

IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0365/088/001

Case No: 2072855

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

Transferred from PA0271/007/001.

UCB Pharma Limited

208 Bath Road, Slough, Berkshire SL1 3WE, United Kingdom

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

Deponit 5mg/24 hours Transdermal Patch

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 **30/10/2009**.

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

Deponit 5 mg/24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 18.7 mg of glyceryl trinitrate in a patch size of 9cm², releasing a nominal 5 mg of glyceryl trinitrate per 24 hours.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal Patch

White, translucent square patch with convex round corners with “deponit[®]5” marked on the outer face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis of angina pectoris alone or in combination with other anti-anginal therapy.

4.2 Posology and method of administration

Adults:

Treatment should be initiated with one patch daily. If necessary the dosage may be increased to two patches.

It is recommended that the patch is applied to healthy, undamaged, relatively crease free and hairless skin. The best places to apply Deponit patches are the easily reached, fairly static areas at the front or side of the chest; however, Deponit patches may also be applied to the upper arm, thigh, abdomen or shoulder. Skin care products should not be used before applying the patch. The replacement patch should be applied to a new area of skin. Allow several days to elapse before applying a fresh patch to the same area of skin.

Tolerance may occur during chronic nitrate therapy. Tolerance is likely to be avoided by allowing a patch-free period of 8-12 hours each day, usually at night. An additional anti-anginal therapy with drugs not containing nitro compounds should be considered for the nitrate-free interval if required.

As with any nitrate therapy, treatment with these patches should not be stopped abruptly. If the patient is being changed to another type of treatment, the two should overlap.

Elderly:

No specific information on use in the elderly is available, however there is not evidence to suggest that an alteration in dose is required.

Children:

The safety and efficacy of this patch in children has yet to be established.

4.3 Contraindications

- Known hypersensitivity to nitrates or to the adhesives used in the patch.
- Acute circulatory failure (shock, collapse).
- Cardiogenic shock.
- Raised intracranial pressure including that caused by head trauma or cerebral haemorrhage.
- Marked anaemia.
- Closed angle glaucoma.
- Hypotensive conditions and hypovolaemia.
- Hypertrophic obstructive cardiomyopathy.
- Aortic stenosis and mitral stenosis.
- Constrictive pericarditis.
- Cardiac tamponade.

Concomitant use of phosphodiesterase type-5 inhibitors. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) have been shown to potentiate the hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contra-indicated.

4.4 Special warnings and precautions for use

This patch should be used with caution in patients with:

- Severe hepatic or renal impairment.
- Hypothyroidism.
- Hypothermia.
- Malnutrition.
- A recent history of myocardial infarction.
- Hypoxaemia or a ventilation/perfusion imbalance due to lung disease or ischaemic heart failure.

The patch is not indicated for use in acute angina attacks. In the event of an acute angina attack, sublingual treatment such as a spray or tablet should be used. As with all nitrate preparations withdrawal of long-term treatment should be gradual by replacement with decreasing doses of long acting oral nitrates.

If the patches are not used as indicated (see section 4.2) tolerance to the medication could develop.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with other vasodilators, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquillisers, as well as the consumption of alcohol, may potentiate the hypotensive effect of the preparation.

The blood pressure lowering effect of these patches will be increased if used together with phosphodiesterase inhibitors (e.g. sildenafil) which are used for erectile dysfunction (see contraindications). This might lead to life threatening cardiovascular complications. Patients who are on nitrate therapy must not use phosphodiesterase inhibitors (e.g. sildenafil).

If administered concurrently, these patches may increase the blood level of dihydroergotamine and lead to coronary vasoconstriction.

The possibility that ingestion of acetylsalicylic acid and non-steroidal anti-inflammatory drugs might diminish the therapeutic response to the patch cannot be excluded.

4.6 Pregnancy and lactation

These patches should not be used during pregnancy or lactation unless considered absolutely essential by the physician.

It is not known whether the active substance passes into breast milk. Benefits to the mother must be weighed against risk to the child.

4.7 Effects on ability to drive and use machines

These patches may affect the reactivity of the patient. Patients should not drive or operate machinery if their ability is impaired.

4.8 Undesirable effects

A very common (>10% of patients) adverse reaction to the patch is headache. The incidence of headache diminishes gradually with time and continued use.

At start of therapy or when the dosage is increased, hypotension and/or light-headedness on standing are observed commonly (i.e. in 1-10% of patients). These symptoms may be associated with dizziness, drowsiness, reflex tachycardia, and a feeling of weakness.

