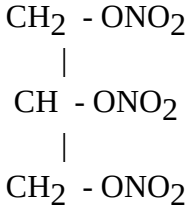
NAME OF DRUG

TRANSIDERM-NITRO®
(glyceryl trinitrate)

DESCRIPTION

Glyceryl Trinitrate is an organic nitrate derivative with the chemical name 1,2,3-propanetriol trinitrate with the following molecular structure:



Transiderm-Nitro is a transdermal therapeutic system for application to intact skin.

Transiderm-Nitro is a flat self-contained multilayer unit designed to provide continuous, controlled release of glyceryl trinitrate through a semipermeable membrane for the recommended application period. In cases where the permeability of the skin is excessive, drug release is limited by the release membrane.

Transiderm-Nitro is composed of four layers. Proceeding from the visible outer surface towards the inner surface which adheres to the skin, these layers are:

1) an impermeable tan-coloured backing film;
2) a drug reservoir containing glyceryl trinitrate;
3) a semi-permeable release membrane that controls the release of glyceryl trinitrate to the skin;
4) a layer of silicone adhesive;
5) a white to off-white coloured protective liner which is removed prior to use.

The following two systems are available:

	Transiderm -Nitro 25	Transiderm -Nitro 50
Glyceryl Trinitrate	25 mg	50mg
Nominal amount of glyceryl trinitrate released over 24 hours.①	5mg	10mg
Nominal amount of glyceryl trinitrate released per hour	≈ 0.2mg	≈ 0.4mg
Drug-releasing area②	10cm²	20cm²

①The remainder of the glyceryl trinitrate in each system serves as a reserve and is not delivered in normal use.
②Since glyceryl trinitrate is released from Transiderm-Nitro at a constant rate per cm², the dose administered is related to the size of the drug-releasing area.

Exipients
Lactose, dimethicone, silica colloidal anhydrous, ethylene va copolymer and silicon medical adhesive.

PHARMACOLOGY

Pharmacodynamics

Glyceryl trinitrate relaxes smooth muscle throughout the body. In the vascular system it acts chiefly on the systemic veins and the large coronary arteries, with more predominant effects on the former.

In angina pectoris a fundamental mechanism of action of glyceryl trinitrate is primarily based on an increase in venous capacitance (venous pooling) leading to a decreased return of blood to the heart. Due to this phenomenon, left-ventricular end-diastolic pressure (preload) and hence filling volume diminishes, resulting in a decreased myocardial oxygen requirement at rest and especially during exercise, with an improvement in exercise capacity in patients with angina pectoris.

In the coronary arterial circulation, glyceryl trinitrate dilates both extramural conductance and small resistance vessels. The drug appears to cause a redistribution of coronary blood flow to the ischaemic subendocardium by selectively dilating large epicardial vessels. It is also capable of dilating atherosclerotic stenoses where the atheroma is eccentrically located.

Glyceryl trinitrate also exerts a dose-dependent dilating effect on the arteriolar vascular bed, as a result of which systemic vascular resistance (after load) and left-ventricular systolic wall tension decrease, leading to a reduction in myocardial oxygen consumption.
Some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, however, the majority of such controlled trials have shown the development of tolerance (ie. 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 greater than 4 mg/hour.

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 to restore response. When administered according to an intermittent regimen, doses of Transiderm-Nitro which deliver 0.4 - 0.8 mg/hr (20-40 cm^2) have resulted in increased exercise capacity for 8 to 12 hours.

Controlled clinical trial data suggest that the 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; however, the possibility of increased angina in the nitrate-free interval should be considered (see "PRECAUTIONS").

Pharmacokinetics

Transiderm-Nitro:

Absorption:

Following the single application of Transiderm-Nitro, the plasma concentration of glyceryl trinitrate reaches a plateau within 2 hours which is maintained for the recommended application period. This steady state concentration of glyceryl trinitrate shows a linear dependence on the size of the system's contact surface with the skin.

Replacement of the system during the steady state phase does not cause a significant fluctuation in plasma concentrations. Removal of the system from the skin causes plasma concentrations of glyceryl trinitrate to fall to below detectable levels within one hour. After repeated application of Transiderm-Nitro no accumulation occurs.

