PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

TRINIPATCH 0.2

TRINIPATCH 0.4

TRINIPATCH 0.6

Nitroglycerin Transdermal Delivery System

Patch, 0.2, 0.4 and 0.6 mg/hour, Transdermal

Antianginal Agent

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	12/2021
7 WARNINGS AND PRECAUTIONS	12/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRINIPATCH (nitroglycerin) used intermittently (see 10 CLINICAL PHARMACOLOGY) 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 beta-blockers and/or calcium antagonists.

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

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

No special information is available on the use of TRINIPATCH in geriatric population. However, there is no evidence suggesting that dosage should be adapted in these patients.

2 CONTRAINDICATIONS

- TRINIPATCH (nitroglycerin) is contraindicated in patients who are hypersensitive to this drug and related organic nitrate compounds or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the patch. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- TRINIPATCH (nitroglycerin) is contraindicated in patients with:
    - 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 of constrictive pericarditis.
    - Increased intracranial pressure.
    - Increased intraocular pressure.
    - Severe anemia.
- Concomitant use of TRINIPATCH (nitroglycerin) either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and LEVITRA® (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of TRINIPATCH which can lead to severe hypotension. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.
- Do not use TRINIPATCH (nitroglycerin) 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. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.

4 DOSAGE AND ADMINISTRATION

4.1 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 (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

Starting dose is one TRINIPATCH 0.2 patch (7 cm^2), usually applied in the morning. If 0.2 mg/hour (7 cm^2) is well tolerated, the dose can be increased to 0.4 mg/hour (14 cm^2) if required. A maximum of 0.8 mg/hour may be used.

Considerations for Special Populations

Pediatric (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatric (>65 years of age): No special information is available on the use of TRINIPATCH in geriatric population. However, there is no evidence suggesting that dosage should be adapted in these patients.

4.4 Administration

TRINIPATCH 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.

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. TRINIPATCH should be applied for 12-14 hours and taken off for 10-12 hours. Maximum daily dose is 0.8 mg/hour.

Following use, the patch should be discarded in a manner that prevents accidental application or ingestion.

4.5 Missed Dose

If the patient has forgotten to apply TRINIPATCH at the scheduled time then they should apply it as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the patient should go back to their regular dosing schedule. The patient should not apply extra patches to make up for a missed dose.

5 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 TRINIPATCH. 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Transdermal	Patch Patch 0.2 mg/hour, 7 cm^2. Each 7 cm^2 patch contains 22.4 mg of nitroglycerin, releasing 0.2 mg of nitroglycerin per hour. Patch 0.4 mg/hour, 14 cm^2. Each 14 cm^2 patch contains 44.8 mg of	Duro Tak 87-2196 and sorbitan mono-oleate.

	nitroglycerin, releasing 0.4 mg of nitroglycerin per hour. Patch 0.6 mg/hour, 21 cm^2. Each 21 cm^2 patch contains 67.2 mg of nitroglycerin, releasing 0.6 mg of nitroglycerin per hour.	

Composition

The TRINIPATCH (nitroglycerin) transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm^2 of applied system delivers approximately 0.03 mg of nitroglycerin per hour. Thus, the 7, 14 and 21 cm^2 systems deliver approximately 0.2, 0.4 and 0.6 mg of nitroglycerin per hour, respectively.

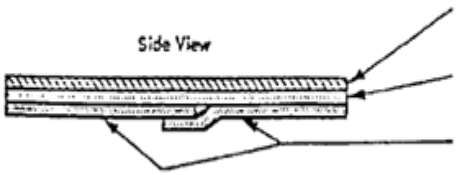
The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered approximately 10% of its original content of nitroglycerin.

The TRINIPATCH system comprises three layers:

1. a thin, occlusive, low density polyethylene (LDPE) backing film layer,
2. an acrylic adhesive matrix/drug reservoir layer,
3. a layer of siliconized polyester release liner comprised of overlapped liner strips that form an easy-opening tab.

Prior to use, a protective peel strip is removed from the adhesive surface.

Cross-section of the system.



1. Low density polyethylene (LDPE) Backing Film
2. Matrix Adhesive Layer
3. Overlapped Release Liner Strips, Peel Tab

Dosage Forms and Packaging

Each TRINIPATCH 0.2 (7 cm^2) contains 22.4 mg of nitroglycerin and delivers approximately 0.2 mg of active substance per hour.

