# PRODUCT MONOGRAPH

**TRINIPATCH 0.2**

**TRINIPATCH 0.4**

**TRINIPATCH 0.6**

**(Nitroglycerin Transdermal Delivery System)**

**Rated release *in vivo* 0.2, 0.4 and 0.6 mg/hour**

**Antianginal Agent**

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**TRINIPATCH 0.2**
**Rated release *in vivo* 0.2 mg/hour, 7 $cm^2$**

**TRINIPATCH 0.4**
**Rated release *in vivo* 0.4 mg/hour, 14 $cm^2$**

**TRINIPATCH 0.6**
**Rated release *in vivo* 0.6 mg/hour, 21 $cm^2$**

**(nitroglycerin transdermal delivery system)**

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Non-medicinal Ingredients |
|---|---|---|
| Dermal | Transdermal delivery system<br>Patch 0.2 mg/hr, 7 $cm^2$<br>Patch 0.4 mg/hr, 14 $cm^2$<br>Patch 0.6 mg/hr, 21 $cm^2$ | None. |

### DESCRIPTION

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.

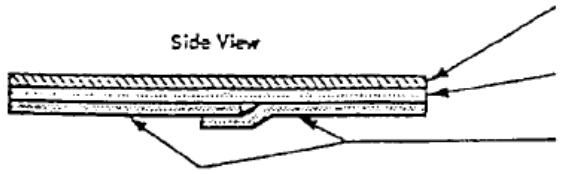
The TRINIPATCH system comprises three layers:

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

## INDICATIONS AND CLINICAL USE

TRINIPATCH (nitroglycerin) used intermittently (see ACTIONS AND 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.

## CONTRAINDICATIONS

1. Known hypersensitivity to nitroglycerin and related organic nitrate compounds.
2. Known or suspected hypersensitivity to components of the patch.
3. Acute circulatory failure associated with marked hypotension (shock and states of collapse).
4. Postural hypotension.
5. Left ventricular dysfunction due to obstruction as in aortic or mitral stenosis or of constrictive pericarditis.
6. Increased intracranial pressure.
7. Increased intraocular pressure.
8. Severe anemia.

9. 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.

## 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.

### 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.

**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 DOSAGE AND ADMINISTRATION). 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.

**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.

**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.

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.

### Special populations

**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.

**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**: Safety and effectiveness have not been established in children.

## ADVERSE REACTIONS

### Adverse Drug 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.

### Post-Market Adverse Drug 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

## DRUG INTERACTIONS

**Serious Drug Interaction**

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.

### Drug-Drug Interactions

**Table 1: Established or Potential Drug-Drug Interactions**

| Nitroglycerin TTS | Ref | 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. |
| 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 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 arterial blood pressure. Dosage adjustment may be necessary. |

| | | | |
|---|---|---|---|
| Tricyclic antidepressants | T | ↑ hypotensive effect | Reinforce the influence of nitroglycerin on the lowering arterial blood pressure. Dosage adjustment may be necessary. |
| Major tranquilizers | T | ↑ hypotensive effect | Reinforce the influence of nitroglycerin on the lowering 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 effets 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. |

T=Theoretical

**Drug-Food Interactions**

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

**Drug-Laboratory Interactions**

Interaction with laboratory tests has not been established.

**Drug-Herb Interactions**

Interaction with herbal products has not been established.

## Drug-Lifestyle Interactions

**Driving and Using Machines:** Dizziness, fatigue and postural hypotension may affect the patient's speed of reaction and impair the individual's ability to operate machinery and motor vehicles.

# DOSAGE AND ADMINISTRATION

## Dosing Considerations

### 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.

## Recommended Dose and Dosage Adjustment

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 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.

**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.

## 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.

## ACTIONS 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 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.

### 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.

### 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 the system 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 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.

**Excretion**
Metabolic derivatives of nitroglycerin are excreted in the urine.

**Special Populations and Conditions**

**Pediatrics**: Safety and effectiveness have not been established in children.

**Geriatrics:** No special information is available on the use of TRINIPATCH in elderly people. However, there is no evidence suggesting that dosage should be adapted in these patients.

