dewaxed shellac,
Dewaxed shellac,
Copolymer of methacrylic acid and methyl methacrylate (1:1),
Copolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride (1:2:0.1),
Talc,
Ethanol 96 %. (ND*)

Capsule shell:
Gelatin
- Titanium dioxide (E 171)

Black ink:
Shellac, propylene glycol, ammonium hydroxide, potassium hydroxide, black iron oxide (E 172)

*Not detected in the finished product

6.2 Incompatibilities
None Known.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Blister packs (20 µm aluminium/250 µm PVC) – boxed in cardboard cartons containing 28, 30, 56 or 60 capsules. Sample blister pack of 8 capsules.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited,
Ballymurray,
Co.Roscommon,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 30464/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/06/2002 / 17/03/2009

10 DATE OF REVISION OF THE TEXT

24/04/2017