Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

EPINITRIL 5 mg/24 h transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One transdermal patch contains 15.70 mg of glyceryl trinitrate/6.38 cm^2 delivering 5 mg of glyceryl trinitrate in 24 hours (0.2 mg/hour).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch. Each patch is circular, light yellow and transparent with printed identification code (NR5), covered by a square both sides aluminised and both sides siliconised protective liner.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Preventive treatment of angina pectoris either alone or in combination with other anti-anginal therapy.

4.2 Posology and method of administration

Different strengths of EPINITRILare available.
Treatment is usually initiated with one EPINITRIL 5 mg/24 h applied to the skin once daily. EPINITRIL5 mg/24 h delivers 0.2 mg/h of glyceryl trinitrate. The dose should be adjusted individually during the treatment to achieve optimum therapeutic effect.
The maximum daily dose for EPINITRIL should be 15 mg of glyceryl trinitrate.

EPINITRIL is administered intermittently, with a daily nitrate-free interval, in order to avoid the development of nitrate tolerance. This free interval should correspond for the patient to a period with no attacks. The timing of administration of concomitant anti-anginal agents (beta-blockers and/or calcium antagonists) should be established in order to provide a therapeutic cover during the nitrate-free interval.

The nitrate-free interval of 8 - 12 hours must be observed.

The development of nitrate tolerance is a well-established event during the preventive treatment of angina. An adequate prescription with a nitrate-free interval guarantees the therapeutic efficacy of nitrates.

Patients experiencing nocturnal angina may benefit from overnight treatment with a nitrate-free interval during the day. In these patients, an additional antianginal therapy may be needed during the day.

Patients with severe angina may also need an additional antianginal therapy during nitrate-free intervals.

Additional information on special populations

Older people
No dose adjustment is recommended in elderly patients since no studies have been performed in these subjects.

Patients with renal impairment
Since no studies have been performed in patients with impaired renal and/or liver function, no dose recommendations can be given.

Paediatric population

EPINITRIL is not recommended in children and adolescents below the age of 18 years.

Method of administration
Each EPINITRIL transdermal patch is contained in a sealed sachet. The adhesive layer is covered by a protective film, which has to be removed before application. The EPINITRIL transdermal patch adheres easily to the skin, and also stays in place whilst bathing or during physical exercise.

It is recommended to apply EPINITRIL transdermal patches to the skin of the chest, or outer upper arm, free of redness or irritation and to rotate the sites of application. Subsequent transdermal patches should not be applied to the same area of skin until several days have elapsed.
Suitable area may be shaved if necessary. Areas that form folds or are subjected to friction during movement should be avoided.

4.3 Contraindications

- Hypersensitivity to the active substance, related organic nitrates or to any of the excipients listed in section 6.1.
- Acute circulatory failure associated with marked hypotension (shock).
- Conditions associated with elevated intracranial pressure, including that caused by head trauma.
- Myocardial insufficiency due to obstruction, as in aortic or mitral stenosis or constrictive pericarditis.
- Concomitant use of EPINITRIL and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil is contraindicated, because PDE5 inhibitors may amplify the vasodilatory effects of EPINITRIL resulting in severe hypotension.
- Concomitant use of Epinitril with the soluble guanylate cyclase stimulator riociguat.
- Severe hypotension (systolic blood pressure less than 90 mmHg).
- Severe hypovolemia.
- Severe anaemia.
- Toxic pulmonary oedema.

4.4 Special warnings and precautions for use

Warnings
As with other nitrate preparationswhen transferring the patient on long-term therapy to another form of medication, glycery trinitrate should be gradually withdrawn and overlapping treatment started.

EPINITRIL patch must be removed before applying magnetic or electrical fields to the body during procedures such as MRI (Magnetic Resonance Imaging), cardioversion or DC defibrillation, or diathermy treatment.

In cases of recent myocardial infarction or acute heart failure, treatment with EPINITRIL should be carried out cautiously under strict medical surveillance and/or haemodynamic monitoring.

Removal of the patch should be considered as part of the management of patients who develop significant hypotension.

EPINITRIL is not a treatment for acute anginal attacks requiring rapid relief, unstable angina and myocardial infarction.

