# PRODUCT MONOGRAPH

# TRANSDERM-NITRO®

(nitroglycerin)
Transdermal Therapeutic System

Antianginal Agent

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# TRANSDERM-NITRO®

nitroglycerin

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | All Nonmedicinal Ingredients |
|---|---|---|
| Transdermal Therapeutic System | Patch: 0.2 mg/hour, 0.4 mg/hour, 0.6 mg/hour | Colloidal silicon dioxide, lactose, and silicone medical fluid<br><br>Patch layers contain aluminized plastic, ethylene/vinyl acetate copolymer and hypoallergenic silicone adhesive.<br><br>*See Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

TRANSDERM-NITRO® (nitroglycerin) is indicated for the prevention of anginal attacks in patients with stable angina pectoris associated with coronary artery disease. It can be used in conjunction with other antianginal agents such as β-blockers and/or calcium channel blockers.

TRANSDERM-NITRO® is not intended for the immediate relief of acute attacks of angina pectoris. Sublingual nitroglycerin preparations should be used for this purpose.

**Geriatrics:**

The safety and effectiveness of TRANSDERM-NITRO® in this patient population have not been established. Additional clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may result in hypotension and increased risk of falling at the therapeutic doses of nitroglycerin. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease

or other drug therapy.

**Pediatrics (<18 years of age):**
Safety and effectiveness have not been established in children. Therefore recommendations for its use cannot be made.

## CONTRAINDICATIONS

- Patients who are hypersensitive to this drug, related organic nitrate compounds or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Acute circulatory failure associated with marked hypotension (shock and states of collapse).
- Postural hypotension.
- Left ventricular dysfunction due to obstruction as in aortic or mitral stenosis or constrictive pericarditis.
- Increased intracranial pressure.
- Increased intraocular pressure.
- Severe anemia.
- Concomitant use of TRANSDERM-NITRO® either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA* (sildenafil), CIALIS* (tadalafil) and LEVITRA* or STAXYN* (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of TRANSDERM-NITRO® which can lead to severe hypotension.
- Do not use TRANSDERM-NITRO® in patients who are taking the soluble guanylate cyclase stimulator ADEMPAS* (riociguat) for chronic thromboembolic pulmonary hypertension or pulmonary arterial hypertension. Concomitant use can cause hypotension.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

Concomitant use of TRANSDERM-NITRO® either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA* (sildenafil), CIALIS* (tadalafil) and LEVITRA* or STAXYN* (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of TRANSDERM-NITRO® which can lead to severe hypotension.

### General

TRANSDERM-NITRO® (nitroglycerin) patches contain an aluminum layer. Therefore, the TRANSDERM-NITRO® patch must be removed before applying a magnetic field to the body during procedures such as an MRI (magnetic resonance imaging) or an electrical field such as in a cardioversion or DC defibrillation, as well as before applying diathermy treatment, since it may be associated with damage to the paddles and burns to the patient.

Headaches or symptoms of hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. A reduction in dose or discontinuation of treatment may be necessary.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

### Cardiovascular

The benefits and safety of transdermal nitroglycerin in angina patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use TRANSDERM-NITRO® in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the potentially deleterious effects of induced hypotension and tachycardia.

Nitroglycerin is a potent vasodilator and causes a significant decrease in mean blood pressure (approximately 10-15 mm Hg) in some patients when used in therapeutic dosages. Caution should be exercised in using the drug in patients who are prone to, or who might be affected by

hypotension. Nitroglycerin should therefore be used with caution in patients who may be volume-depleted, are on multiple medications, or who, for whatever reason, are already hypotensive (e.g. below 90 mm Hg). Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

**Dependence/Tolerance**

In industrial workers who have had long-term exposure to unknown (presumably high) doses of nitroglycerin, tolerance clearly occurs. There is moreover, physical dependence since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from these workers. In clinical trials of angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The importance of these observations to the routine clinical use of nitroglycerin has not been fully elucidated, but patients should be monitored closely for increased anginal symptoms during drug-free periods.

Tolerance to nitroglycerin with cross tolerance to other nitrates or nitrites may occur (see CLINICAL PHARMACOLOGY). Co-administration of other long-acting nitrates could jeopardize the integrity of the nitrate-free interval and therefore must be avoided. As tolerance to nitroglycerin patches develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

**Driving and using machinery**

When driving or using machines, patients should be aware that TRANSDERM-NITRO® (nitroglycerin), especially at the start of treatment, may cause faintness and/or dizziness.