## STORAGE AND STABILITY

Storage: under controlled room temperature (between 15ºC - 30ºC).

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.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Composition

The TRINIPATCH 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. Nitroglycerin remaining in the patch serves as a thermodynamic energy source to keep the pattern of delivery constant.
The drug product is a matrix transdermal patch design consisting of three laminated film layers:

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

Non medicinal ingredients include: sorbitan mono-oleate and Duro Tak 87-2196.

### 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.

## PART II: SCIENTIFIC INFORMATION

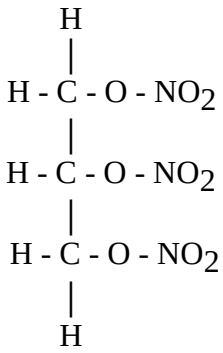
## PHARMACEUTICAL INFORMATION

**Drug Substance:**

Proper name: Nitroglycerin

Chemical name: 1,2,3-propanetriol-trinitrate

Structural formula:



Molecular formula and mass: $C_3H_5N_3O_9$, 227.09

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

## CLINICAL TRIALS

**Comparative Bioavailability Studies**

A comparative bioavailability study was performed using healthy human volunteers. 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).

The results are summarized as follows:

Comparative Bioavailability Data -TRINIPATCH
(TRINIPATCH)
(0.4 mg/hr nitroglycerin Transdermal patch)

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%) | |

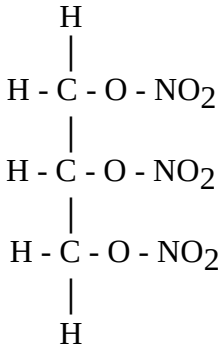
1,3 DINITROGLYCERIN

| 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%)

## DETAILED PHARMACOLOGY

Nitroglycerin (1,2,3-propanetriol trinitrate) has the following structural formula:



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.

**Metabolism**
Nitroglycerin is rapidly metabolized by a 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.

## 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 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.

**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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# PART III: CONSUMER INFORMATION

**TRINIPATCH 0.2**

**TRINIPATCH 0.4**

**TRINIPATCH 0.6**

**(Nitroglycerin Transdermal Delivery System)**

**This leaflet is part III of a three-part "Product Monograph" published when TRINIPATCH was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRINIPATCH. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
Your doctor has prescribed TRINIPATCH to help reduce the frequency and severity of attacks of anginal pain (chest pain). This leaflet provides you with information about the TRINIPATCH patch and its use. **Please read it carefully.**

**What it does:**
When TRINIPATCH 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. Because nitroglycerin is released slowly from TRINIPATCH, it **will not relieve an attack that has already started.**

The amount of TRINIPATCH you need will depend upon your body's needs. Observe the dosing instructions given to you by your doctor and report to him/her if chest pain attacks continue to occur.

TRINIPATCH is designed as a complete unit. **Do not cut the patch.**

**When it should not be used:**
There are certain things you and your doctor should be aware of before you use TRINIPATCH.

Be sure to tell your doctor if you have ever had any of the following medical problems:

- any unusual or allergic reactions to nitrates, nitrites, or other substances
- poor circulation with very low blood pressure
- increased intracranial pressure (a condition that your doctor can tell you about)
- a recent heart attack, or other serious heart disease, stroke, or head injury
- narrowing of the heart valves
- blood vessel disorder other than angina
- severe anemia
- lung disease

To help the doctor decide whether you should use TRINIPATCH and what extra care should be taken during its use, tell your doctor:

- if you are breast feeding or pregnant or intend to become pregnant while using this medicine.
- what other medicines or remedies, if any, you are using. There are some medicines which may affect how TRINIPATCH works.
- if you are taking medicines used to treat erectile dysfunction with inhibitors of an enzyme called phosphodiesterase type 5 (PDE5), including VIAGRA® (sildenafil), CIALIS® (tadalafil) and LEVITRA® (vardenafil).