Each TRINIPATCH 0.4 (14 cm^2) contains 44.8 mg of nitroglycerin and delivers approximately 0.4 mg of active substance per hour.

Each TRINIPATCH 0.6 (21 cm^2) contains 67.2 mg of nitroglycerin and delivers approximately 0.6 mg of active substance per hour.

Available in boxes of 30 and 100 systems. Each system is individually sealed in a separate pouch.

7 WARNINGS AND PRECAUTIONS

General
Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

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

Carcinogenesis and Mutagenesis
See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular
TRINIPATCH must be removed before cardioversion or DC defibrillation is attempted, as well as before applying diathermy treatment.

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 TRINIPATCH in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the potentially deleterious effects of induced hypotension and tachycardia.

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.

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.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Concomitant use of TRINIPATCH (nitroglycerin) either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and

LEVITRA® (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of TRINIPATCH which can lead to severe hypotension. See 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS.

Do not use TRINIPATCH (nitroglycerin) 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. See 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS.

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. 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.

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 has appeared even when doses greater than 4 mg/hour were delivered continuously, a dose 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. Thus, 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.

Several studies have demonstrated that when nitroglycerin is administered according to an intermittent regimen, doses of 0.4 - 0.8 mg/hr 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 exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is

unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered.

The dose of TRINIPATCH should be periodically reviewed in relation to continuing antianginal control.

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

Hematologic
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, may be required.

Neurologic
Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

Respiratory
Caution should be exercised in patients with arterial hypoxemia due to anemia (see 2 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.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with nitroglycerin. It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman. Therefore use TRINIPATCH only if the potential benefit justifies the risk to the fetus.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No special information is available on the use of TRINIPATCH in geriatric population. However, there is no evidence suggesting that dosage should be adapted in these patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 (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, postural hypotension which may be associated with reflex tachycardia. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon. Rarely nausea, and vomiting.

8.5 Post-Market Adverse Reactions

The most common adverse drug reaction reported post-market is localized skin reaction (local erythema, pruritus, rash). Other adverse reactions reported rarely in post-marketing use include:

Ophthalmic: blurred vision
Renal: Acute renal failure
Skin: application site pruritus, eczema, rash
Cardiovascular: hypotension, orthostatic hypotension

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of TRINIPATCH (nitroglycerin) either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and LEVITRA® (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of TRINIPATCH which can lead to severe hypotension. See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.

- Do not use TRINIPATCH (nitroglycerin) 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. See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.

9.2 Drug Interactions Overview

Concomitant treatment with other vasodilators, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, diuretics, tricyclic antidepressants and major tranquillizers may potentiate the blood pressure lowering effect of TRINIPATCH. Dose adjustment may be necessary.

Concurrent administration of TRINIPATCH with dihydroergotamine may increase the bioavailability of dihydroergotamine.

Use of Acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDS) might diminish the therapeutic response to nitrates and nitroglycerin, and heparin effectiveness may be decreased when used concurrently with nitroglycerin. See 9.4 Drug-Drug Interactions.

9.3 Drug-Behavioural Interactions

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Phosphodiesterase 5 (PDE 5) inhibitors	T	↑ hypotensive effect	This could result in life-threatening hypotension with syncope or myocardial infarction and death. See 2 CONTRAINDICATIONS.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Calcium channel blockers	T	↑ hypotensive effect	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.
Angiotensin converting enzyme (ACE) inhibitors	T	↑ hypotensive effect	Reinforce the influence of nitroglycerin on the lowering of arterial blood pressure. Dosage adjustment may be necessary.
Beta-Blockers	T	↑ hypotensive effect	Reinforce the influence of nitroglycerin on the lowering arterial blood pressure. Dosage adjustment may be necessary.
Diuretics	T	↑ hypotensive effect	Reinforce the influence of nitroglycerin on the lowering of arterial blood pressure. Dosage adjustment may be necessary.
Tricyclic antidepressants	T	↑ hypotensive effect	Reinforce the influence of nitroglycerin on the lowering of arterial blood pressure. Dosage adjustment may be necessary.
Major tranquilizers	T	↑ hypotensive effect	Reinforce the influence of nitroglycerin on the lowering of arterial blood pressure. Dosage adjustment may be necessary.
Dihydroergotamine	T	↑ bioavailability of dihydroergotamine	Warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonizes the action of nitroglycerin and this can lead to a coronary vasoconstriction.
Acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDS)	T	↓ therapeutic response	Ingestion of acetylsalicylic acid and non-steroidal anti-inflammatory drugs might diminish the therapeutic response to nitrates and nitroglycerin. Nitroglycerin's vasodilatory and hemodynamic effects may be altered by concomitant administration of acetylsalicylic acid and NSAIDS.
Heparin	T	↓ effectiveness of heparin	Use of nitroglycerin may decrease the effect of heparin. The effect of heparin should be frequently monitored when these two agents are used together. The dose of both agents may need to be adjusted.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Soluble guanylate cyclase stimulators	T	↑ hypotensive effect	Exaggerated cGMP-mediated vasodilation associated with both nitroglycerin and soluble guanylate cyclase stimulators can lead to severe hypotension. See 2 CONTRAINDICATIONS.

