PRODUCT MONOGRAPH

MINITRAN® 0.2 mg/hr
MINITRAN® 0.4 mg/hr
MINITRAN® 0.6 mg/hr

Nitroglycerin

Transdermal Delivery System

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

Antianginal

Valeant Canada LP
2150 St-Elzear Blvd., West
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Canada

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March 6, 2013

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Table of Contents

MINITRAN®

Nitroglycerin

MINITRAN 0.2 mg/hr (Rated Release in vivo = 0.2 mg/hr, 6.7 cm^2)
MINITRAN 0.4 mg/hr (Rated Release in vivo = 0.4 mg/hr, 13.3 cm^2)
MINITRAN 0.6mg/hr (Rated Release in vivo = 0.6 mg/hr, 20.0 cm^2)

Antianginal Agent

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Transdermal	Transdermal Delivery System / MINITRAN® 0.2 mg/hr (Rated Release in vivo = 0.2 mg/hr, 6.7 cm2) MINITRAN® 0.4 mg/hr (Rated Release in vivo = 0.4 mg/hr, 13.3 cm2) MINITRAN® 0.6mg/hr (Rated Release in vivo = 0.6 mg/hr, 20.0 cm^2)	Hypoallergenic medical grade, acrylate-based polymer adhesive

The MINITRAN® (nitroglycerin) Transdermal Delivery System is a 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 6.7, 13.3 and 20 system delivers approximately 0.2, 0.4 and 0.6 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 about 14% of its original content of nitroglycerin.

INDICATIONS AND CLINICAL USE

MINITRAN (nitroglycerin) used intermittently (See ACTIONS AND CLINICAL PHARMACOLOGY) is indicated for the prevention of angina 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.

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

CONTRAINDICATIONS

- Known hypersensitivity to nitroglycerin or other nitrates or nitrites.
- Known or suspected hypersensitivity to components of the patch.
- Acute circulatory failure associated with marked hypotension (shock and states of collapse).
- Concomitant use of MINITRAN (nitroglycerin) either regularly and/or intermittently, with VIAGRA® (sildenafil citrate) or any other phosphodiesterase type 5 (PDE5) inhibitor such as CIALIS® (tadalafil), LEVITRA® or STAXYN® (vardenafil), is absolutely contraindicated.
- Do not use MINITRAN 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.
- Postural hypotension.
- Myocardial insufficiency due to obstruction (e.g., in the presence of aortic or mitral stenosis or constrictive pericarditis).
- Increased intracranial pressure.
- Increased intraocular pressure.
- Severe anemia.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

INFORMATION FOR THE PATIENT

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.

A patient leaflet is supplied with the patches (see CONSUMER INFORMATION).

Cardiovascular

MINITRAN (nitroglycerin) must be removed before cardioversion or DC defibrillation is attempted, as well as before applying diathermy treatment, since it may be associated with damage to the paddles and burns to the patient.

The benefits and safety of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use MINITRAN (nitroglycerin) in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of 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 angina 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 ACTIONS AND CLINICAL PHARMACOLOGY). Co-administration of other long-acting nitrates could jeopardize the integrity of the nitrate-free interval and therefore must be avoided.

As tolerance to nitroglycerin patches develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

Hematologic
METHEMOGLOBINEMIA
Case reports of clinically significant methemoglobinemia are rare at conventional doses of nitroglycerin. The formation of methemoglobin is dose-related, and in the case of genetic abnormalities of hemoglobin that favour methemoglobin formation, even conventional doses of organic nitrates can produce harmful concentrations of methemoglobin. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2.

Classically, methemoglobinemic blood is described as chocolate brown, without colour change on exposure to air. If methemoglobinemia is present, intravenous administration of 1 to 2 mg/kg of methylene blue 1% solution for injection 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.

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

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 a 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.

Special Populations

Pregnant Women: It is not known whether nitroglycerin can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Therefore, use MINITRAN (nitroglycerin) only if the potential benefit justifies the risk to the fetus.

Nursing Women: It is not known whether nitroglycerin is excreted in human milk. Benefits to the mother must be weighed against the risk to the infant.

Pediatrics: Safety and effectiveness of MINITRAN use in children had not been established. Therefore recommendations for its use cannot be made.

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

ADVERSE 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 high 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, with or without a mild local itching 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, and postural hypotension which may be associated with reflex tachycardia. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon. Nausea and vomiting have been reported rarely.

