# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Zemon 40 XL

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide-5-mononitrate 40 mg
International non-proprietary name (INN): Isosorbide mononitrate.

Excipients with known effect: Each tablet contains 25.46mg of lactose.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablets (prolonged release)

Round, cream coloured tablets, marked ‘IM40’ on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prophylactic treatment of angina pectoris.

### 4.2 Posology and method of administration

**Posology**

*Adults:* One tablet (40mg) once daily given in the morning. The dose may be increased to two tablets (80mg), the whole dose to be given together (dose range 30mg to 120mg.) The dose can be titrated to minimize the possibility of headache by initiating treatment with lesser dose for the first two to four days.

*Paediatric population:* The safety and efficacy of Zemon 40 XL prolonged release tablets has not been established.

*Elderly:* No 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.

The lowest effective dose should be used.

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

As with other drugs for the treatment of angina pectoris, therapy should not be discontinued suddenly, as may lead to exacerbation of symptoms. Both the dosage and frequency should be tapered gradually over several days and the patient carefully monitored (see section 4.4).

**Method of administration**

The tablets should not be chewed or crushed and should be swallowed with half a glass of fluid.

## 4.3 Contraindications

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

Severe cerebrovascular insufficiency.

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).

Zemon 40XL 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, hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, cardiac tamponade, aortic/mitral valve stenosis, hypovolaemia, closed-angle glaucoma, severe anaemia, conditions associated with a raised intra-cranial pressure e.g. following a head trauma and including cerebral haemorrhage.

Concomitant use with the soluble guanylate cyclase stimulator, riociguat, can cause hypotension and is contraindicated (see section 4.5).

## 4.4 Special warnings and precautions for use

Zemon 40 XL tablets are not indicated for relief of acute anginal attacks. In the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets should be used.

Caution should be exercised in patients suffering from hypothyroidism, malnutrition, severe renal or hepatic impairment, hypothermia and recent history of myocardial infarction.

The lowest effective dose should be used.

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

Therapy should not be discontinued suddenly. Both the dosage and frequency should be tapered gradually (see section 4.2).

The administration of isosorbide mononitrate causes a decrease of ERPF (Effective Renal Plasma Flow) in cirrhotic patients and should be used with caution.

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

Severe postural hypotension with light-headedness and dizziness is frequently observed after concomitant consumption of alcohol.

Zemon 40XL tablets contain lactose and therefore patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

The hypotensive effects of nitrate are potentiated by concurrent administration of phosphodiesterase type-5 inhibitors (e.g. sildenafil) (see section 4.3). This might lead to life threatening cardiovascular complications.
Any medication which may cause hypotension may have its hypotensive

effects potentiated by concurrent administration of Zemon 40XL ( beta-blockers, ACE-inhibitors, alcohol, vasodilators (hydralazine), alprostadil, aldesleukin, angiotensin II receptor antagonists, calcium channel blockers, antihypertensives and diuretics).

Reports suggest that concomitant administration of Isosorbide Mononitratemay increase the blood level of dihydroergotamine and its hypertensive effect

Concomitant use with the soluble guanylate cyclase stimulator, riociguat, can cause hypotension and is contraindicated (see section 4.3).

## 4.6 Fertility, Pregnancy and lactation

Pregnancy

No data have been reported which would indicate the possibility of adverse effects resulting from the use of isosorbide mononitrate in pregnancy. The safety

and efficacy of Zemon 40 XL prolonged release tablets during pregnancy 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 possible hazards.

Breast-feeding

The safety and efficacy of Zemon 40 XL modified release tablets 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 women. Isosorbide mononitrate should only be used during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the possible hazards.

## 4.7 Effects on ability to drive and use machines

The patient should be warned not to drive or operate machinery if hypotension, dizziness, tiredness or blurred vision occurs.

These effects may be increased by alcohol.

## 4.8 Undesirable effects

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

Headache is very common (>10% pf patients). Throbbing headache may occur when treatment is initiated, but usually disappears after 1-2 weeks of treatment.

Hypotension including postural hypotension with symptoms such as dizziness, nausea and fatigue has occasionally been reported. Infrequently, flushing and allergic reaction (including rashes) can occur. These symptoms usually disappear during long-term treatment.

Cases of exfoliative dermatitis have been reported.

Drowsiness, diarrhoea or vomiting may occur.

Severe hypotensive responses have been reported for organic nitrates and include 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 symptoms.

There have been isolated reports of myalgia.

Dizziness, nausea, tachycardia and paroxysmal bradycardia have been reported.

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.go.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Treatment should be symptomatic. The main symptom is likely to be hypotension.

Symptoms:

Headache, excitation, cold perspiration, vertigo,nausea, vomiting, restlessness, warm flushed skin, blurred vision, fainting, tachycardia, hypotension and palpitations.A rise in intracranial pressure with confusion and neurological deficits can sometimes occur.

Methaemoglobinaemia (cyanosis, hypoxaemia, changes in mental status, respiratory depression, convulsions, cardiac arrhythmias, circulatory failure, raised intracranial pressure).

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 (intravenous fluids should be administered and ionotropes considered). Other measures as indicated by the patient's clinical condition.

If methaemoglobinaemia occurs treat with supplemental oxygen and methylene blue. In cases not responding to methylene blue or where methylene blue is contraindicated, consider exchange transfusion or red blood cell concentrates. In case of cerebral convulsions, consider diazepam or clonazepam IV or, if therapy fails, phenobarbital, phenytoin or propofol anaesthesia.

If severe hypotension persists despite the above measures consider use of inotropes such as dopamine or dobutamine.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Vasodilators used in Cardiac Diseases/Organic Nitrates

ATC-Code:G04BD

Mechanism of action

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 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 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

Absorption:

Isosorbide-5-mononitrate is readily absorbed from the gastro-intestinal tract.
Distribution:

Following oral administration of conventional tablets, peak plasma levels are reached in about 1 hour. Unlike isosorbide dinitrate, ISMN does not undergo first-pass hepatic metabolism and bioavailability is 100%. ISMN has a volume of distribution of about 40 litres and is not significantly protein bound.

Metabolism:

ISMN is metabolised to inactive metabolites including isosorbide and isosorbide glucuronide.

Elimination:

The pharmacokinetics are unaffected by the presence of heart failure, renal or hepatic insufficiency. Only 20% 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

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

Stearic acid

Carnauba wax

Hydroxypropylmethylcellulose

Lactose

Magnesium stearate

Talc

Silica colloidal anhydrous

Polyethylene glycol 4000

Titanium dioxide (E171)

Yellow iron oxide (E172)

### 6.2 Incompatibilities

None known

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

### 6.5 Nature and contents of container

The tablets are packed in blisters which consist of 250µm PVC with a 25µm PVdC coating which is sealed to 25µm aluminium foil coated with 20µm PVdC sealing lacquer.

Packs sizes: 28,30, 56, 60 and 100 tablets

### 6.6 Special precautions for disposal

Not applicable

## 7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited,
2nd Floor
Connect 38
1 Dover Plac,
Ashford, Kent
England,
TN23 1FB.

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 51463/0028

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

25/02/2009

## 10 DATE OF REVISION OF THE TEXT

17/01/2023