

PRODUCT MONOGRAPH

MINITRANTM

(nitroglycerin)

Transdermal Delivery System

Antianginal

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PRODUCT MONOGRAPH

for

MINITRAN™

(nitroglycerin)

Transdermal Delivery System

MINITRAN 0.2 mg (Rated Release in vivo = 0.2 mg/hr, 6.7 cm²)

MINITRAN 0.4 mg (Rated Release in vivo = 0.4 mg/hr, 13.3 cm²)

MINITRAN 0.6 mg (Rated Release in vivo = 0.6 mg/hr, 20.0 cm²)

MINITRAN 0.8 mg (Rated Release in vivo = 0.8 mg/hr, 26.6 cm²)

THERAPEUTIC CLASSIFICATION

Antianginal Agent

DESCRIPTION

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 cm² of applied system delivers approximately 0.03 mg of nitroglycerin per hour. Thus, the 6.7, 13.3, 20 and 26.6 cm² system delivers approximately 0.2, 0.4, 0.6 and 0.8 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 about 14% of its original content of nitroglycerin.

ACTIONS AND CLINICAL PHARMACOLOGY

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.

When MINITRAN 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. 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 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.

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.

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 cm²) 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 suggests 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.

INDICATIONS AND CLINICAL USES

MINITRAN (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.

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), is absolutely contraindicated.
- 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

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.

MINITRAN 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.

PRECAUTIONS

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.

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.

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.

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.

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

PREGNANCY

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.

LACTATION

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

PEDIATRIC USE

Safety and effectiveness of MINITRAN use in children have not been established.

DRUG INTERACTIONS

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 and VIAGRA® (sildenafil citrate) 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) should not be given to patients receiving MINITRAN therapy.

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

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 (nitroglycerin) 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 nitroglycerin 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.

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.

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.

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 INFORMATION FOR THE CONSUMER).

ADVERSE REACTIONS

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.

SYMPTOMS AND TREATMENT OF OVERDOSE

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

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.

DOSAGE AND ADMINISTRATION

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 ACTIONS 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.

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.

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.

PHARMACEUTICAL INFORMATION

2.10.1 Drug Substance

Proper Name: Nitroglycerin

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

Molecular Formula: $C_3H_5N_3O_9$

Structural Formula:

$$\begin{array}{c} H_2CONO_2 \\ | \\ HCONO_2 \\ | \\ H_2CONO_2 \end{array}$$

Molecular Weight: 227.09

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

2.10.2 Composition

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.

2.10.3 Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

MINITRAN SYSTEMS

Rated Release in vivo (mg/hr)	System Size (cm²)	Nitroglycerin in System (mg)
0.2	6.7	18
0.4	13.3	36
0.6	20.0	54
0.8	26.6	72

MINITRAN Transdermal Delivery System, 0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr and 0.8 mg/hr are available in cartons of 30 and 100 patches.

INFORMATION FOR THE CONSUMER

Patient Information:

MINITRAN, the long-acting form of nitroglycerin which your doctor has prescribed for you, is a transdermal nitroglycerin system which is applied to the skin. Unlike oral medications, which have to be taken frequently, or messy ointments, **MINITRAN** provides nitroglycerin in a convenient once-a-day dosage form. You cannot see the nitroglycerin in **MINITRAN** because it is mixed in with the adhesive on the patch.

When you apply **MINITRAN** to your skin, 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. **MINITRAN** helps prevent angina (heart pain) attacks and reduces the need for under-the-tongue nitroglycerin tablets.

Possible Side Effects:

As with all nitroglycerin products, you may develop a headache at the start of **MINITRAN** treatment. Such headaches are usually mild and often disappear as treatment is continued or dosage is adjusted. Headache may be treated with mild pain medications such as aspirin. Although uncommon, dizziness, faintness or flushing may occur, especially when you move suddenly from a lying down to sitting up position. Be sure to inform your doctor if these symptoms occur.

Skin irritation may occur. It can usually be avoided if you change the place you wear your patch every day and you make sure the area is thoroughly dry before applying. If irritation persists, ask your doctor about it.

Important:

MINITRAN is to be used for preventing attacks of angina. It is not meant to be used like under-the-tongue nitroglycerin tablets for stopping an attack that has already started.

If your angina attacks become more severe, last longer or occur more frequently, tell your doctor immediately.

If you are using MINITRAN, you must not take VIAGRA® (sildenafil citrate). Such a combination can produce severe lowering of blood pressure, loss of consciousness, heart attack or death.

Additional Information:

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 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.

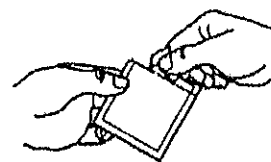
Where to Apply MINITRAN:

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 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.



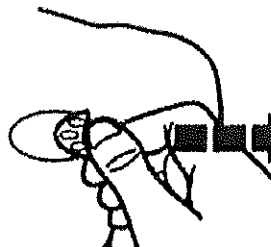
2. Bend patch so that the dotted liner notch pops up:

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.



STORE AT CONTROLLED ROOM TEMPERATURE, 15°-30° C (59°-86°F)

WARNING: Store and discard systems in a manner that prevents accidental application or ingestion by children or others.

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 sulphhydryl-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 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 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 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 cytogenetics analyses of bone marrow and kidney cells from dogs (up to 25mg/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.

MINITRAN™ (nitroglycerin) transdermal delivery system

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