ELANTAN LONG™
ISOSORBIDE MONONITRATE


NAME OF THE MEDICINAL PRODUCT

Isosorbide mononitrate, 50 mg, prolonged release capsule

QUALITATIVE AND QUANTITATIVE COMPOSITION

Prolonged release capsule

Each 50 mg, prolonged release capsule contains 50 mg isosorbide mononitrate.

Excipients

Prolonged release capsule

Sugar spheres (corn starch and sucrose), lactose monohydrate, poly_(O-ethyl) cellulose, talc, hydroxypropylcellulose, polyethylene glycol 20 000. The capsule cap and the capsule body contain: gelatine, titanium dioxide (E 171), iron oxide red (E 172), iron oxide black (E 172)

PHARMACEUTICAL FORM

Elantan Long is formulated to release 30 % of the active substance immediately (initial dose) and the remaining 70 % of the active principle in sustained release formulation.

Prolonged release capsule

50mg

Hard gelatine capsules, size 3 with a brown, opaque capsule cap and flesh opaque capsule body

CLINICAL INFORMATION

Indications

For the treatment of:
• long-term treatment of coronary heart disease;
• prevention of angina pectoris
• post-treatment of myocardial infarction with persisting angina symptoms
• long-term treatment of chronic congestive heart failure in combination with cardiac glycosides, diuretics

**Dosage and Administration**

All dosage forms should be swallowed whole with water.
The lowest effective dose should be used.

**Route of Administration**

For oral use

**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.

**Children**

The safety and efficacy of isosorbide mononitrate has yet to be established in children.

**Elderly**

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

**Renal and Hepatic impairment**

Isosorbide mononitrate should be used with caution in patients with severe liver disease or severe renal disease.

**Contraindications**

Isosorbide mononitrate is contraindicated in:

• known hypersensitivity to the active substance, to any of the excipients, or to other nitrates,
• acute myocardial infarction with low filling pressure,
• acute circulatory failure (shock, vascular collapse),
• very low blood pressure,
• hypertrophic obstructive cardiomyopathy (HOCM),
• constrictive pericarditis,
• cardiac tamponade,
• low cardiac filling pressures,
• aortic/mitral valve stenosis,
• diseases associated with a raised intra-cranial pressure e.g. following a head trauma and including cerebral haemorrhage,
• marked anaemia,
• closed angle glaucoma,
• 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 Interactions).

**Warnings and Precautions**

*Concomitant diseases*
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.

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

*Postural hypotension and syncope*
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.

*Paradoxical bradycardia and angina*
Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina (see Section Adverse Reactions).

*Acute angina attack*
In the event of an acute angina attack, a sublingual treatment such as a glycerine trinitrate (GTN) spray or tablet should be used instead of isosorbide mononitrate.
Tolerance to the medication

If isosorbide mononitrate is not taken as indicated (see Section Dosage and Administration) 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.

Gradually withdrawn

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 Dosage and Administration).

Lactose

This medicine contains lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Sucrose

Due to the presence of sucrose (prolonged release capsules 25 mg, 50 mg), patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interactions

Blood pressure lowering drugs

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 isosorbide mononitrate. This may also occur with neuroleptics and tricyclic antidepressants.

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

Dihydroergotamine

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

Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

Isosorbide mononitrate should only be used in pregnancy if, in the opinion of the physician, the possible benefits outweigh the possible hazards.

No data have been reported which would indicate the possibility of adverse effects resulting from the use of isosorbide mononitrate in pregnancy. Safety in pregnancy, however, has not been established.

Lactation

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

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

Ability to perform tasks that require judgement, motor or cognitive skills

Dizziness, tiredness or blurred vision might occur at the start of treatment. The patient should therefore be advised that if affected, they should not drive or operate machinery. This effect may be increased by alcohol.
Adverse Reactions

Clinical Trial Data and Post Marketing Data

Adverse reactions are ranked under headings of frequency using the following convention:

Very common \( \geq 1/10 \)
Common \( \geq 1/100 \) to \( <1/10 \)
Uncommon \( \geq 1/1000 \) to \( <1/100 \)
Rare \( \geq 1/10000 \) to \( <1/1000 \)
Very rare \( <1/10000 \)
Not known (cannot be estimated from the available data).

