Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Transiderm-Nitro 15milligrams/24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch contains glyceryl trinitrate 75 mg.
The average amount of glyceryl trinitrate absorbed per patch in 24 hours is 15 mg.
The surface measurement of the patch is 30 cm^2.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

A flat, foil like patch sealed at the edges with white paste like filling, one side with a grayish-orange backing film with imprint 'CG EJE', the other side with an off-white protective liner.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylactic treatment of attacks of angina pectoris, as monotherapy or in combination with other anti-anginal agents.

4.2 Posology and method of administration

General rules

Transiderm-Nitro is not intended for the immediate relief of acute attacks of angina pectoris; if these occur, rapid-acting nitrate preparations should be used.

The response to nitrate preparations varies from patient to patient; the lowest effective dose should be prescribed. The application site should be changed regularly to prevent local irritation.

Development of tolerance or attenuation of therapeutic effects commonly occurs with prolonged or frequent administration of all long-acting nitrates. A patch-off period of 8-12 hours, usually at night, during each 24 hour period is recommended to avoid tolerance. Clinical trials have shown that in most patients, intermittent therapy is more effective than continuous administration. Continuous application of Transiderm-Nitro may be appropriate for patients in whom long-term clinical responsiveness can be reliably assessed.

It is recommended that the patch is applied to the lateral chest wall. If necessary, a suitable area should be shaved free of hair. 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. If a patch loosens it should be replaced with a new patch. Transiderm-Nitro is not intended for immediate relief of acute attacks of angina; if these occur, rapidly acting nitrate preparations may be required.

Adults
Treatment should be initiated with one Transiderm-Nitro 5mg/24hr patch daily. If a higher dosage is required a Transiderm-Nitro 10mg/24hr or Transiderm-Nitro 15mg/24hr patch may be substituted. The dosage may be increased to a maximum equivalent to two Transiderm-Nitro 10mg/24hr patches daily.

Elderly
No specific information on use in the elderly is available. However, no evidence exists to suggest that an alteration in dosage is required.

Children
Not enough is known about the effects of Transiderm-Nitro in children, which means that it cannot be recommended for use in this age group.

4.3 Contraindications

- Known hypersensitivity to nitroglycerin, and related organic nitrates or any excipient of Transiderm-Nitro.
- Acute circulatory failure associated with marked hypotension (shock).
- Conditions associated with elevated intracranial pressure.
- Myocardial insufficiency due to obstruction, as in aortic or mitral stenosis or constrictive pericarditis.
- Concomitant use of Transiderm-Nitro and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil (Viagraâ) is contraindicated, because PDE5 inhibitors may amplify the vasodilatory effects of Transiderm-Nitro resulting in severe hypotension.
- Severe hypotension (systolic blood pressure less than 90mmHg)
- Severe hypovolaemia

4.4 Special warnings and precautions for use

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

Transiderm Nitro 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 Transiderm Nitro 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.

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 nitroglycerin 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, nitroglycerin 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 concomitant anti-anginal therapy is desirable.

Tolerance to sublingual nitroglycerin

If tolerance to nitroglycerin patches develops, the effect of sublingual nitroglycerin 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 Transiderm-Nitro and other vasodilators e.g. PDE5 inhibitors such as sildenafil, potentiates the blood pressure lowering effects of Transiderm-Nitro.

Interactions to be considered
Concomitant treatment with calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquillisers may potentiate the blood pressure-lowering effect of Transiderm-Nitro, as may alcohol.

Concurrent administration of Transiderm-Nitro with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonises the effect of nitroglycerin and may lead to coronary vasoconstriction.

The non-steroidal anti-inflammatory drugs except acetyl salicylic acid may diminish the therapeutic response of Transiderm-Nitro.

Concurrent administration of Transiderm Nitro with amifostine and acetyl salicyclic acid may potentiate the blood lowering effects of Transiderm Nitro.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
There is no data supporting any special recommendations in women of child-bearing potential.

Pregnancy
Like any drug, Transiderm-Nitro should be employed with caution during pregnancy, especially in the first 3 months.

