IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1151/078/002
Case No: 2069197

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Elantan LA 25, 25 --Unknown--

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/08/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Elantan LA 25 mg Prolonged Release Capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release hard capsule contains 25 mg isosorbide mononitrate.
Excipients: contains lactose monohydrate and sucrose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard.
Product imported from the UK.
Hard gelatin capsule with brown capsule cap and white body, containing white to off-white pellets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the prophylaxis of angina pectoris

4.2 Posology and method of administration

For oral administration

Adults
One capsule to be taken in the morning.
For patients with higher nitrate requirement, the dose may be increased to two capsules taken simultaneously. The lowest effective dose should be used.

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

Children
The safety and efficacy of Elantan LA 25 has yet to be established in children.
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 Elantan LA 25, as with any other nitrate, should not be stopped suddenly. Both dosage and frequency should be tapered gradually (see section 4.4).

4.3 Contraindications

Elantan LA 25 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, 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 a cerebral haemorrhage.
This product should not be given to patients with a known sensitivity to Isosorbide mononitrate, the listed ingredients or other nitrates.

Elantan LA 25 should not be used in patients with marked anaemia, severe hypotension, closed angle glaucoma or hypovolaemia.
Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tardenafil 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).

4.4 Special warnings and precautions for use

The capsules should be used with caution in patients who have a recent history of myocardial infarction or who are suffering from hypothyroidism, hypothermia, malnutrition, severe liver or severe renal disease.
Symptoms of circulatory collapse may arise after first dose, particularly in patients with labile circulation.
This product may give rise to postural hypotension and syncope in some patients. Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol.
Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina.
Elantan LA 25 capsules 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.
Elantan LA 25 capsules also contain sucrose and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
In the event of an acute angina attack, a sublingual treatment such as a GTN spray or tablet should be used instead of Elantan LA 25 capsules.
If these capsules are not taken as indicated (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 Elantan LA 25, as with any other nitrate, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually (See section 4.2).

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 Elantan LA 25. This may also occur with neuroleptics and tricyclic antidepressants.
Any blood pressure lowering effect of Elantan LA 25 will be increased if used together with phosphodiesterase type-5 inhibitors which are used for erectile dysfunction (see special warnings and contraindications, sections 4.4 and 4.3 respectively). This might lead to life threatening cardiovascular complications. Patients who are on Elantan LA 25 therapy therefore must not use phosphodiesterase type-5 inhibitors.
Reports suggest that concomitant administration of Elantan LA 25 may increase the blood level of dihydroergotamine and its hypertensive effect.

4.6 Pregnancy and lactation

Safety in pregnancy has not been established for isosorbide mononitrate and it is not known whether nitrates are excreted in human milk. Therefore Elantan LA 25 should only be used in pregnancy and during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the hazards.

4.7 Effects on ability to drive and use machines

Dizziness, tiredness or blurred vision may 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

A very common (>10%) adverse reaction to Elantan LA 25 is throbbing headache. The evidence of headache diminishes gradually with time and continued use.
At the start of therapy or when the dosage is increased, hypotension and/or light headedness in upright position are observed commonly (i.e. in 1 – 10 % of patients).

These symptoms may be associated with dizziness, drowsiness, reflex tachychardia and a feeling of weakness.
Infrequently (i.e. in <1% of patients) nausea, vomiting, flushing and allergic skin reaction (e.g. rash) may occur sometimes severely. In single cases, exfoliative dermatitis 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 and syncope). Uncommonly severe hypotension may lead to enhanced angina symptoms.
A few reports of heartburn most likely due to nitrate-induced sphincter relaxation have been reported.
Tachycardia and paroxysmal bradycardia have been reported.

4.9 Overdose

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.

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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C01D A 14 – Vasodilator used in cardiac diseases
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.

5.2 Pharmacokinetic properties

Isosorbide mononitrate is a vasodilator, which is rapidly absorbed following oral administration. These capsules have a bioavailability of 80 – 90% when compared to the immediate release isosorbide mononitrate tablets.
The capsules contain pellets which are formulated to release 30% of the dose immediately whilst 70% of the dose is released slowly.
Isosorbide mononitrate is extensively metabolised to nitric oxide (NO – which is the active agent) and isosorbide (inactive). In patients with cirrhotic disease or cardiac failure or renal failure, pharmacokinetic parameters were similar to those obtained in healthy volunteers.

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 (LD_{50} oral approximately 2000 – 2500 mg/kg body weight (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 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 in 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 neoplastigenic properties of isosorbide mononitrate. Therefore, it can be concluded that carcinogenic risk in humans is low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hyprolose
Ethylcellulose
Talc
Macrogol 20,000
Sucrose
Corn starch
Gelatin
Titanium dioxide (E171)
Black iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Over-labelled carton containing 2 blister strips (14 capsules per strip).
Pack size of 28 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/78/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13th March 2009

10 DATE OF REVISION OF THE TEXT

August 2009