T=Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interaction with herbal products has not been established.

9.7 Drug-Laboratory Test Interactions

Interaction with laboratory tests has not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 system 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.

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.

10.2 Pharmacodynamics

TRINIPATCH transdermal system seems to cause redistribution of coronary blood flow in the endocardium. Nitroglycerin allows the improvement of balance between oxygen supply and demand, while dissipating spontaneously and completely the symptoms of angina pectoris attacks.

The response to nitrate products may differ from patient to patient, while absorption of nitroglycerin resulting from the system may vary between subjects.

Following the application of TRINIPATCH transdermal system onto the skin, constant, continued and prolonged absorption of the active ingredient (nitroglycerin) is initiated, resulting in prolonged venous diastolic action. Onset of action is achieved 30-60 minutes after the application of TRINIPATCH. The duration of action is approximately 24 hours.

10.3 Pharmacokinetics

Absorption
When TRINIPATCH 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. Bioavailability studies in healthy volunteers have shown that the released amount of nitroglycerin (5 mg or 10mg/24 hours) represents the mean release rate of nitroglycerin resulting from the system and represents the amount available for absorption.

Distribution
The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The serum therapeutic level remains undefined. With 50-500 ng/ml plasma concentrations, nitroglycerin is bound to plasma proteins at a rate of approximately 60%, while 1,2 and 1,3-dinitroglycerides are approximately 60% and 30% bound respectively.

The observed clearance rates (close to 1 L/kg/min.) greatly exceed hepatic blood flow, known sites of extrahepatic metabolism include red blood cells and vascular walls.

In healthy volunteers, after the application of TRINIPATCH in different dosages (2 x 7 cm^2 patch, 1 x 14 cm^2 patch and 1 x 21 cm^2 patch), the concentrations of nitroglycerin reached in the plasma were uniform and dose-related, i.e. dependent on drug-release area. They remained constant as long as the system is in contact with the skin (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentrations were maintained for about 30 min. Since the rate of release of nitroglycerin is linearly dependent upon the area of the applied system, two patches of 0.4 mg (or one patch of 0.2 mg and one patch of 0.6 mg) can be used for a dose of 0.8 mg.

Metabolism
Nitroglycerin is rapidly metabolized, principally by a glutathione-dependent organic nitrate reductase in the liver, 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.

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.

Elimination
Metabolic derivatives of nitroglycerin are excreted in the urine.

Special Populations and Conditions

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use**.**
- **Geriatrics:** No special information is available on the use of TRINIPATCH in geriatric population. However, there is no evidence suggesting that dosage should be adapted in these patients.

11 STORAGE, STABILITY AND DISPOSAL

Storage and stability
Store at controlled room temperature (between 15°C - 30°C).

Each patch is individually sealed in a separate pouch. Do not store out of the pouch. Keep TRINIPATCH out of reach of children and pets before use and when disposing of used patches.

Do not use beyond the expiry date indicated on the label. Do not refrigerate.

Disposal
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 and pets.

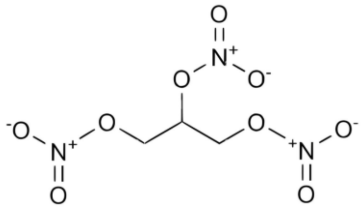
12 SPECIAL HANDLING INSTRUCTIONS

None required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper name: Nitroglycerin
Chemical name: 1, 2, 3-propanetriol-trinitrate
Molecular formula and molecular mass: $C_3H_5N_3O_9$, 227.09
Structural formula:



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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Prevention of anginal attacks
The clinical trial data on which the original indication was authorized is not available.