Nervous system disorders

Very common: throbbing headache (the incidence of headache diminishes gradually with time and continued use)
Common: light headedness in the upright position, dizziness, drowsiness
Not known: dizziness, drowsiness

Cardiac disorders

Not known: reflex tachycardia, tachycardia, paroxysmal bradycardia

Vascular disorders

Common: hypotension in the upright position
Uncommon: flushing
Not known: collapse (sometimes accompanied by bradyarrhythmia and syncope), severe hypotension that may lead to enhanced angina symptoms

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

Gastrointestinal disorders

Uncommon: nausea, vomiting
Not known: heartburn (most likely due to a nitrate-induced sphincter relaxation)

Skin and subcutaneous tissue disorders

Uncommon: allergic skin reaction (e.g. rash)
Not known: exfoliative dermatitis

General disorders and administration site conditions

Not known: feeling of weakness
**Overdosage**

**Symptoms and signs**

Headache, hypotension, nausea, vomiting, sweating, tachycardia, vertigo, restlessness, warm flushed skin, blurred vision and syncope. A rise in intracranial pressure with confusion and neurological deficits can sometimes occur. Methaemoglobinaemia (cyanosis, hypoxaemia, restlessness, respiratory depression, convulsions, cardiac arrhythmias, circulatory failure, raised intracranial pressure) occurs rarely.

**Treatment**

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 use of inotropes.

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.

**Clinical Pharmacology**

**Pharmacodynamics**

**Pharmacotherapeutic group**

Vasodilatators used in cardiac diseases

**ATC Code**

C 01 DA 14

**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.

**Pharmacodynamic effects**

Isosorbide mononitrate causes a relaxation of vascular smooth muscle thereby inducing a vasodilatation.

Both, peripheral arteries and veins are relaxed by isosorbide mononitrate. The latter effect promotes venous pooling of blood and decreases venous return to the heart, thereby reducing ventricular end-diastolic pressure and volume (preload).

The action on arterial, and at higher dosages arteriolar vessels, reduces the systemic vascular resistance (afterload). This in turn reduces the cardiac work.

The effects on both preload and afterload lead subsequently to a reduced oxygen consumption of the heart.

Furthermore, isosorbide mononitrate causes redistribution of blood flow to the subendocardial regions of the heart when the coronary circulation is partially occluded by arteriosclerotic lesions. This latter effect is likely to be due to a selective dilation of large coronary vessels. Nitrate-induced dilation of collateral arteries can improve the perfusion of poststenotic myocardium. Nitrates also dilate eccentric stenoses as they can counteract possible constricting factors acting on the residual arch of compliant smooth muscle at the site of the coronary narrowing. Furthermore, coronary spasms can be relaxed by nitrates.

Nitrates were shown to improve resting and exercise haemodynamics in patients suffering from congestive heart failure. In this beneficial effect several mechanisms including an improvement of valvular regurgitation (due to the lessening of ventricular dilatation) and the reduction of myocardial oxygen demand are involved.

By decreasing the oxygen demand and increasing the oxygen supply, the area of myocardial damage is reduced. Therefore, isosorbide mononitrate may be useful in selected patients who have had a myocardial infarction. Effects on other organ systems include a relaxation of the bronchial muscle, the muscles of the gastrointestinal, the biliary and the urinary tract. Relaxation of the uterine smooth muscles is reported as well.
Pharmacokinetics

_Prolonged release capsules_

**Absorption**
Isosorbide mononitrate is rapidly and completely absorbed after oral administration. After intake of isosorbide mononitrate 20 mg or 40 mg the bioavailability is 90–100 %. The bioavailability of the slow release preparations is 80–90 % compared to an immediate release tablet. Food does not significantly affect absorption.

**Distribution**
The apparent volume of distribution is about 50 l, implying that isosorbide mononitrate is distributed mainly in total body water. 

$C_{\text{max}}$ for tablets 20 mg or 40 mg is seen about one hour after administration. Prolonged release capsules 50 mg contain pellets formulated to release 30 % of the dose immediately, whilst 70 % of the dose is released slowly.

**Metabolism**
Isosorbide mononitrate is extensively metabolised to NO and isosorbide; while the first is the active agent, the latter is inactive.

**Elimination**
Elimination half-life was determined to be between 4 and 5 hours.

**Special patient populations**

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

Isosorbide mononitrate is dialysable.

**Clinical Studies**
Not relevant for this product.

**NON-CLINICAL INFORMATION**
Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, oncogenicity and toxicity to reproduction.
PHARMACEUTICAL INFORMATION

Shelf-Life
As registered locally.

Storage
Do not store above 25°C.

Nature and Contents of Container
Elantan Long™ is blister packed in cartons of 20 capsules.

Incompatibilities
There are no relevant data available.

Use and Handling
There are no special requirements for use or handling of this product.

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