Lactation
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 Trnsiderm Nitro therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There is no data available on the effect of Transiderm-Nitro on fertility in humans.

4.7 Effects on ability to drive and use machines

Transiderm-Nitro, 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 operating machinery.

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. In addition, the corresponding frequency category, using the following convention (CIOMS III): Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000), including isolated reports:

Nervous system disorders	
Common:	Headache [1]
Very rare:	Dizziness
Cardiac disorders	
Rare:	Tachycardia [2]
Vascular disorders	
Rare:	Orthostatic hypotension, flushing [2]

Gastrointestinal disorders	
Very common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Uncommon:	Dermatitis contact
General disorders and administration site conditions	
Uncommon:	Application site erythema, pruritus, burning, irritation [3]
Investigations	
Rare:	Heart rate increase

[1] Like other nitrate preparations, Transiderm-Nitro 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 nitroglycerin or discontinuing treatment.
[2] A slight reflex-induced increase in heart rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.
[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 with Transiderm-Nitro 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. Within each System-Organ Class, adverse drug reactions are presented in order of decreasing seriousness.

- 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, 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

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 Transiderm-Nitro 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

Pharmacotherapeutic group
Vasodilators used in cardiac diseases, ATC code: CO1DA02

Mechanism of action
Nitroglycerin relaxes smooth muscle throughout the body. In the vascular system it acts chiefly on the systemic veins and accessorily on the large coronary arteries. Nitroglycerin at low doses is bioactivated by mitochondrial aldehyde dehydrogenase activity, and is converted to nitrites and denitrated metabolites (1,2-glyceryl dinitrate,1-3-glyceryl dinitrate) by glutathione-dependent organic nitrate reductase. Nitrite is further activated by cytochrome oxidase or acidic disproportionation in the intermembrane space (H^+), finally yielding nitric oxide (NO) or a related species, which activate soluble guanylyl cyclase and trigger cyclic guanosine monophospate (cGMP) signaling via cGMP dependent protein kinase, which causes relaxation. Glyceryl dinitrate, mononitrate and nitroglycerin at high doses are bioactivated by P450 enzyme(s) in the smooth endoplasmic reticulum directly yielding NO which causes relaxation.

In angina pectoris a fundamental mechanism of action of nitroglycerin is an increase in venous capacitance (venous pooling) leading to a decreased return of blood to the heart. This lowers left ventricular end-diastolic pressure (preload) and hence filling volume, which in turn lowers the myocardial oxygen requirement at rest and especially during exercise, hence enhancing exercise capacity.

In the coronary arterial circulation nitroglycerin dilates both extramural conductance and small resistance vessels. The drug appears to redistribute coronary blood flow to ischaemic subendocardium by selectively dilating large epicardial vessels. It can also dilate stenoses caused by eccentric atheroma. In addition, nitroglycerin relaxes vasospasm, whether spontaneous or induced by ergonovine.

Nitroglycerin dose-dependently dilates the arteriolar vascular bed, thereby lowering systemic vascular resistance (afterload) and left ventricular systolic wall tension, and further reducing myocardial oxygen consumption.

Dosing regimens for most chronically used drugs aim for plasma concentrations that continuously exceed the minimally effective concentration, but this strategy is probably inappropriate for organic nitrates. Although some well-controlled clinical trials using exercise tolerance testing showed that efficacy is maintained when patches are worn continuously, most of them reported the development of tolerance (i.e. attenuation of effect as measured by exercise testing) within the first day. As might be expected on pharmacological grounds, tolerance is also observed with high transdermal doses exceeding 4 mg/h.

Efficacy of organic nitrates is restored after a nitrate-free interval. The shortest drug-free interval sufficient to restore response has not been defined. Intervals of 8 to 12 hours are known to be sufficient, shorter intervals have not been fully studied. When administered according to an intermittent regimen, doses of Transiderm-Nitro delivering 0.4-0.8 mg/h (20-40 cm^2) have shown increased exercise capacity for 8 to 12 hours.