**Hematologic**

Caution should be exercised when using nitroglycerin in patients prone to, or who might be affected by hypotension. The drug therefore should be used with caution in patients who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure

(e.g. below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

**Respiratory**

Caution should be exercised in patients with arterial hypoxemia due to anemia (see CONTRAINDICATIONS), because in such patients the biotransformation of nitroglycerin is reduced. Similarly, caution is called for in patients with hypoxemia and ventilation/perfusion imbalance due to lung disease or ischemic heart failure. Patients with angina pectoris, myocardial infarction, or cerebral ischemia 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 to poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

**Sexual Function/Reproduction**

There is no data supporting any special recommendations in women of child-bearing potential. Therefore, use TRANSDERM-NITRO® only if the potential benefit justifies the risk.

***Special Populations***

**Pregnant Women:** It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman. Therefore use TRANSDERM-NITRO® only if the potential benefit justifies the risk to the fetus.

**Women of child-bearing potential:** There is no data supporting any special recommendations in women of child-bearing potential. Therefore, use TRANSDERM-NITRO® only if the potential benefit justifies the risk.

**Nursing Women:** It is not known whether nitroglycerin is excreted into breast milk. Benefits to the mother must be weighed against the risks to the child

**Pediatrics (< 18 years of age):** Safety and effectiveness have not been established in children. Therefore recommendations for its use cannot be made.

**Geriatrics:**
The safety and effectiveness of TRANSDERM-NITRO® in this patient population have not been established. Additional clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may result in hypotension and increased risk of falling at the therapeutic doses of nitroglycerin. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE DRUG REACTIONS

Adverse drug reactions are listed by MedDRA System-Organ Class in Table 1.

**Table 1 – Adverse Drug Reactions**

| | | |
|---|---|---|
| **Nervous system disorders** | | |
| | Common: | Headache |
| | Very rare: | Dizziness |
| **Cardiac disorders** | | |
| | Rare: | Tachycardia |
| **Vascular disorders** | | |
| | Rare: | Orthostatic hypotension, flushing |
| **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 |
| **Investigations** | | |
| | Rare: | Heart rate increased |

Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses of nitroglycerin. Headaches may be treated with concomitant administration of mild analgesics. If such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or the product discontinued. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy.

Reddening of the skin (application site erythema), with or without a mild local itching (pruritus) or burning sensation, as well as allergic contact dermatitis may occasionally occur. 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.

Less frequently reported adverse reactions include dizziness, faintness, facial flushing, orthostatic hypotension which may be associated with reflex tachycardia. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

**Post-Market Adverse Drug Reactions**

The following adverse drug reactions have been derived from post-marketing experience with TRANSDERM-NITRO® (nitroglycerin) 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.

## DRUG INTERACTIONS

**Serious Drug Interactions**

Concomitant administration of TRANSDERM-NITRO® and other vasodilators e.g. PDE5 inhibitors such as VIAGRA* (sildenafil), CIALIS* (tadalafil) and LEVITRA* or STAXYN* (vardenafil) potentiates the hypotensive effect of TRANSDERM-NITRO®. This could result in life-threatening hypotension with syncope or myocardial infarction and death. Therefore, PDE5 inhibitors are absolutely contraindicated in patients receiving TRANSDERM-NITRO® therapy in any manner (see CONTRAINDICATIONS).

Established or potential drug-drug interactions are listed in Table 2.

**Table 2 - Established or Potential Drug-Drug Interactions**

| Proper name | Ref | Effect | Clinical comment |
|---|---|---|---|
| Soluble guanylate cyclase stimulators such as ADEMPAS* (riociguat) | T | Can cause severe hypotension. | Exaggerated cGMP-mediated vasodilation associated with both nitroglycerin and soluble guanylate cyclase stimulators can lead to severe hypotension (See CONTRAINDICATIONS) |
| Calcium channel blockers, ACE inhibitors, β-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquilizers | C and CT | May potentiate the blood pressure lowering effect of TRANSDERM-NITRO® | Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dosage adjustments of either class of agents may be necessary. |
| Dihydroergotamine | C | May increase the bioavailability of dihydroergotamine. | Special attention is warranted in patients with coronary artery disease because dihydroergotamine antagonizes the effect of nitroglycerin and may lead to vasoconstriction. |
| Acetylsalicylic acid and non-steroidal anti-inflammatory drugs | T | Might diminish the therapeutic response to nitrates and nitroglycerin | The possibility that the ingestion of acetylsalicylic acid and non-steroidal anti-inflammatory drugs might diminish the therapeutic response to nitrates and nitroglycerin |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### Drug-Food Interactions

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

### Drug-Herb Interactions

Interactions with herbal products have not been established.

### Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

### Drug-Lifestyle Interactions

As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

The daily dosage schedule is based on intermittent therapy to prevent the development of tolerance to nitroglycerin. The optimal dose should be selected based upon the clinical response, side effects, and the effects of therapy on blood pressure.