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of MINITRAN (nitroglycerin), either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA® (sildenafil citrate), CIALIS® (tadalafil), and LEVITRA® (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of MINITRAN which can potentiate the hypotensive effect of MINITRAN. This could result in life-threatening hypotension with syncope or myocardial infarction and death. Therefore, VIAGRA® (sildenafil citrate) and other PDE5 inhibitors should not be given to patients receiving MINITRAN therapy.

Overview
Concomitant treatment with other vasodilators, calcium channel blockers, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquilizers may potentiate the blood pressure lowering effect of MINITRAN. Dose adjustment may be necessary.

Concomitant use of MINITRAN with soluble guanylate cyclase stimulators such as ADEMPAS® (riociguat) is contraindicated (see CONTRAINDICATIONS).

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.

Concurrent administration of MINITRAN with dihydroergotamine may increase the bioavailability of dihydroergotamine. Special attention should be paid to this point in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitroglycerine and may lead to coronary vasoconstriction.

The possibility that the ingestion of acetylsalicylic acid and non-steroidal anti-inflammatory drugs might diminish the therapeutic response to nitrates and nitroglycerin cannot be excluded.

Drug-Food Interactions
Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

Drug-Herb Interactions
Interactions with herbal products has not been established.

Drug-Laboratory Interactions
Interaction with laboratory tests has not been established.

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

DOSAGE AND ADMINISTRATION

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

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

The doses of MINITRAN (nitroglycerin) should be periodically reviewed in relation to continuing antianginal control.

Recommended Dose and Dosage Adjustment

Daily Dosage Schedule

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.

The suggested starting dose is between 0.2 mg/hr and 0.4 mg/hr. Doses between 0.2 mg/hr and 0.8 mg/hr have shown continued effectiveness for 12 hours daily for at least one month (the longest period of studies) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data shows that a nitrate-free interval of 10-12 hours is sufficient (see ACTION AND CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours during waking hours and a patch-off period of 10-12 hours, usually overnight.

Administration

Site of Application

MINITRAN should be applied to the chest, shoulders, upper arm or back and should not be applied to the distal extremities. The skin area should be free of hair in order to provide direct contact of the patch to the skin. If hair is likely to interfere with adhesion of the patch, the area may be lightly shaved. The skin area should be clean, dry and free of irritation or cuts. A different skin site should be used each time a new MINITRAN patch is applied. It may be necessary to apply more than one patch in order to achieve the optimal dose level. Following use, the patch should be discarded in a manner that prevents accidental application or ingestion by curious children or others.

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), nausea and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright posture), methemoglobinemia with cyanosis, initial 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 MINITRAN patches. Passive movement of the extremities may aid venous return. Administer oxygen and artificially ventilate if necessary. Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose; it and related compounds are contraindicated in this situation.

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.

Methemoglobinemia should be treated with methylene blue if the patient develops cardiac or CNS effects of hypoxia. The initial dose is 1 to 2 mg/kg infused intravenously over 5 minutes. Repeat methemoglobin levels should be obtained 30 minutes later and a repeat dose of 0.5 to 1.0 mg/kg may be used if the level remains elevated and the patient is still symptomatic. Relative contraindications for methylene blue include known NADH methemoglobin reductase deficiency or G-6-PD deficiency. Infants under the age of 4 months may not respond to methylene blue due to immature NADH methemoglobin reductase. Exchange transfusion has been used successfully in critically ill patients when methemoglobinemia is refractory to treatment.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilation of 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 systematic 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.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is probably inappropriate for organic nitrates. Some controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously. The large majority of such controlled trials, however, has shown the development of tolerance (i.e., complete loss of effect as measured by exercise testing) within the first day. Tolerance has

occurred even when doses greater than 4 mg/hour were delivered continuously. This dose is far in excess of the effective dose of 0.2 to 0.8 mg/hour delivered intermittently.

Efficacy of organic nitrates is restored after a period of absence of nitrates from the body. Drug-free intervals of 10 to 12 hours are known to be sufficient to restore response. Several studies have demonstrated that when nitroglycerin is administered according to an intermittent regimen, doses of nitroglycerin 0.4 – 0.8 mg/hr (20 – 40 cm^2) have increased exercise capacity for up to 8 hours, with a trend of increased exercise capacity to 12 hours.

The results of one controlled clinical trial suggest that the intermittent use of nitrates may be associated with decreased exercise tolerance during the last part of the nitrate-free interval, in comparison to placebo. The clinical relevance of this observation is unknown.