Controlled clinical trial data suggest that intermittent use of nitrates may be associated with a decrease in exercise tolerance compared with placebo during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown (see under "Special warnings and special precautions for use").

In chronic heart failure the venodilator action of nitroglycerin lowers the elevated left ventricular filling pressure, while maintaining or slightly increasing cardiac output. In this indication the beneficial effects of nitroglycerin are restricted to severe heart failure with predominant symptoms of pulmonary venous congestion due to a pronounced increase in left ventricular filling pressure. Where improved stroke volume is desired, combined treatment with an arterial vasodilator such as hydralazine is recommended.

5.2 Pharmacokinetic properties

Transiderm-Nitro
Absorption
Following single application of Transiderm-Nitro, the plasma concentrations of nitroglycerin reach a plateau within 2 hours, which is maintained over the recommended application period. The height of this plateau is directly proportional to the size of the system's drug-releasing area. The same plasma levels are attained regardless of whether the system is applied to the skin of the upper arm, pelvis, or chest. Levels fall rapidly after patch removal. Accumulation does not occur on repeated application of Transiderm-Nitro.

Nitroglycerin
Distribution
The plasma protein binding fraction is 61-64%, for nitroglycerin, 23% and 11% for 1, 2-glyceryl dinitrate and 1, 3-glyceryl dinitrate respectively.

Metabolism
The active substance is rapidly biotransformed to glyceryl dinitrates and mononitratesby glutathione-dependent organic nitrate reductase in the liver. In addition, and probably more importantly, *in vitro* studies have shown that the human erythrocyte is also a site of biotransformation via a sulfhydryl-dependent enzymatic process and interaction with reduced haemoglobin. In human erythrocytes, the reduced haemoglobin level seems to play a major role in metabolic activity, and caution should therefore be exercised in patients with anaemia. In animal studies it has been found that extrahepatic vascular tissues (femoral vein, inferior vena cava, aorta) likewise play an important role in nitroglycerin metabolism, a finding which is consistent with the large systemic clearance seen with nitrates. It has also been shown in vitro that the biotransformation of nitroglycerin occurs concurrently with vascular smooth muscle relaxation; this observation is consistent with the hypothesis that nitroglycerin biotransformation is involved in the mechanism of nitroglycerin-induced vasodilatation.

Excretion
Nitroglycerin is excreted renally as dinitrate and mononitrate metabolites, glucuronide conjugates and glycerol. The elimination half-lives of nitroglycerin, 1,2-glyceryl dinitrate and glyceryl mononitrates are 10, 30-60, 5-6 minutes respectively.

5.3 Preclinical safety data

Mutagenicity
Standard mutagenicity tests provided contradictory results in vitro. Cell culture and in vivo studies revealed no evidence of mutagenic activity of nitroglycerin, and therefore its use is considered devoid of genotoxic potential at exposures relevant to man.

Carcinogenicity
Dietary studies in rodents led to the conclusion that nitroglycerin has no carcinogenic effects relevant for the therapeutic dose range in man.

Reproduction toxicity
Animal teratology studies have not been conducted with nitroglycerin transdermal systems. Conventional reproduction studies involving the oral, intravenous, intraperitoneal and dermal (as ointment) administration routes of nitroglycerin have been performed in rats and rabbits. Nitroglycerin showed no teratogenic potential in these animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Dimeticone
Colloidal anhydrous silica
Ethylene vinyl acetate copolymer
Medical Adhesive CH15 hotmelt
Polyethylene terephthalate
Backing film - Aluminium
Printing ink - Durloux 544310

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Once opened: The patches should be applied immediately after removal from the pouch.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Each patch is contained in an aluminium Surlyn/polyethylene/paper pouch.

28 or 30 pouches are contained in a cardboard box.

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

The patch should not be used if the seal is broken. When changing the patch, the used patch should be removed, the adhesive layer folded in wards on itself, and the patch disposed of safely and out of reach and sight of children. Any used or unused patches should be discarded according to local requirements or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA23311/005/003

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