Infrequently (i.e. in less than 1% of patients), nausea, vomiting, flushing and allergic skin reaction (e.g. rash), which may be severe can occur. 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 a nitrate-induced sphincter relaxation, have been recorded.

Allergic skin reactions to glyceryl trinitrate and ingredients can occur, but they are uncommon (i.e. >0.1% but <1%). Patients may commonly experience slight itching or burning at the site of application. Slight reddening usually disappears without therapeutic measures after the patch has been removed. Allergic contact dermatitis is uncommon.

During the treatment with these patches, a temporary hypoxaemia 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.

4.9 Overdose

In view of the transdermal mode of delivery, an overdose of glyceryl trinitrate is unlikely to occur. However, in the unlikely event of an overdose, the symptoms could include the following:

- Fall in blood pressure \leq 90 mmHg.
- Paleness.
- Sweating.
- Weak pulse.
- Tachycardia.
- Flushing.
- Light-headedness on standing.
- Headache.

- Weakness.
- Dizziness.
- Nausea.
- Vomiting.
- Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During glyceryl trinitrate 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 glyceryl trinitrate may cause this adverse reaction.
- In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

General procedure:

- Stop delivery of the drug.

Since these patches are applied to the skin, removing the patch immediately stops delivery of the drug.

General procedures in the event of nitrate-related hypotension:

- Patient should be kept horizontal with the head lowered and legs raised.
- Supply oxygen.
- Expand plasma volume.
- For specific shock treatment 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.
 - Red blood cell or exchange transfusion.

Resuscitation measures:

In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C01 DA02, Vasodilators used in cardiac diseases, organic nitrates.

The main pharmacological activity of organic nitrates is the relaxation of smooth vascular muscles. The systemic vasodilation induces an increase of venous capacitance. Venous return is reduced. Ventricular volume, filling pressures and diastolic wall tension are diminished (preload reduction).

A diminished ventricular radius and reduced wall tension, lower myocardial energy and oxygen consumption, respectively.

The dilation of the large arteries near the heart leads to a decrease in both the systemic (reduction of afterload) and the pulmonary vascular resistance. In addition, this relieves the myocardium and lowers oxygen demands.

By dilating the large epicardial coronary arteries, glyceryl trinitrate enhances blood supply to the myocardium, improving its pump function and increasing the oxygen supply.

At molecular level, nitrates form nitric oxide (NO), which corresponds to the physical EDRF (endothelium derived relaxing factor). EDRF mediated production of cyclic guanosine monophosphate (CGMP) leads to relaxation of smooth muscle cells.

5.2 Pharmacokinetic properties

(a) General characteristics of the active substance:

The transdermal absorption of glyceryl trinitrate circumvents the extensive hepatic first pass metabolism so the bio-availability is about 70% of that achieved after i.v. administration.

The steady-state concentration in the plasma depends on the patch dosage and the corresponding rate of absorption. At a rate of absorption of 0.4 mg/h, the steady-state concentration is about 0.2 micrograms/l on average. Plasma protein binding is about 60%. Glyceryl trinitrate is metabolized to 1,2- and 1,3-dinitroglycerols. The dinitrates exert less vasodilatory activity than glyceryl trinitrate. The contribution to the overall effect is not known. The dinitrates are further metabolized to inactive mononitrates, glyceryl and carbon dioxide.

The elimination half-life of glyceryl trinitrate is 2-4 min. The metabolism of glyceryl trinitrate, which is effected in the liver, but also in many other cells, e.g. the red blood cells, includes the separation of one or more nitrate groups. In addition to the metabolism of glyceryl trinitrate, there is a renal excretion of the catabolites.

(b) Characteristics in patients:

There is no evidence that a dosage adjustment is required in the elderly or in diseases such as renal failure or hepatic insufficiency.

5.3 Preclinical safety data

Glyceryl trinitrate is a well-known substance, established for more than a hundred years. Thus new preclinical studies have not been carried out with Deponit 5.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acrylate/vinyl acetate co-polymer
Polypropylene backing foil
Siliconised polyethylene release liner

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Multilaminate paper/polyethylene/aluminium/ surlyn sachet containing a single patch. 28 transdermal patches in a cardboard outer.

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 MARKETING AUTHORISATION HOLDER

UCB Pharma Limited
208 Bath Road
Slough
Berkshire SL1 3WE
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0365/088/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 February 1996

Date of last renewal: 16 February 2006

10 DATE OF REVISION OF THE TEXT

October 2009