Starting dose is one TRANSDERM-NITRO® (nitroglycerin) 0.2 patch (10 $cm^2$), usually applied in the morning. If 0.2 mg/hour (10 $cm^2$) is well tolerated, the dose can be increased to 0.4 mg/hour (20 $cm^2$) if required. A maximum of 0.8 mg/hour (40 $cm^2$) may be used.

**Prevention of Tolerance**

Although some controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e. complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustments even to levels much higher than generally used did not prevent the development of tolerance.

Tolerance can be prevented or attenuated by use of an intermittent dosage schedule. Although the minimum nitrate-free interval has not been defined, clinical trials have demonstrated that an appropriate dosing schedule for nitroglycerin patches would provide for a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours. The patch-free time should coincide with the period in which angina pectoris is least likely to occur (usually at night). Patients should be watched carefully for an increase of angina pectoris during the patch-free period. Adjustment of background medication may be required.

The dose of TRANSDERM-NITRO® should be periodically reviewed in relation to continuing antianginal control.

**Site of Patch Application**

TRANSDERM-NITRO® can be applied to any area of skin except the distal extremities. Many patients prefer the chest. Each successive application should be to a different site to minimize local irritation.

The area should be clean, dry, and preferably hairless. If hair is likely to interfere with patch adhesion or removal, clipping may be necessary prior to application. Take care to avoid areas with cuts or irritations.

## OVERDOSAGE

### Symptoms

Nitroglycerin overdose may result in severe hypotension, persistent throbbing headache, vertigo, palpitations, visual disturbances, flushing and perspiring skin (later becoming cold and cyanotic), anorexia, nausea and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright posture), methemoglobinemia with cyanosis, hyperpnea, dyspnea and slow breathing, slow pulse (dicrotic and intermittent), heart block and bradycardia, increased intracranial pressure with cerebral symptoms of fever, confusion, and coma possibly followed by paralysis, clonic convulsions and death due to circulatory collapse.

### Treatment

Keep the patient recumbent in a shock position and comfortably warm. Remove the TRANSDERM-NITRO® (nitroglycerin) patch.

Passive movement of the extremities may aid venous return. Administer oxygen and artificial ventilation if necessary.

Intravenous infusion of normal saline or similar fluid may also be required to produce sufficient central volume expansion. However, in patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose; it and related compounds are contraindicated in this situation.

### Methemoglobinemia

Case reports of clinically significant methemoglobinemia are rare at conventional doses of nitroglycerin. The formation of methemoglobin is dose-related, and in the case of genetic abnormalities of hemoglobin that favour methemoglobin formation, even conventional doses of organic nitrates can produce harmful concentrations of methemoglobin. Methemoglobin levels

are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial $pO_2$. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. If methemoglobinemia is present, administration of methylene blue (1% solution), 1 to 2 mg/kg intravenously over 5 minutes, may be required. Repeat methemoglobin levels should be obtained 30 minutes later and a repeat dose of 0.5 to 1.0 mg/kg may be used if the level remains elevated and the patient is still symptomatic. Relative contraindications for methylene blue include known NADH methemoglobin reductase deficiency or G-6-PD deficiency. Infants under the age of 4 months may not respond to methylene blue due to immature NADH methemoglobin reductase.

Exchange transfusion has been used successfully in critically ill patients when methemoglobinemia is refractory to treatment.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins, with more prominent effects on the latter. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload). Dilation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilation remains undefined.

When TRANSDERM-NITRO® (nitroglycerin) is applied to the skin, nitroglycerin is absorbed directly into the systemic circulation. Thus, the active drug reaches target organs before inactivation by the liver. The transdermal absorption of nitroglycerin occurs in a continuous and well-controlled manner. Nitroglycerin is rapidly metabolized, principally by a liver reductase, to form glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, the 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, appear to be less potent than nitroglycerin as

vasodilators but have longer plasma half-lives. The dinitrates are further metabolized to mononitrates (biologically inactive with respect to cardiovascular effects) and ultimately to glycerol and carbon dioxide. There is extensive first-pass deactivation by the liver following gastrointestinal absorption.

**Pharmacodynamics**

Single-blind, placebo-controlled studies in healthy volunteers revealed that uniform steady state plasma concentrations were reached within two hours after application of the patch and remained at the same level until removal of the patch at 24 hours. Between 2 and 24 hours, the mean concentration was 0.16 $\pm$ 0.03 ng/mL (1 x 10 cm² patch), 0.25 $\pm$ 0.04 ng/mL (2 x 10 cm² patch), and 0.57 $\pm$ 0.11 ng/mL (4 x 10 cm² patch), the area under the curve showing a linear correlation between drug-release area and plasma concentration. Within one hour of removal of the patch, the plasma concentration declines to about 50% of steady state concentration and to undetectable concentrations by two hours.