14.2 Comparative Bioavailability Studies

A randomized, two-way crossover study comparing the relative bioavailability of a single-dose application of TRINIPATCH 0.4 mg/hr (44.8 mg/14 cm^2) patch against the reference drug product, Transderm Nitropatch 0.4 (50 mg/20 cm^2) patch in a total of 30 healthy, non-smoking, male volunteers under fasting conditions.

The rate and extent of absorption of nitroglycerin and its metabolites, 1.2 and 1.3-dinitroglycerin were measured and compared after a single patch application of TRINIPATCH (0.4 mg/hr) and Transderm Nitropatch (0.4 mg/hr).

Table 3 - Comparative bioavailability data

NITROGLYCERIN

Parameter	Test[$]	Reference[&]	Ratio of geometric means (%)
$AUC_{(0\rightarrow 12)}$ ($pg.hr.mL^{-1}$)	2302.88	2160.33	107
$AUC_{(0\rightarrow 14)}$ ($pg.hr.mL^{-1}$)	2774.70	2577.49	108
C_{max} ($pg.\ mL^{-1}$)	376.97	355.69	106
T_{max} (h)*	10.03 (64%)	7.87 (64%)	
$T_{½}$ (h)*	18.76 (16%)	19.35 (53%)	

1,2 DINITROGLYCERIN

Parameter	Test[$]	Reference[&]	Ratio of geometric means (%)
$AUC_{(0\rightarrow 12)}$ ($ng.hr.mL^{-1}$)	29.46	26.36	113
$AUC_{(0\rightarrow 14)}$ ($ng.hr.mL^{-1}$)	35.18	31.09	114
C_{max} ($ng.mL^{-1}$)	3.25	2.87	114
T_{max} (h)*	9.33 (45%)	11.07 (63%)	
$T_{½}$ (h)*	43.79 (18%)	46.38 (19%)	

1,3 DINITROGLYCERIN

Parameter	Test[$]	Reference[&]	Ratio of geometric means (%)
$AUC_{(0\rightarrow 12)}$ ($ng.hr.mL^{-1}$)	4.43	4.58	98
$AUC_{(0\rightarrow 14)}$ ($ng.hr.mL^{-1}$)	5.30	5.41	99
C_{max} ($ng.mL^{-1}$)	0.49	0.50	99
T_{max} (h)*	9.40 (46%)	9.57 (62%)	
$T_{½}$ (h)*	55.04 (24%)	61.60 (30%)	

*These are arithmetic means (CV%)

[$] TRINIPATCH 0.4 (0.4mg/hr)

[&] Transderm Nitropatch (0.4 mg/hr).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity:

The intravenous lethal dose of nitroglycerin was found to be 83.5 mg/kg in the guinea pig, while the intravenous LD50 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 and 20 doses, respectively. The surviving animals showed jaundice and albuminuria, and hemorrhages of the cerebellum, heart, liver and spleen were seen at post-mortem.

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.

Genotoxicity:
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/day 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.

Reproductive and Developmental Toxicology:
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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TRINIPATCH 0.2, TRINIPATCH 0.4 and TRINIPATCH 0.6
Nitroglycerin Transdermal Delivery System

Read this carefully before you start taking **TRINIPATCH** 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 **TRINIPATCH**.

What is TRINIPATCH used for?
TRINIPATCH is used in adults to help reduce the amount and severity of attacks of anginal pain (chest pain). It can be used with other medications used to treat chest pain.

TRINIPATCH will **not** provide immediate relief for an acute attack of chest pain (an attack that has already started). Sublingual (under the tongue) nitroglycerin should be used for an acute attack.

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

What are the ingredients in TRINIPATCH?
Medicinal ingredients: Nitroglycerin.

Non-medicinal ingredients: Duro Tak 87-2196 and sorbitan mono-oleate.
Patch layers contain LD Polyethylene film, SDM 71 Nitroglycerin mixture and siliconized polyester film.

TRINIPATCH comes in the following dosage forms:
Patch: 0.2 mg/hour, 0.4 mg/hour and 0.8 mg/hour.

Do not use TRINIPATCH if:
- you are allergic to nitroglycerin, nitrates, nitrites, or to any of the ingredients in TRINIPATCH (see **What are the ingredients in TRINIPATCH**);
- you have poor blood circulation with very low blood pressure;
- you experience low blood pressure when you go from lying down to sitting up;
- you have increased pressure in your skull (intracranial pressure);
- you have narrowing of the heart valves;
- you have severe anemia;
- you have an eye disease called glaucoma or any other condition that increases the pressure in your eyes;
- you are taking any medications called “phosphodiesterase type 5 (PDE5) inhibitors”. This includes erectile dysfunction medications such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and LEVITRA® (vardenafil);

- you are taking ADEMPAS® (riociguat), a medication used to treat high blood pressure in the lungs; if you are unsure, ask your healthcare professional.