**What the medicinal ingredient is:**
The **active substance** of TRINIPATCH is nitroglycerin.

**What the important nonmedicinal ingredients are:**
Non medicinal ingredients include: sorbitan mono-oleate and DuroTak 87-2196.

**What dosage forms it comes in:**

TRINIPATCH is available in three different patch strengths:

TRINIPATCH 0.2 (release 0.2 mg/hr, 7 $cm^2$)
TRINIPATCH 0.4 (release 0.4 mg/hr, 14 $cm^2$)
TRINIPATCH 0.6 (release 0.6 mg/hr, 21 $cm^2$)

## WARNINGS AND PRECAUTIONS

Check with your doctor **as soon as possible** if any of the following occur:

- angina (chest pain), particularly while patch is off
- greyish-blue colored lips, fingernails or palms of hands
- dizziness or fainting
- feeling of pressure in the head
- shortness of breath
- unusual tiredness or weakness
- weak or unusually fast heartbeat.

## INTERACTIONS WITH THIS MEDICATION

**If you are using TRINIPATCH (nitroglycerin), you must not take any medicines used to treat erectile dysfunction which are part of the group of products called phosphodiesterase**

**type 5 (PDE5) inhibitors, including VIAGRA® (sildenafil), CIALIS® (tadalafil) and LEVITRA® (vardenafil). Such a combination can produce severe lowering of blood pressure, loss of consciousness, heart attack or death.**

## PROPER USE OF THIS MEDICATION

The TRINIPATCH Nitroglycerin Transdermal Delivery System is easy to use, it has a clear plastic backing and a special adhesive that keeps the system firmly in place. The active nitroglycerin is contained in the adhesive which is directly in contact with your skin.

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

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

Choose any area of skin which is most comfortable for you, but not 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. Do NOT apply the system immediately after showering or bathing. It is best to wait until you are certain the skin is completely dry.

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

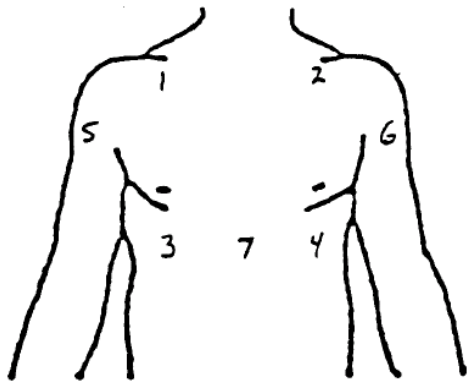



Figure 1

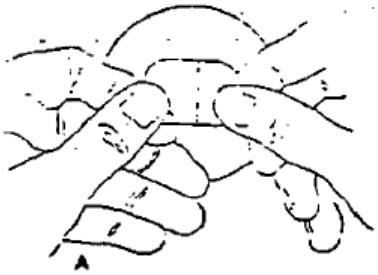
**2. Preparing the Skin**

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 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)

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

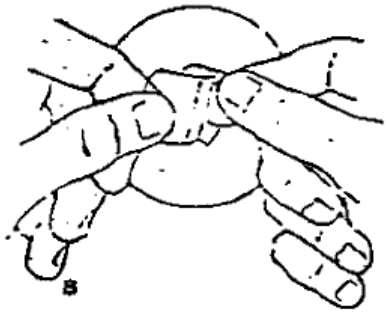


**4. Recognizing the Patch and Removing the Liner**

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

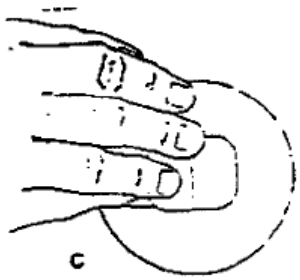
Remove one side of the overlapping film, exposing the adhesive layer on one side of the system Figure 4.