Although dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration, such a strategy is probably inappropriate for organic nitrates. Some controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously. The large majority of such controlled trials, however, have shown the development of tolerance (i.e. complete loss of effect as measured by exercise testing) within the first day. Tolerance has appeared even when doses greater than 4 mg/hour were delivered continuously. This dose is far in excess of the effective dose 0.2 to 0.8 mg/hour applied intermittently.

Efficacy of organic nitrates is restored after a period of absence of nitrates from the body. Drug-free intervals of 10 to 12 hours are known to be sufficient to restore response. Several studies have demonstrated that when nitroglycerin is administered according to an intermittent regimen, doses of TRANSDERM-NITRO® 0.4 - 0.8 mg/hr (20 - 40 cm²) have increased exercise capacity for up to 8 hours, with a trend of increased exercise capacity to 12 hours. One controlled clinical trial suggested that the intermittent use of nitrates may be associated with a decreased, in

comparison to placebo, exercise tolerance during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown. In another clinical trial there was an increase in nocturnal angina attacks during the drug-free period in some patients treated with nitroglycerin as compared to placebo. Therefore, the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered.

The primary pharmacological effect of nitroglycerin is its smooth muscle relaxant effect. Therapeutic effectiveness depends on its actions on vascular smooth muscle.

Dose-related vasodilation is seen in both the arterial and venous beds, but is most prominent in the latter. The increased venous capacitance (venous pooling) results in a reduction of venous return, ventricular end-diastolic volume, and preload.

In addition, the vasodilating effect on the resistance vessels tends to reduce systolic blood pressure, left ventricular systolic wall tension and afterload. These effects combine to reduce myocardial oxygen requirements.

**Pharmacokinetics**

**Absorption:** Following single application of TRANSDERM-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 TRANSDERM-NITRO®.

**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:** Nitroglycerin is rapidly metabolized to glyceryl dinitrates and mononitrates by glutathione-dependent organic nitrate reductase in the liver. In addition, studies with human erythrocytes *in vitro* have shown that the erythrocyte is also a site of biotransformation of nitroglycerin by a sulphydryl-dependent enzymatic process and by an interaction with reduced hemoglobin. The amount of reduced hemoglobin in human erythrocytes seems to play a major role in their metabolic activity, and caution should therefore be exercised in cases of anemia. 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 vasodilation.

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 cGMPdependent protein kinase, which causes vasorelaxation. Glyceryl dinitrate, mononitrate and nitroglycerin at high doses are bioactivated by P450 enzyme(s) in the smooth endoplasmic reticulum directly yielding NO which causes vasorelaxation.

**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 minutes, 30-60 minutes, 5-6 hours respectively.

***Special Populations and Conditions***

**Geriatrics:**
The safety and effectiveness of TRANSDERM-NITRO® in this patient population have not been established. Additional clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may result in hypotension and increased risk of falling at the therapeutic doses of nitroglycerin. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Pediatrics:** Safety and effectiveness have not been established in children. Therefore recommendations for its use cannot be made.

## STORAGE AND STABILITY

Store patches below 25°C. Do not freeze.

Each patch is individually sealed in a separate pouch. Do not store out of the pouch.

Keep TRANSDERM-NITRO® out of reach of children and pets both before use and when disposing of used patches.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

| | TRANSDERM-NITRO® 0.2 | TRANSDERM-NITRO® 0.4 | TRANSDERM-NITRO® 0.6 |
|---|---|---|---|
| Rated Release of Nitroglycerin *in vivo* | 0.2 mg/hour | 0.4 mg/hour | 0.6 mg/hour |
| Nitroglycerin Content | 25 mg | 50 mg | 75 mg |
| Drug Releasing Area | 10 cm² | 20 cm² | 30 cm² |
| Printed Code | Transderm-Nitro®<br>0.2 MG/HR<br>CG DOD | Transderm-Nitro®<br>0.4 MG/HR<br>CG DPD | Transderm-Nitro®<br>0.6 MG/HR<br>CG EJE |
| Colour of Protective Liner (peel off and discard) | off-white | off-white | off- white |

### Composition / Description

TRANSDERM-NITRO® (nitroglycerin) transdermal therapeutic system, is a flat multilayer unit designed to release nitroglycerin continuously through a semipermeable membrane following its application to intact skin. In cases where permeability of the skin is excessive, drug release is limited by this release membrane.

The rate of nitroglycerin release is linearly dependent upon the drug releasing area of the applied patch (see AVAILABILITY OF DOSAGE FORMS). The nominal rate of nitroglycerin release *in vivo* is approximately 0.02 mg/cm²/hour. Nitroglycerin remaining in the patch serves as a thermodynamic energy source to keep the pattern of drug delivery constant.