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

- have recently had a heart attack or stroke;
- have congestive heart failure;
- have low blood pressure or take diuretics ("water pills");
- are dehydrated or suffer from excessive vomiting, diarrhea or sweating;
- have low oxygen levels in your blood due to anemia, lung disease or heart failure;
- are pregnant, think you may be pregnant or are planning to become pregnant;
- are breastfeeding.

Other warnings you should know about:

Tolerance and physical dependence: Tolerance and physical dependence can occur when you use TRINIPATCH for a long period of time. Long-term use can lead to chest pain attacks happening more easily. Do **NOT** stop taking TRINIPATCH abruptly without talking to your doctor first, as you may experience unwanted side effects.

Headaches: Daily headaches can occur during treatment with TRINIPATCH. Resist the urge to change your treatment schedule to avoid headaches. The headaches may indicate that the medication is working. You can take mild pain relievers to relieve the headaches, but if they become severe, talk to your healthcare professional.

Discarding the patch: When you remove the patch, there may still be enough nitroglycerin left in the patch to cause harm to children and pets. Make sure to fold the patch in half (sticky side inwards) and dispose of it properly. If your patch becomes stuck to a child or another person, immediately remove the patch and talk to a healthcare professional.

Methemoglobinemia (a type of blood disorder): There are rare cases of people developing this blood disorder when taking nitroglycerin. This is a type of blood disorder which affects your blood's ability to carry oxygen. If you develop methemoglobinemia your blood may appear chocolate brown and not change colour when exposed to air. Tell your healthcare professional if you think you have methemoglobinemia, there are tests that they can do to check your blood.

Driving and using machines: TRINIPATCH may make you feel lightheaded, faint or dizzy. Give yourself time after using TRINIPATCH to see how you feel before driving a vehicle or using machinery.

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

Serious Drug Interactions

Do **NOT** take TRINIPATCH with:

- Drugs known as "PDE5 Inhibitors". This includes erectile dysfunction medications such as VIAGARA® (sildenafil), CIALIS® (tadalafil) and LEVITRA® (vardenafil).
- ADEMPAS® (riociguat), a medication used to treat high blood pressure in your lungs.

The following may also interact with TRINIPATCH:

- alcohol;
- medications used to lower blood pressure such as "calcium channel blockers", "angiotensin converting enzyme (ACE) inhibitors", "beta-blockers" and diuretics ("water pills");
- medications used to treat depression called "tricyclic antidepressants";
- medications used to manage psychosis (antipsychotics) called "tranquilizers";
- dihydroergotamine, a drug used to treat migraines and headaches;
- medications used to relieve pain and reduce inflammation such as acetylsalicylic acid (ASPIRIN®) and "non-steroidal anti-inflammatory drugs" (NSAIDs);
- heparin, a drug used to decrease blood clotting.

How to take TRINIPATCH:

- Read the entire Instructions for Use below for information on how to apply and use the patch.
- **Do not cut the patch.**
- Use TRINIPATCH exactly as your doctor has told you to.

INSTRUCTIONS FOR USE:

Each patch has a clear plastic backing and a special adhesive (sticky layer) that keeps the patch firmly in place. The medicinal ingredient, nitroglycerin, is contained in the adhesive, which is directly in contact with your skin.

Follow the steps below for the proper use of the TRINIPATCH patch:

1. Deciding Where to Apply the Patch

Choose any area of skin which is most comfortable for you, that is above 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 medication you get.

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 (Figure 1).

For example:

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

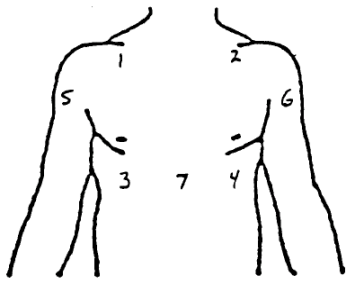


Figure 1

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. Do NOT apply the patch immediately after showering or bathing. It is best to wait until you are certain your skin is completely dry. 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 TRINIPATCH patch is individually sealed in a protective pouch. Open this pouch by tearing at the small notch or cut in the side of the pouch. Do not use scissors, since you may accidentally cut the patch. (Figure 2).

