1. NAME OF THE MEDICINAL PRODUCT

Elantan 40 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of isosorbide mononitrate.

Excipients with known effect: lactose monohydrate 131.7mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Elantan 40 mg tablets: white, round tablet, flat with bevelled edge, score and engraving (E/40) on the upper side and rounded on the lower side.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For the prophylaxis and long term management of angina pectoris.
As adjunctive therapy after acute myocardial infarction and chronic congestive heart failure.

4.2. Posology and method of administration

Posology

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 120 mg per day.
Dosage regime should be designed according to the clinical response of the patient.
Tablets should be taken after meals, unchewed with a little fluid.
The lowest effective dose should be used.
In patients taking Elantan twice daily, the second dose should be taken 8 hours after the 1st 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.

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

Paediatric population
The safety and efficacy of Elantan has yet to be established in children.

Treatment with Elantan, 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

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

Elantan should not be used in cases of acute myocardial infarction with low filling pressure, 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.

Elantan 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

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.

Elantan 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.

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

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

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

<u>Elantan 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.</u>

In the event of an acute angina attack, a sublingual treatment such as a GTN spray or tablet should be used instead of Elantan tablets. The onset of action of Elantan 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 Elantan, 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 Elantan should be informed that they must not use phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil).

Elantan 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, ACE-inhibitors, monoamine oxidase inhibitors, angiotensin II receptor antagonists etc. and/or alcohol may potentiate the hypotensive effect of Elantan. This may also 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 Elantan will be increased if used together with phosphodiesterase type-5 inhibitors which are used for erectile dysfunction (see4.3 and 4.4). This might lead to life threatening cardiovascular complications. Patients who are on Elantan 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 Elantan may increase the blood level of dihydroergotamine and its hypertensive effect.

Sapropterine (Tetrahydrobiopterine, BH4) 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 Elantan 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 treatment. If affected, do not drive or operate machinery. This effect may be increased by alcohol.

4.8. Undesirable effects

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

During administration of Elantan 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 Elantan, 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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL-Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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 ≤ 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

Pharmacotherapeutic group: Vasodilators used in cardiac diseases, ATC Code: CO1DA14 –

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 afterload 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 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.

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

Lactose monohydrate
Talc
Colloidal anhydrous silica
Potato starch
Microcrystalline cellulose
Aluminium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

5 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Cartons of blister strips of PP/aluminium or of PP/PP.
Aluminium foil thickness 16 µm or 20 µm.
Pack sizes: 28, 30, 50, 56, 60, 84, 90 and 100 tablets

Not all pack sizes may be marketed.

6.6. Special precautions for the disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merus Labs Luxco II S.à.R.L.
26-28, rue Edward Steichen
L-2540 Luxembourg

8. MARKETING AUTHORISATION NUMBER

PA2118/002/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd August 1983
Date of latest renewal: 2nd August 2008

10. DATE OF REVISION OF THE TEXT

December 2017