The patch comprises five layers:

(1) a tan-coloured backing layer (aluminized plastic) impermeable to nitroglycerin;

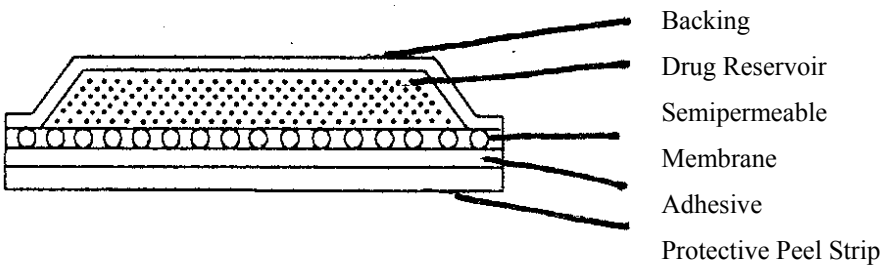
(2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide and silicone medical fluid;

(3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin;

(4) a layer of hypoallergenic silicone adhesive;

(5) a protective liner (peel strip) which is removed prior to use to expose the adhesive surface.

Cross section of the patch:



# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

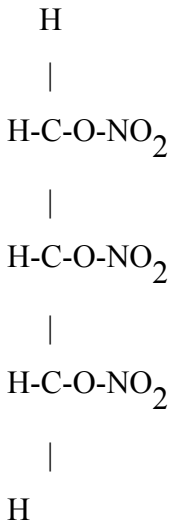
### Drug Substance

Proper name: Nitroglycerin

Chemical name: 1,2,3-propanetriol trinitrate

Molecular formula and molecular mass: $C_3H_5N_3O_9$; 227.1

Structural formula:



Physicochemical properties: Freely soluble in ethanol, ether, acetic acid, ethyl acetate and chloroform; soluble in methanol; slightly soluble in water.

## TOXICOLOGY

### Acute Toxicity

The intravenous lethal dose of nitroglycerin was found to be 83.5 mg/kg in the guinea pig, while the intravenous $LD_{50}$ in rabbits was 43 mg/kg. The lethal dose following intramuscular

administration to rabbits, guinea pigs, rats and cats varied between 150 and 500 mg/kg. Orally, doses of 80 to 100 mg/kg were found to be lethal in the guinea pig and rat. Signs and symptoms of toxicity include methemoglobinemia and circulatory collapse leading to convulsions and death.

**Subacute Toxicity**

Subcutaneous administration of nitroglycerin at a low dose of 0.1 mg/kg daily to cats for a period of 40 days produced anemia and fatty degeneration of the liver. Daily doses as high as 7.5 or 15 mg/kg given subcutaneously for a period of 50 days were given to cats. Two died after 10 to 20 doses, respectively. The surviving animals showed jaundice and albuminuria, and hemorrhages of the cerebellum, heart, liver and spleen were seen at post-mortem.

**Reproduction Studies**

A three generation reproduction study in rats found adverse effects on fertility in the high dose group (363 and 434 mg/kg/day in the diet for males and females, respectively) resulting from decreased feed intake and consequent poor nutritional status and decreased body weight gain of the females, and decreased spermatogenesis (accompanied by increased interstitial tissue) in the males. Although litter size, birth weight, viability, lactation indices and weaning weight were reduced, there were no specific nitroglycerin-induced teratogenic effects.

**Carcinogenicity**

Rats receiving high doses of nitroglycerin in the diet (363 mg/kg/day in males and 434 mg/kg/day in females) for 2 years had an incidence of hepatocellular carcinomas and/or neoplastic nodules of 67% and interstitial cell tumours of the testes of about 50%. Mid-dose rats receiving 31.5 mg/kg/day (males) and 38.1 mg/kg/day (females) had an incidence of hepatocellular carcinomas and/or neoplastic nodules of about 11% versus about 2% in the controls. Mice receiving 1022 mg/kg/day (males) or 1058 mg/kg/day (females) for the same period showed no treatment-related tumours.

**Mutagenicity**

There were no apparent nitroglycerin-induced mutagenic effects in the cytogenetics analyses of bone marrow and kidney cells from dogs (up to 25 mg/kg in capsules for one year) and rats fed nitroglycerin for 2 years (up to 363 mg/kg/day in males and 434 mg/kg/day in females) and in the dominant lethal mutation study in rats.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**
**PATIENT MEDICATION INFORMATION**

**TRANSDERM-NITRO®**
**nitroglycerin patch**

Read this carefully before you start taking **TRANSDERM-NITRO®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TRANSDERM-NITRO®**

**Serious Warnings and Precautions**

Do **NOT** take any medication for the treatment of impotence (erectile dysfunction) such as VIAGRA* (sildenafil citrate), CIALIS* (tadalafil), LEVITRA* or STAXYN* (vardenafil) while using **TRANSDERM-NITRO®**. Using **TRANSDERM-NITRO®** together with medication for erectile dysfunction can result in life-threatening low blood pressure (hypotension) causing fainting, heart attack and death.