The patch should be removed if collapse or shock occurs.

It may be advisable to titrate the dose gradually upwards until the optimal effect is achieved: if too high a starting dose is used severe headache or hypotension may occur in some patients. These unwanted effects are less likely to occur when transferring from intravenous nitrates to the transdermal form.

Cross tolerance with other nitrates may occur.

The use of products for topical application, especially if prolonged, may give rise to sensitisation phenomena, in which case treatment should be suspended, and suitable therapeutic measures adopted.

Paradoxical bradycardia and increased angina may occur in patients with glyceryl trinitrate-induced hypotension.

EPINITRILshould be used with extreme caution in patients predisposed to closed angle glaucoma.

Precautions

Hypoxaemia
Caution should be exercised in patients with arterial hypoxaemia due to severe anaemia (including G6PD deficiency induced forms), because in such patients the biotransformation of glyceryl trinitrate is reduced. Similarly, caution is called for in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure. In Patients with alveolar hypoventilation a vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung (Euler–Liljestrand mechanism). Patients with angina pectoris, myocardial infarction, or cerebral ischaemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, glyceryl trinitrate could reverse this protective vasoconstriction and thus 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.

Hypertrophic cardiomyopathy
Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Increased angina
The possibility of increased frequency of angina during patch-off periods should be considered. In such cases the use of additional anti-anginal therapy is desirable.

Tolerance to sublingual glyceryl trinitrate
As tolerance to glyceryl trinitrate patches develops, the effect of sublingual glyceryl trinitrate on exercise tolerance may be partially diminished.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a concomitant use contraindicated
Concomitant administration of EPINITRIL and other vasodilators (e.g PDE5 inhibitors such as sildenafil) potentiates the blood-pressure-lowering effect of EPINITRIL.
The use of EPINITRIL with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (see section 4.3) since concomitant use can cause hypotension.

Interactions to be considered
Concomitant treatment with calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, neuroleptics and major tranquillisers may potentiate the blood-pressure-lowering effect of EPINITRIL, as may alcohol.
Concurrent administration of EPINITRIL with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of glyceryl trinitrate and may lead to coronary vasoconstriction.
Non-steroidal anti-inflammatory drugs except acetyl salicylic acid may diminish the therapeutic response to EPINITRIL.
Concurrent administration of EPINITRIL with amifostine and acetyl salicylic acid may potentiate the blood pressure lowering effects of EPINITRIL.

4.6 Fertility, pregnancy and lactation

Pregnancy
Like any drug, EPINITRILshould not be prescribed during pregnancy, especially in the first 3 months, unless there are compelling reasons for doing so. The benefits for the mother must be weight against the risk for the child.

Breastfeeding
There is limited information on the excretion of the active substance in human or animal breast milk. A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from EPINITRIL therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data available on the effect of EPINITRIL on fertility in humans.

4.7 Effects on ability to drive and use machines

EPINITRIL, especially at the start of treatment or dose adjustments, may impair the reactions or might rarely cause orthostatic hypotension and dizziness (as well as exceptionally syncope after overdosing). Patients experiencing these effects should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions are listed by MedDRA System-Organ Class (SOC). Within each System-Organ Class the adverse drug reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse drug reactions are ranked in order of decreasing seriousness.

Organ system class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**
Nervous system disorders		- Headache[1]			- Dizziness - Syncope
Cardiac disorders				- Tachycardia[2]	
Vascular disorders				- Orthostatic hypotension - Flushing[2]	
Gastrointestinal disorders	- Nausea - Vomiting				
Skin and subcontaneous tissue disorders			- Dermatitis contact		
General disorders and administration site conditions			- Application site erythema - Pruritus - Burning - Irritation[3]		
Investigations				- Heart rate increase	

1 Like other nitrate preparations, EPINITRIL commonly causes dose-dependent headaches due to cerebral vasodilatation. These often regress after a few days despite the maintenance of therapy. If headaches persist during intermittent therapy, they should be treated with mild analgesics. Unresponsive headaches are an indication for reducing the dosage of glyceryl trinitrate or discontinuing treatment.
2 A slight reflex-induced increase in heart rate can be avoided by resorting, if necessary, to combined treatment with a betablocker.
3 Upon removal of the patch, any slight reddening of the skin will usually disappear within a few hours. The application site should be changed regularly to prevent local irritation.

