

# Isosorbide-5-Mononitrate

Elantan<sup>®</sup>

## Oral Preparations

### PRODUCT DESCRIPTION

Each tablet of Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>20*) contains 20 mg of Isosorbide-5-Mononitrate.

Each tablet of Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>40*) contains 40 mg of Isosorbide-5-Mononitrate.

Each sustained-release capsule of Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>*) contains 50 mg of Isosorbide-5-Mononitrate.

Each scored capsule- shaped tablet of Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>*) contains 60 mg of Isosorbide-5-Mononitrate.

### PHARMACOLOGIC PROPERTIES

#### Pharmacodynamics

##### *Mechanism of Action*

Like all organic nitrates, Isosorbide-5-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-5-Mononitrate causes a relaxation of vascular smooth muscle thereby inducing a vasodilatation.

Both, peripheral arteries and veins are relaxed by Isosorbide-5-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, reduce 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-5-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-5-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

##### *Tablets*

##### *Absorption*

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.

##### *Metabolism*

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.

##### *Elimination*

Isosorbide-5-mononitrate is eliminated from the plasma with a half-life of about 5.1 hours.

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

##### *Sustained release capsule*

##### *Absorption*

Isosorbide-5-Mononitrate is rapidly and completely absorbed after oral administration. After intake of Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>*) 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 50L, implying that Isosorbide-5-Mononitrate is distributed mainly in total body water.

C<sub>max</sub> for Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>*) 20 mg or 40 mg tablet is seen about one hour after administration.

Isosorbide-5-Mononitrate (*Elantan<sup>®</sup>*) sustained release capsule contain pellets formulated to release 30 % of the dose immediately, whilst 70% of the dose is released slowly.

##### *Metabolism*

Isosorbide-5-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 h.

#### Special Patient Population

##### *Other Patient Characteristics*

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

Isosorbide-5-Mononitrate is dialyzable.

### Preclinical Safety Data

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

Studies on acute toxicity in mice and rats with different routes of administration indicate a low acute toxicity (LD<sub>50</sub> 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-5-Mononitrate were observed.

**Mutagenicity:** Isosorbide-5-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-5-Mononitrate. Therefore, it can be concluded that the carcinogenic risk in humans is low.

### INDICATIONS

For the treatment of:

- long-term treatment of coronary artery disease
- long-term treatment and prevention of angina pectoris (including post myocardial infarction)

*The following indication is specific for Isosorbide-5-Mononitrate (Elantan®) 50 mg sustained release capsule:*

- long-term treatment of congestive heart failure in combination with digitalis and/or diuretics

### DOSAGE AND ADMINISTRATION

All dosage forms should be swallowed whole with water.

The lowest effective dose should be used.

**Isosorbide-5-Mononitrate (Elantan®) 20 mg and 40 mg tablet:** One tablet to be taken at regular time intervals (to allow a nitrate low period) two or three times a day.

For patients not already receiving prophylactic nitrate therapy it is recommended that the initial dose be one tablet of Isosorbide-5-Mononitrate (Elantan®) twice a day.

The dosage may be increased up to 120 mg per day.

**Isosorbide-5-Mononitrate (Elantan®) 50 mg sustained release capsule:** One capsule to be taken in the morning.

For patients with higher nitrate requirements the dose may be increased to two capsules taken simultaneously.

**Isosorbide-5-Mononitrate (Elantan®) 60 mg extended release tablet:** The recommended starting dose is 30 mg (given as a single 30 mg tablet or ½ of 60 mg tablet) or 60 mg (given as a single tablet) once daily.

#### Children

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

#### Elderly

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

#### Renal and Hepatic impairment

Isosorbide-5-Mononitrate (Elantan®) should be used with caution in patients with severe liver disease or severe renal disease.

### CONTRAINDICATIONS

Isosorbide-5-Mononitrate (Elantan®) is contraindicated in:

- known hypersensitivity to the active substance, to any of the excipients, or to other nitrates or nitrites
- acute myocardial infarction with low filling pressure
- low cardiac filling pressures
- aortic/mitral valve stenosis
- hypertrophic obstructive cardiomyopathy (HOCM)
- constrictive pericarditis
- cardiac tamponade
- Acute circulatory failure (shock, vascular collapse)
- very low blood pressure
- 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 *Drug Interactions*).

### WARNINGS AND PRECAUTIONS

#### Concomitant disease

Isosorbide-5-Mononitrate (Elantan®) 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 *Adverse Effects*).

#### *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-5-Mononitrate (*Elantan*<sup>®</sup>).

#### *Tolerance to the medication*

If Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>) is not taken as indicated (see *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-5-Mononitrate (*Elantan*<sup>®</sup>), as with any other nitrate, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually (see *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 in Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>), patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

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

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.

## **DRUG 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-5-Mononitrate (*Elantan*<sup>®</sup>). 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 *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-5-Mononitrate (*Elantan*<sup>®</sup>) may increase the blood level of dihydroergotamine and its hypertensive effect.

## **PREGNANCY AND LACTATION**

### **Fertility**

There are no relevant data available.

### **Pregnancy**

Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>) 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-5-Mononitrate (*Elantan*<sup>®</sup>) 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.

## **ADVERSE EFFECTS**

### **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

*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 AND TREATMENT

### Symptoms and signs

Headache, hypotension, nausea, vomiting, sweating, tachycardia, vertigo, 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.

## STORAGE CONDITIONS

Store at temperatures not exceeding 25°C.

## AVAILABILITY

\*Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>20) 20 mg tablet: 10 tablets per blister (box of 50's)

\*Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>40) 40 mg tablet: 10 tablets per blister (box of 50's)

\*Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>) 50 mg sustained-release capsule: 10 capsules per blister (box of 20's)

\*\* Isosorbide-5-Mononitrate (*Elantan*<sup>®</sup>) 60 mg extended-release tablet: bottle of 100 tablets

## CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Keep all medicines out of reach of children.

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NCDS. Isosorbide Mononitrate.

Version #: 02      Revision Date: 26 May 2014



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PH/ELA/0002/15

August 2015

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