**What is TRANSDERM-NITRO® used for?**
**TRANSDERM-NITRO®** is used in adults to prevent angina (chest pain). It can be used alone or together with other antianginal agents such as beta-blockers and/or calcium channel blockers.

**TRANSDERM-NITRO®** is not intended to be used for acute angina attacks. Sublingual nitroglycerin medications should be used if you are having an acute angina attack.

**How does TRANSDERM-NITRO® work?**
When TRANSDERM-NITRO® is applied to the skin, it releases small amounts of nitroglycerin at a steady rate. This passes through the skin, into your bloodstream. It relaxes and widens the blood vessels and increases the supply of blood and oxygen to the heart. This helps prevent attacks of anginal pain (chest pain) from occurring.

**What are the ingredients in TRANSDERM-NITRO®?**
Medicinal ingredients: Nitroglycerin
Non-medicinal ingredients: colloidal silicon dioxide, lactose, and silicone medical fluid
Patch layers contain aluminized plastic, ethylene/vinyl acetate copolymer and hypoallergenic silicone adhesive.

**TRANSDERM-NITRO® comes in the following dosage forms:**
TRANSDERM-NITRO® is available in three different patch strengths:
TRANSDERM-NITRO® 0.2 mg/hour (10 $cm^2$)
TRANSDERM-NITRO® 0.4 mg/hour (20 $cm^2$)
TRANSDERM-NITRO® 0.6 mg/hour (30 $cm^2$)

**Do not use TRANSDERM-NITRO® if you:**

- are allergic to nitroglycerin, nitrates, nitrites or any non-medicinal ingredient in the formulation.
- have had a recent heart attack, or other serious heart problems, stroke or head injury
- experience lightheadedness, dizziness or fainting when going from lying or sitting to standing up (postural hypotension).
- have narrowing of the heart valves.
- have a condition caused by an increase in normal brain pressure (increased intracranial pressure).
- have an eye disease called closed angle glaucoma or any other condition that increases the pressure in your eyes.
- have severe anemia (low iron levels in your blood or low red blood cell count).
- are taking medication for erectile dysfunction such as VIAGRA* (sildenafil citrate), CIALIS* (tadalafil), LEVITRA* or STAXYN* (vardenafil).
- are taking medications used to treat high blood pressure in your lungs such as ADEMPAS* (riociguat), REVATIO* (sildenafil citrate) or ADCIRCA* (tadalafil).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRANSDERM-NITRO®. Talk about any health conditions or problems you may have, including if you:**

- have heart failure
- have low blood pressure or take diuretics ("water pills")
- have lung disease
- are breast feeding, pregnant or intend to become pregnant. Your healthcare professional will decide whether you should use TRANSDERM-NITRO® and what extra care should be taken during its use.
- are less than 18 years old or older than 65 years of age
- are dehydrated or suffer from excessive vomiting, diarrhea or sweating
- have angina due to hypertrophic cardiomyopathy

**Other warnings you should know about:**

**Driving and using machines:** Before you perform tasks which may require special attention, wait until you know how you respond to TRANSDERM-NITRO®. Dizziness, lightheadedness, or fainting can occur, especially after the first dose and when the dose is increased.

Tolerance to TRANSDERM-NITRO® and similar drugs can occur after long periods of use. Chronic use can lead to angina attacks being brought on more easily. Do not suddenly stop using TRANSDERM-NITRO®. Talk to your healthcare professional if you wish to discontinue using TRANSDERM-NITRO®.

TRANSDERM-NITRO® is not for use in children.

After normal use, there is enough residual nitroglycerin in discarded TRANSDERM-NITRO® patches that they are a potential hazard to children and pets.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Serious Drug Interactions**

**If you are currently taking medications for the treatment of impotence (erectile dysfunction), such as sildenafil citrate, tadalafil or vardenafil or any other similar medication (PDE5 inhibitors), the use of TRANSDERM-NITRO® may lead to extreme low blood pressure resulting in fainting, heart attack and death.**

If you are being treated with any of these drugs and need TRANSDERM-NITRO® (e.g. in case of chest pain caused by an acute attack of angina) please seek emergency medical assistance immediately.