Glyceryl trinitrate:

Metabolism:

The volume of distribution of glyceryl trinitrate is about 3L/kg. and glyceryl trinitrate is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1L/kg/min) greatly exceed hepatic blood flow. Glyceryl trinitrate is rapidly metabolised by a glutathione-dependent organic nitrate reductase in the liver. In addition, and probably more importantly, studies with human erythrocytes *in vitro* have shown that the erythrocyte is also a site of biotransformation of glyceryl trinitrate by a sulphhydryl-dependent enzymatic process and by an interaction with

reduced haemoglobin. The amount of reduced haemoglobin in human erythrocytes seems to play a major role in their metabolic activity, and caution should therefore be exercised in cases of anaemia. In *in vitro* studies it has been found that extrahepatic vascular tissues (femoral vein, inferior vena cava, aorta) likewise play an important role in glyceryl trinitrate 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 glyceryl trinitrate occurs concurrently with vascular smooth muscle relaxation; this observation is consistent with the hypothesis that glyceryl trinitrate biotransformation is involved in the mechanism of glyceryl trinitrate-induced vasodilatation.

INDICATIONS

Transiderm-Nitro is indicated for the prevention of chronic stable angina pectoris due to coronary artery disease.

CONTRAINDICATIONS

Transiderm-Nitro should not be prescribed to patients:

- who are hypersensitive or intolerant to organic nitrate compounds.
- who are known or suspected to be hypersensitive to components of the patch.
- have acute circulatory failure associated with marked hypotension (shock, states of collapse).
- have marked anaemia.
- have conditions associated with elevated intracranial pressure.
- have increased intra-ocular pressure eg. glaucoma.
- have myocardial insufficiency due to obstruction (eg. in the presence of aortic or mitral stenosis or of constrictive pericarditis).

Concomitant use of Transiderm-Nitro and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil (Viagra®) is contraindicated because PDE5 inhibitors may amplify the vasodilatory effects of Transiderm-Nitro, resulting in severe hypotension.

PRECAUTIONS

Defibrillation/diathermy:
The Transiderm-Nitro patch contains an aluminium layer. Therefore the patch must be removed before applying magnetic or electrical fields to the body during procedures such as Magnetic Resonance Imaging (MRI), or attempting cardioversion or DC defibrillation, as well as before applying diathermy treatment.

Myocardial infarction/acute heart failure:
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.

Hypoxaemia:
Glyceryl trinitrate should not be used in patients with arterial hypoxaemia due to severe anaemia, because in such patients the biotransformation of the drug is reduced [refer to "Pharmacokinetics" and "CONTRAINDICATIONS"]. Similarly, caution is called for in patients with hypoxaemia and a ventilation/perfusion imbalance due to lung disease, ischaemic heart failure or cerebral ischaemia. 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.

Abrupt withdrawal:
Abrupt withdrawal of the drug following chronic use may be associated with withdrawal reactions including an increase in the frequency of anginal attacks. The withdrawal may also exacerbate Raynaud's phenomenon in susceptible patients.

As with other nitrate preparations, when transferring the patient on long-term therapy to another form of medication, glyceryl trinitrate should be gradually withdrawn over a period of 4 to 6 weeks and overlapping treatment started.

Acute anginal attack:
Transiderm-Nitro is not suitable for the treatment of acute attacks of angina pectoris. To arrest such attacks, the additional use of rapid-acting nitrate preparations is indicated.

Tolerance to sublingual glyceryl trinitrate:
As tolerance to glyceryl trinitrate patches develops (Refer to "DOSAGE AND ADMINISTRATION"), the effect of sublingual glyceryl trinitrate on exercise tolerance may be partially diminished. This should also be borne in mind when sublingual glyceryl trinitrate tablets are used to treat acute anginal attacks.

Increased angina:
In some controlled clinical trials of glyceryl trinitrate patch therapy in which a nitrate-free interval was used, a minority of patients experienced an increase in the frequency of angina attacks occurring during the patch-off period. If such symptoms do develop in a patient, the

use of concomitant anti-anginal therapy (eg. beta blockers, calcium channel antagonists) is desirable.

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

Hypotension:
Severe hypotension, particularly with upright posture, may occur with even small doses of glyceryl trinitrate. This drug should, therefore, be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by glyceryl trinitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Symptoms of hypotension, particularly of the orthostatic type, such as faintness, weakness or dizziness, may be due to overdosage. When these symptoms occur, the dosage should be reduced or the product discontinued.

Use in Pregnancy (Category: B2)
The safety of Transiderm-Nitro in pregnancy has not been established. Therefore, Transiderm-Nitro should not be administered to women who are or who may become pregnant unless, in the judgement of the physician, the probable clinical benefits outweigh the possible risks.

Use in Lactation
No information is available on the secretion of glyceryl trinitrate in breast milk, therefore, Transiderm-Nitro is not recommended in nursing mothers unless in the judgement of the physician, the probable clinical benefits outweigh the possible risks.