Figure 2

Carefully pick up the system with the overlapping split film facing you (Figure 3).

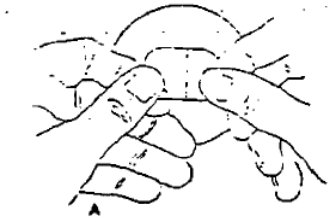


Figure 3

4. Recognizing the Patch and Removing the Liner

A plastic liner covers the adhesive (sticky) side of the patch during storage, and must be removed and discarded before patch use.

Remove one side of the overlapping film, exposing the adhesive layer on one side of the patch (Figure 4).

Avoid touching the adhesive. If another person applies the patch for you, they must be careful not to touch the surface which will be applied to the skin (Figure 4).

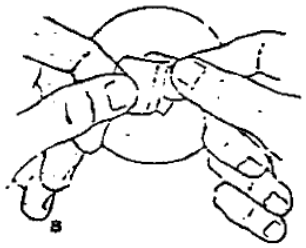


Figure 4

5. Applying the Patch

Remember, the skin should be clean and dry without creams, lotions, oil or powder. Apply the side of the patch with the adhesive exposed to your chosen application site (Figure 5).

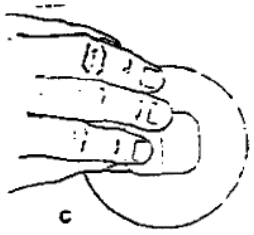


Figure 5

Gently fold the patch in half and roll the patch across the application site. The overlapping films may be discarded (Figure 6).

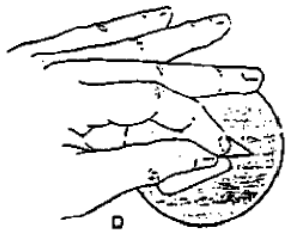


Figure 6

Firmly press the entire surface of the patch to make sure it is secured to your skin (Figure 7).

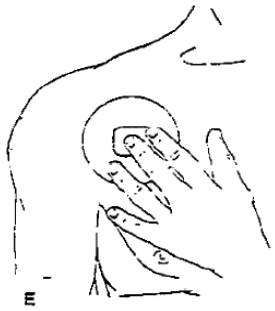


Figure 7

6. When and How to Remove the Patch

The 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, remove it as soon as possible but continue to follow your original schedule.
Remove the patch by peeling up one edge and then pulling it off. The application area may be gently wiped with a dry tissue. Do not wash the application site or apply lotions or creams until the skin has had a chance to return to normal, about two to three hours.

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 and pets.

7. What to Do if TRINIPATCH Falls Off

Contact with water (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 dose:

The starting dose is one 0.2 mg/hour patch per day, usually applied in the morning. Depending on your response and if the dose is well tolerated, your doctor may increase your dose to one 0.4 mg/hour patch per day.

The maximum dose is one 0.8 mg/hour patch per day.

Each patch should be worn for 12 to 14 hours. After this time, take off the patch and do not apply another one for 10 to 12 hours.

Overdose:

If you think you, or a person you are caring for, have taken too much TRINIPATCH, remove the patch immediately and thoroughly wash the application site. Contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to apply TRINIPATCH at the scheduled time, apply it as soon as possible. Apply the next patch at the regular time. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not apply extra patches to make up for a missed dose.

What are possible side effects from using TRINIPATCH?
These are not all the possible side effects you may have when taking TRINIPATCH. If you experience any side effects not listed here, tell your healthcare professional.

- headache
- dizziness or lightheadedness
- flushing of the face
- redness, itching/burning or rash at the application site
- nausea or vomiting
- blurry vision

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**	
COMMON			
Allergic reactions: skin rash or redness	✓		
UNCOMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)			✓
Dizziness (excessive) or collapse			✓
Sense of excessive head pressure			✓
Breathing difficulty			✓
Unusual fatigue or faintness		✓	
Fainting or unusually rapid heartbeat			✓
UNKNOWN			
Sudden kidney failure: weight gain and swelling of the feet and ankles due to water retention, decreased amount of urine, fatigue, loss of appetite, nausea, overall itchiness			✓

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Store TRINIPATCH between 15˚C - 30˚C. Do not refrigerate. Keep each patch in its individually sealed pouch until ready to use.

Keep out of reach and sight of children and pets both before and after use.

If you want more information about TRINIPATCH:
- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.paladinlabs.com, or by calling 1-888-867-7426.

This leaflet was prepared by Paladin Labs Inc.

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