**The following may interact with TRANSDERM-NITRO®:**

- Do not take any drugs used to treat erectile dysfunction such as VIAGRA* (sildenafil citrate), CIALIS* (tadalafil), LEVITRA* or STAXYN* (vardenafil) if you are using TRANSDERM-NITRO®.
- Drugs used to treat high blood pressure such as:
  - Diuretics ("water pills")
  - Calcium Channel Blockers (e.g. diltiazem, nifedipine, verapamil)
  - ACE Inhibitors
  - Beta-Blockers
- Drugs used to treat depression called "tricyclic antidepressants".
- Tranquillizers.
- Other drugs that may have the same effect as TRANSDERM-NITRO®.
- Alcohol
- Drugs used to treat migraine headaches (e.g. dihydroergotamine)
- Acetylsalicylic acid (Aspirin*)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling (such as ibuprofen, naproxen, and celecoxib).
- Do not use TRANSDERM-NITRO®.if you are taking drugs used to treat high blood pressure in your lungs such as ADEMPAS* (riociguat), REVATIO* (sildenafil citrate) or ADCIRCA* (tadalafil).

**How to use TRANSDERM-NITRO®:**

**1. Deciding Where to Apply the Patch**

Choose any area of skin which is most comfortable for you, but <u>not</u> past the knees or elbows. Many patients prefer the chest. It is best if the area is hairless. Avoid skin folds. The skin

should not be scarred, burned, irritated or broken, since this may alter the amount of medicine you get. You should apply the patch to a different area of skin each day, and wait several days before using the same area again. To help you remember to change the site of patch application regularly, you may wish to use the same area of skin on a particular day of the week.
For example:

| | | |
|---|---|---|
| Sunday | 1 | |
| Monday | 2 | |
| Tuesday | 3 | |
| Wednesday | 4 | |
| Thursday | 5 | |
| Friday | 6 | |
| Saturday | 7 | |
| Sunday | 1 | |
| Monday | 2 | etc. |

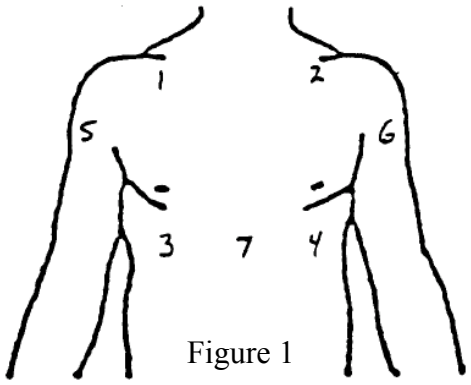

Figure 1

**2. Preparing the Skin**

In order for the patch to stick, the skin must be clean and dry without any creams, lotions, oil or powder. If hair is likely to interfere with the patch sticking or removal, it can be clipped but not shaved since this may irritate the skin.

**3. Opening the Pouch**

Each TRANSDERM-NITRO® patch is individually sealed in a protective pouch. Tear open this pouch at the indentation and remove the patch. Do not use scissors, since you may accidentally cut the patch. (Figure 2 & 3). TRANSDERM-NITRO® is designed as a complete unit. Do not cut the patch.

Figure 2

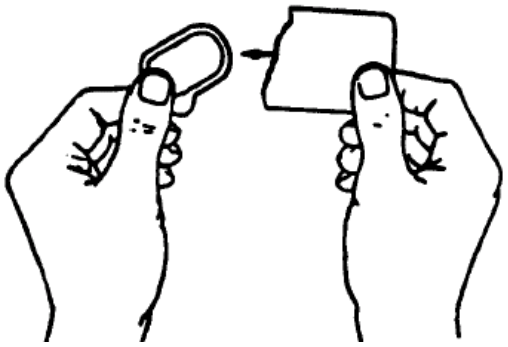

Figure 3

**4. Recognizing the Patch and Removing the Liner**

The patch itself is tan-coloured. A plastic liner covers the adhesive (sticky) side of the patch during storage, and must be removed and discarded before patch use. The plastic liner will be either white on both sides or clear, depending on the size of the patch.

Pick up the patch lengthwise with the tab up, and the plastic liner facing you (Figure 4). If you are left-handed it might be easier to start with the tab down and the tan-coloured side facing you. Firmly bend the tab forward with the thumb. With both thumbs, carefully remove the plastic protective liner from the patch starting at the tab (Figure 5). Continue to peel back the plastic liner along the length of the patch, allowing the patch to rest on the outside of your fingers. (Figure 6)

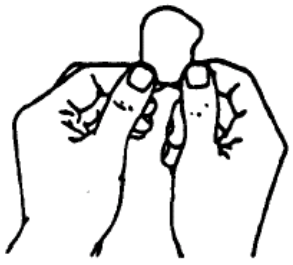

Figure 4

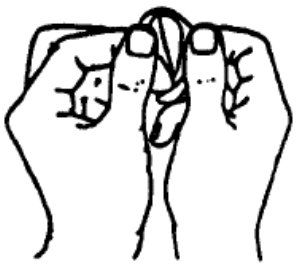

Figure 5

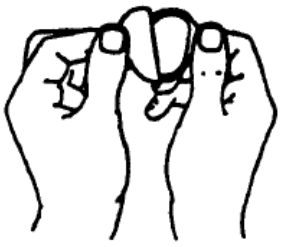

Figure 6

By removing the plastic liner you have exposed the adhesive side. The adhesive side of the patch appears to have a silver-coloured edge. From this side you should also be able to see the white cream containing nitroglycerin within the patch.