In another clinical trial, there was an increase in nocturnal angina attacks during the drug-free period in some patients treated with nitroglycerin as compared to placebo; therefore, the possibility of increased frequency of severity of angina during the nitrate-free interval should be considered. However, in one controlled clinical study, involving 291 patients with angina, involving exercise tolerance testing at 4 hours duration post-dosing, MINITRAN did not demonstrate any significant evidence of vascular tolerance or rebound angina attacks during long-term intermittent treatment.

Pharmacokinetics

Absorption: When MINITRAN (nitroglycerin) is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. Thus, the active drug reaches target sites before inactivation by the liver.

Distribution: In healthy volunteers, steady-state plasma concentrations of nitroglycerin were reached within two hours after application of the patch and were maintained at the same level for the duration of the study (24 hours). Upon removal of the patch, plasma concentrations decline rapidly.

Metabolism: Nitroglycerin is rapidly metabolized, principally by a liver reductase, to form glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, 1, 2- and 1, 3-dinitroglycerols, the products of hydrolysis, appear to be less potent than nitroglycerin as vasodialators 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.

Special Populations and Conditions

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

Geriatrics: The safety and effectiveness of MINITRAN in this patient population have not been

established. Additional clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may result in hypotension and increased risk of falling at the therapeutic doses of nitroglycerin. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

STORAGE AND STABILITY

Store at controlled room temperature 15°-30°C (59°-86°F). Extremes of temperature and/or humidity should be avoided.

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

The MINITRAN Transdermal Delivery System contains nitroglycerin in a hypoallergenic medical grade, acrylate-based polymer adhesive. Each patch is packaged in foil/polymer film laminate.

MINITRAN SYSTEMS

Rated Release in vivo (mg/hr)	System Size (cm^2)	Nitroglycerin in System (mg)
0.2	6.7	18
0.4	13.3	36
0.6	20.0	54

MINITRAN Transdermal Delivery System, 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr are available in cartons of 30 and 100 patches.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

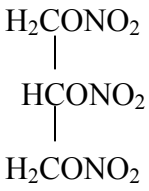
Drug Substance

Proper name: Nitroglycerin

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

Molecular formula and molecular mass: $C_3H_5N_3O_9$, 227.09

Structural formula:



Physicochemical properties: **Description:** Nitroglycerin is a colourless, slightly volatile, odourless, oily liquid, with a sweet, aromatic and pungent taste. **Solubility:** 1 in 800 of water, 1 in 4 of alcohol, 1 in 120 of carbon disulphide, and 1 in 6 of almond oil; miscible with acetone, chloroform, ether and glacial acetic acid; sparingly soluble in glycerol and light petroleum. **Melting Point:** 13.2°C.

CLINICAL TRIALS

Not applicable to present Product Monograph.

DETAILED PHARMACOLOGY

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 be exercised in cases of anemia. In animal studies it has been found that extrahepatic vascular tissues (femoral vein, inferior vein 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 biotransformaton 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 doses of 0.1 mg/kg daily to cats for a period of 40 days produced anemia and fatty degeneration of the liver. Daily doses as high as 7.5 or 15 mg/kg given subcutaneously for a period of 50 days were given to cats. Two died after 10 to 20 doses, respectively. The surviving animals showed jaundice and albuminuria, and hemorrhages of the cerebellum, heart, liver and spleen were seen post-mortem.

Dermal Irritation:
Dermal irritation resulting from the use of MINITRAN (nitroglycerin) Transdermal Delivery System was minimal and typical of the erythema and edema observed with hypoallergenic medical and surgical tapes. The system was not considered to be a sensitizer or to induce photoallergic contact dermatitis. In a cytotoxicity array with L929 mouse fibroblast cells, the transdermal system was judged to be mildly cytotoxic, a rating consistent with adhesive formulations in the medical device field.

Reproduction Studies:
A three generation reproduction study in rats found adverse effects on the 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 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 cytogenetic 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.

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PART III: CONSUMER INFORMATION

MINITRAN®
(Nitroglycerin Transdermal Delivery System)

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

ABOUT THIS MEDICATION

What the medication is used for:
MINITRAN is used in adults to prevent angina (chest pain). It can be used alone or together with other antianginal agents such as beta-blockers and/or calcium channel blockers.

MINITRAN is not intended to be used for acute angina attacks. Sublingual nitroglycerin medications should be used if you are having an acute angina attack.

What it does:
MINITRAN is a patch which is applied to the skin. When you apply MINITRAN, the nitroglycerin is slowly absorbed through your skin and into your bloodstream. The nitroglycerin in MINITRAN enters your body in a controlled way, a little at a time. The nitroglycerin causes the blood vessels to relax and increases the supply of blood and oxygen to the heart reducing the likeliness of having an angina attack.