Use in Children
There are insufficient data on the use of Transiderm-Nitro in children, therefore, it is not recommended in this patient population.

Interaction with Other Drugs
Concomitant use of alcohol may enhance the vascular effects of glyceryl trinitrate.
Concomitant treatment with other vasodilators or antihypertensives (e.g. PDE5 inhibitors such as sildenafil (Viagra®), calcium antagonists, beta-blockers, ACE-inhibitors, diuretics), tricyclic antidepressants, major tranquillisers and dihydroergotamine may potentiate the blood pressure lowering effects of glyceryl trinitrate, therefore, adjustment of dosage may be required in these circumstances.
There is a possibility that the ingestion of acetylsalicylic acid and non-steroidal anti-inflammatory drugs might diminish the therapeutic response to Transiderm-Nitro.

Ability to drive or use machinery

Transiderm-Nitro, especially at the start of treatment, may impair the patient's reactions either when driving a vehicle or operating machinery (Refer to "ADVERSE EFFECTS-Cardiovascular and Nervous system disorders").

Safety and disposal:

Patients should be warned not to cut the patches and to dispose of them carefully as they still contain glyceryl trinitrate after use. TRANSIDERM-NITRO should be kept out of the reach of children both before and after use.

ADVERSE EFFECTS

The adverse effects 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 and < 1/10, uncommon ≥ 1/1000 and < 1/100, rare ≥1/10000 and < 1/1000, very rare < 1/10000, including isolated reports.

Nervous system disorders	
Very common:	Headache
Rare:	Dizziness
Cardiac disorders	
Rare:	Tachycardia
Vascular disorders	
Rare:	Orthostatic hypotension, flushing
Gastrointestinal disorders	
Very common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Common:	Dermatitis contact
General disorders and administration site conditions	
Common:	Application site erythema, pruritus, burning , irritation
Investigations	
Rare:	Heart rate increase

Like other nitrate preparations, Transiderm-Nitro may frequently give rise to headache, which is due to cerebral vasodilatation and is dose-dependent. Such headaches often regress after a few days despite the maintenance of therapy. The possibility of persistent headaches during intermittent therapy should be considered. When they present as a problem, they should be

treated with mild analgesics. In cases where the headaches are unresponsive to treatment, the dosage of glyceryl trinitrate should be reduced or use of the product discontinued.

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.

A slight reflex-induced increase in heart rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.

The following adverse drug reactions have been derived from post-marketing experience with Nitroderm TTS 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

DOSAGE AND ADMINISTRATION

Dosing Regimen

The response to nitrate preparations varies from patient to patient; the lowest effective dose should be prescribed.

Therapy should be initiated with the application of one Transiderm-Nitro 25 every 24 hours. According to the clinical response, the daily dose may be titrated upwards as follows:

- one Transiderm-Nitro 50 (normal maintenance dose)
- one Transiderm-Nitro 25 + one Transiderm-Nitro 50
- two Transiderm-Nitro 50.

Tolerance:

Development of tolerance or attenuation of therapeutic effects commonly occurs with prolonged or frequent administration of long-term nitrates, including Transiderm-Nitro or other transdermal systems. A patch off period of 8-12 hours, usually at night, every 24 hours is recommended to overcome tolerance. Clinical trials have shown that in the majority of 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 judged reliably.

Application

The Transiderm-Nitro system should be applied to intact, clean dry skin which is free of hair (clipping may be necessary). The system must be changed daily to minimise skin irritation and the application site should be changed regularly to prevent local irritation. A number of

days should elapse before using the same site again. Suitable application sites include the chest, inner side of the upper arm or shoulders. Transiderm-Nitro should not be applied to the distal parts of the extremities.

OVERDOSAGE

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 of glyceryl trinitrate.

However, with Transiderm-Nitro, the release membrane will reduce the likelihood of overdosage occurring. The nitrate effect of Transiderm-Nitro can be rapidly terminated simply by removing the system(s). Hypotension or any signs of collapse that may occur can be treated by elevating the patient's legs and, if necessary, bandaging them.

PRESENTATION

Transiderm-Nitro 25 contains glyceryl trinitrate 25mg and has a release rate of 0.2mg/hour. The tan coloured backing film is marked with the letters "CG DOD".

Transiderm-Nitro 50 contains glyceryl trinitrate 50mg and has a release rate of 0.4mg/hour. The tan coloured backing film is marked with the letters "CG DPD".

All systems are supplied in cartons containing 10 or 30 individually pouched units.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Poison schedule: Schedule 4

TGA Approval Date: 14 August 1996

Date of most recent amendment: 24 August 2011