Avoid touching the adhesive. If another person applies the patch for you, he/she must be careful not to touch the surface which will be applied to the skin. Apply the tan-coloured patch immediately after opening the pouch and removing the plastic liner. Discard the plastic liner.

**5. Applying the Patch**

Remember, the skin should be clean and dry without creams, lotions, oil or powder. Place the exposed adhesive side of the patch (i.e. the silver-edged side) on the area you have chosen as explained above. Press it <u>firmly</u> in place with the palm of your hand for 10 - 20 seconds (Figure 7). Circle the outside edge of the patch with one or two fingers. Once the patch is in place, do not test the adhesion by pulling on it. When applied correctly, the tan-coloured side will be seen when looking at the patch on the skin.

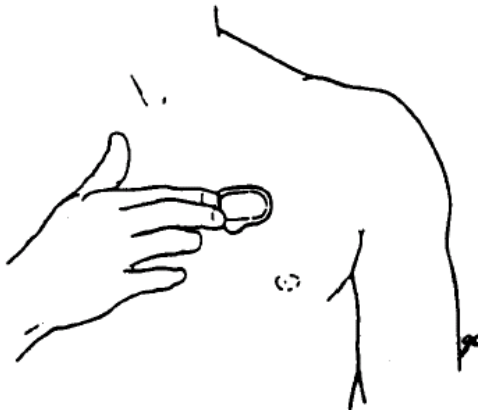

Figure 7

**6. When and How to Remove the Patch**

The TRANSDERM-NITRO® patch should be changed according to the schedule prescribed by your doctor. It is important to respect the patch-off period recommended by your doctor. If you

forget to remove it at the scheduled time just remove it as soon as possible and continue to follow your original schedule.

Remove the patch by pulling on the tab. Each patch can only be applied once. After use, fold the patch in half with the adhesive side inwards. Throw it away safely out of the reach of children. Any adhesive left on the skin can be removed with rubbing alcohol or light mineral oil.

## 7. What to Do if TRANSDERM-NITRO® Falls Off

Contact with water (as in bathing, swimming, showering) or physical activity will not affect the patch. It is unlikely that the patch will fall off. If the patch does fall off, discard it and put a new patch on a different area of skin. Continue to follow your original schedule.

**Usual adult dose:**
The daily dosage schedule is based on intermittent therapy (patch on period followed by a patch-off period) to prevent the development of tolerance to nitroglycerin.

Starting dose is one TRANSDERM-NITRO® 0.2 mg/hour patch (10 cm²), usually applied in the morning. If 0.2 mg/hour (10 cm²) is well tolerated, the dose can be increased to 0.4 mg/hour (20 cm²) if required. A maximum of 0.8 mg/hour (40 cm²) may be used.

**Overdose:**

| |
|---|
| If you think you have used too much TRANSDERM-NITRO®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. |

## What are possible side effects from using TRANSDERM-NITRO®?

These are not all the possible side effects you may feel when taking TRANSDERM-NITRO®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Headache
- Flushing of the face
- Nausea
- Vomiting
- Rash, redness, itching and/or burning in the area where the patch is applied.

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **UNKNOWN** | | | |
| **Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing. | | | √ |
| **Unstable Angina:** chest pain that has changed or gotten worse, nausea, anxiety, sweating, shortness of breath, dizziness, fatigue | | | √ |
| **Increased levels of methemoglobin in the blood**: shortness of breath, blue or purple coloration of the lips, fingers and/or toes, headache, fatigue, dizziness, loss of consciousness. | | | √ |
| **Low Blood Pressure:** dizziness, fainting, lightheadedness, fast heartbeat. May occur when you go from lying or sitting to standing up. | √ | | |
| **High Blood Pressure:** headache, vision problems, irregular heartbeat | √ | | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**
TRANSDERM-NITRO® should be stored at temperatures below 25˚C. Do not freeze. Do not store it out of the individually sealed pouch.

TRANSDERM-NITRO® should be kept out of the reach of children and pets both before use and when disposing of used patches. If your patch becomes stuck to a child or another person, remove the patch at once and contact a doctor.

**If you want more information about TRANSDERM-NITRO®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://www.hc-sc.gc.ca); the manufacturer's website http://www.novartis.ca or by calling 1-800-363-8883

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc., 385 Bouchard, Dorval, Quebec, H9S 1A9.

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