The following adverse drug reactions have been derived from post-marketing experience via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.
• Cardiac disorders: palpitation.
• Skin and subcutaneous tissue disorders: rash generalized.

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, EarlsfortTerrace, IRL-Dublin 2; Tel: + 353 1 6764971; Fax: +353 1 6762517.Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Signs
High doses of glyceryl trinitrate may lead to severe hypotension and reflex tachycardia or to collapse and syncope. Methaemoglobinaemia has also been reported following accidental overdosage.

Management
The nitrate effect of EPINITRIL can be rapidly terminated simply by removing the system(s).
Hypotension or collapse can be treated by elevation or, if necessary, compression bandaging of the patient's legs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacoterapeutic group: Vasodilators used in cardiac disease, organic nitrates; ATC code: C01DA02
Glyceryl trinitrate, as other organic nitrates, is a potent dilator of vascular smooth muscle. The effect on veins predominates over that on arteries resulting in decreased cardiac preload. Systemic vascular resistance is relatively unaffected, heart rate is unchanged or slightly increased and pulmonary vascular resistance is consistently reduced.

5.2 Pharmacokinetic properties

Glyceryl trinitrate is rapidly hydrolysed by liver enzymes, which are a major factor in bioavailability. Peak concentrations of glyceryl trinitrate following sub-lingual administration occur within 4 minutes in man with a half-life of 1 to 3 minutes. Transdermal delivery systems are an alternative route to bypass the hepatic circulation with longer term gradual absorption providing prophylactic dosing. The systemic bioavailability of glyceryl trinitrate is in the range of 75 to 90% following patch administration. The drug and its two metabolites 1,2-GDN (1,2-glyceryl dinitrate) and 1,3-GDN (1,3-glyceryl dinitrate) are detected in plasma 30 to 60 minutes after patch application; steady-state plasma concentrations persist from about 2 to 24 hours and no drug is measurable in plasma within 1 hour after patch removal. After administration of one transdermal patch the average plasma concentration of glyceryl trinitrate, 1,2-GDN and 1,3-GDN are about

- 105, 859 and 134 pg/ml for EPINITRIL 5 mg/ 24 h

5.3 Preclinical safety data

Glyceryl trinitrate is an organic nitrate which has been used for many years in clinical therapy in a variety of pharmaceutical forms and which is very well documented in the scientific literature. Local tolerability studies performed in the rabbit have demonstrated the good tolerability of the transdermal patch after single and repeated applications. The patch did not show any sensitisation potential in the guinea pig.
The animal studies performed on the non-active ingredients that form the adhesive matrix demonstrated the topical safety of these components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Acrylate-vinylacetate copolymer (Durotak 387-2516)
- hydroabietyl phthalate (Cellolyn 21 E)
- butyltitanate polymer
- lacquered polypropylene foil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Immediate packaging:
the adhesive side of the patch is covered by a square both side aluminised and siliconised protective liner that is removed before use; each patch is sealed in a sachet consisting of Surlyn, heat sealable material, aluminium foil, polyethylene and paper.
Secondary packaging:
cardboard box.

Each cardboard box contains 15 or 30 patches.
Not all pack sizes may be marketed.

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

Tear open the sachet at the indentation (do not use scissors to avoid damaging the patch) and remove the patch. The patch must be used immediately after opening the sachet.
Hold the patch between the thumb and index finger at the corner of the pull-off-tag. Detach the protective liner with the other hand and discard it.
Do not touch the adhesive side of the patch. Apply the patch to the skin holding between the thumb and index finger the part still covered by the protective liner. Detach the remaining part of the protective liner and press firmly for about 10 seconds on the whole surface of the patch. Pass a finger along the edges to assure good adhesion.

Hands should be washed before and after applying EPINITRIL.

After use, the patch should be folded with the adhesive part inside and discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rottapharm Ltd
Damastown Industrial Park
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PA0868/003/001

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