When it should not be used:
Do not use MINITRAN if you:

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

What the medicinal ingredient is:
Nitroglycerin

What the nonmedicinal ingredients are:
Hypoallergenic medical grade, acrylate-based polymer adhesive

What dosage forms it comes in:
MINITRAN is available in three different patch strengths:

MINITRAN 0.2mg/hour (6.7 cm^2)
MINITRAN 0.4mg/hour (13.3 cm^2)
MINITRAN 0.6mg/hour (20.0 cm^2)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

BEFORE you use MINITRAN talk to your doctor or pharmacist if you:

- have heart failure
- have lung disease
- have low blood pressure or take diuretics ("water pills")
- have angina due to hypertrophic cardiomyopathy
- are pregnant or trying to become pregnant, or if you think that you might be pregnant
- are breastfeeding
- are dehydrated or suffer from excessive vomiting, diarrhea or sweating
- are less than 18 years old or older 65 years of age.

Tolerance to MINITRAN and similar drugs can occur after long periods of use. Chronic use can lead to angina attacks being brought on more easily. Do not suddenly stop using MINITRAN. Talk to your prescribing physician if you wish to discontinue using MINITRAN.

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

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

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

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

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with MINITRAN:

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

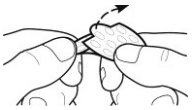
PROPER USE OF THIS MEDICATION

Where to Apply MINITRAN:
You can apply MINITRAN to the chest, shoulders, upper arm or back. Do not apply MINITRAN to the lower arm or lower leg. You should apply the patch to a non-hairy area so that the hair will not prevent direct contact of the patch with the skin. If hair is likely to interfere with adhesion of the patch, the area may be lightly shaved. The skin area should be clean, dry and free of irritation or cuts. Use a different skin site each time you use a new MINITRAN patch.

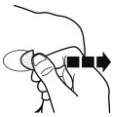
Patient Instructions:

1. Start at notched corner. Tear pouch along dotted line. Remove patch from pouch.

2. Bend patch so that the dotted liner notch pops up: remove tab and discard dotted liner.



3. Apply sticky side of patch to upper arm or chest. Remove and discard dotted liner.



4. Press patch firmly in place.

MINITRAN sticks well to the skin and remains in place during bathing, swimming and showering. In the unlikely event that the patch becomes loose, discard it and put a new one on a different skin site.

Do not apply MINITRAN immediately after showering or bathing – wait until you are sure that the skin is completely dry.

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

Do not reuse a MINITRAN patch once it has been removed from the skin.

Allow MINITRAN to stay in place for 12-14 hours unless otherwise instructed by your physician.

Apply MINITRAN at the same time every day.

The MINITRAN patch should be changed according to the schedule prescribed by your doctor. It is important to respect the patch-off period recommended by your doctor. If you forget to remove it at the scheduled time, just remove it as soon as possible and continue to follow your original schedule.

After you remove the MINITRAN patch it must be discarded in a manner that prevents accidental ingestion or application by curious children or pets. After normal use, there is still enough medicine in the patch to cause serious harm or death if they are accidentally ingested or applied.

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

Starting dose is one MINITRAN 0.2 mg/hour patch, usually applied in the morning. If 0.2 mg/hour is well tolerated, the dose can be increased to 0.4 mg/hour if required. A maximum of 0.8 mg/hour may be used.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Headache
- Flushing of the face
- Nausea, vomiting
- Rash, redness, itching and/or burning in the area where the patch is applied.

If any of these affects you severely, tell your doctor or pharmacist.

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 seek immediate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness, fast heartbeat May occur when you go from lying or sitting to standing up.	√		
Uncommon	**Unstable Angina:** chest pain that has changed or gotten worse, nausea, anxiety, sweating, shortness of breath, dizziness, fatigue			√
	High Blood Pressure: headache, vision problems, irregular heartbeat	√		

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 seek immediate medical help
		Only if severe	In all cases	
Unknown	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Increased levels of methemoglobin in the blood: Shortness of breath, blue or purple coloration of the lips, fingers and/or toes, headache, fatigue, dizziness, loss of consciousness.			√

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

HOW TO STORE IT

MINITRAN should be stored at controlled room temperature (15 - 30˚C).

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Valeant Canada LP, at:
1-800-361-4261

This leaflet was prepared by Valeant Canada LP
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