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

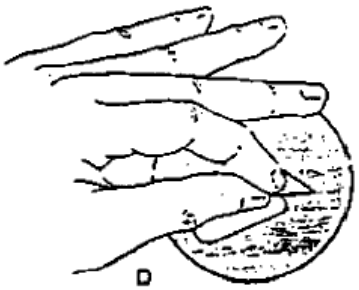



**5. Applying the Patch**

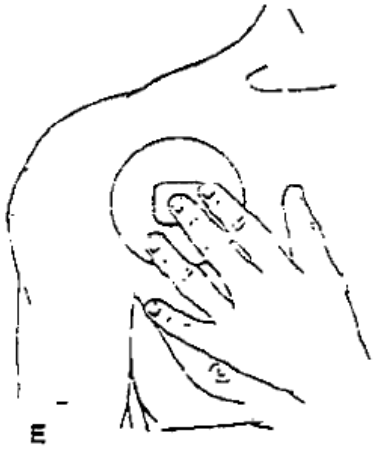
Remember, the skin should be clean and dry without creams, lotions, oil or powder. Apply the side of the system with the adhesive exposed to the application site which you have selected.




Gently fold the system in half and roll the patch across the application site. The overlapping films may be discarded.




Firmly press the entire surface of the patch to insure good adherence to your skin.




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

The TRINIPATCH 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 but continue to follow your original schedule.

At the time recommended by your doctor remove the patch. Removal may be accomplished by peeling up one edge and then pulling off the patch. 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 (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.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, along with its helpful effects, TRINIPATCH may cause unwanted effects. You should know about them so that if they do occur, you can report them to your doctor right away.

When you start using TRINIPATCH, you may get a headache. This is a common effect. If you need to, you may take a mild pain reliever for this. If it continues or becomes severe, check with your doctor. Flushing of the face may also occur. TRINIPATCH may also lower the blood pressure and cause dizziness, lightheadedness, or a fainting feeling, especially when you get up quickly from lying or sitting positions. Getting up slowly may help. If you feel dizzy, sit or lie down. You may be more likely to experience headaches, dizziness, or

lightheadedness if you drink alcohol, stand for a long time, or if the weather is hot. While using TRINIPATCH, be careful about the amount of alcohol you drink. Also use extra care when exercising, standing for a long time, driving, or during hot weather.

In certain cases TRINIPATCH may cause mild itching under the patch and reddening of the skin. The reddening usually goes away within a few hours. It is also important to apply each patch to a different area of skin.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist § |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| **Common** | *Hypersensitivity reactions* Skin rash or redness | ✓ | | |
| **Uncommon** | *Hypotension* Fainting when the blood pressure is too low | | | ✓ |
| | Dizziness (excessive) or collapse | | | ✓ |
| | Sense of excessive head pressure | | | ✓ |
| | Breathing difficulty | | | ✓ |
| | Unusual fatigue or faintness | | ✓ | |
| | Fainting or Unusually rapid hearbeat | | | ✓ |

**§ If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.**

***This is not a complete list of side effects. For any unexpected effects while taking TRINIPATCH, contact your doctor or pharmacist.***

## HOW TO STORE IT

TRINIPATCH should be stored under controlled room temperature (between 15ºC - 30ºC). Do not store it out of the individually sealed pouch.

TRINIPATCH should be kept out of the reach of children and pets both before and after use. If your patch becomes stuck to a child or another person, remove the patch at once and contact a doctor.

**ALWAYS REMEMBER**
Your doctor has prescribed TRINIPATCH for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else since their needs may be different from yours. If you have any questions, contact your doctor or pharmacist.

**REPORTING SUSPECTED SIDE EFFECTS**

**To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:**

**toll-free telephone: 866-234-2345**
**toll-free fax 866-678-6789**
**By email: cadrmp@hc-sc.gc.ca**

**By regular mail:**
**National AR Centre**
**Marketed Health Products Safety and Effectiveness Information Division**
**Marketed Health Products Directorate**
**Tunney's Pasture, AL 0701C**
**Ottawa ON K1A 0K9**

***NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Paladin Labs Inc. at 1-888-867-7426.

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