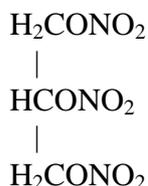


PRODUCT INFORMATION
MINITRAN™
TRANSDERMAL DELIVERY SYSTEM

NAME OF THE MEDICINE

Glyceryl trinitrate

Glyceryl trinitrate (GTN) is a 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is:



CAS: 55-63-0

It has a molecular weight of 227.09. GTN is also known as nitroglycerin.

DESCRIPTION

The Minitran Transdermal Delivery System is a unit designed to provide continuous controlled release of glyceryl trinitrate through intact skin to overcome the problems of the short half-life and extensive first-pass metabolism of glyceryl trinitrate.

The rate of release of glyceryl trinitrate from Minitran is linearly dependent upon the area of the applied system; each cm² of applied system delivers approximately 0.75 mg of glyceryl trinitrate over 24 hours which is equivalent to 0.03 mg/h.

| | Total GTN in System | System Size | Rate of Release <i>in-vivo</i> | Amount of GTN Released over 24 h |
|-------------|---------------------------|----------------------|--------------------------------------|---|
| MINITRAN 5 | 18 mg | 6.7 cm ² | 0.2 mg/h | 5 mg |
| MINITRAN 10 | 36 mg | 13.3 cm ² | 0.4 mg/h | 10 mg |
| MINITRAN 15 | 54 mg | 20 cm ² | 0.6 mg/h | 15 mg |

The remainder of the glyceryl trinitrate in the system serves as a reservoir and is not delivered in normal use.

The Minitran Transdermal Delivery System consists of a thin, transparent, low-density, polyethylene film covered by a hypoallergenic, medical grade, acrylate-based polymer adhesive containing glyceryl trinitrate. The excipients in Minitran are ethyl oleate, glyceryl laurate and polymer 3273. Each patch is packaged in foil/polymer film laminate. Prior to use, a protective peel strip is removed from the adhesive surface.

PHARMACOLOGY

Pharmacodynamic Properties

The principal pharmacological action of glyceryl trinitrate is relaxation of the vascular smooth muscle and consequent dilation of peripheral arteries and veins, especially the latter. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure and mean

arterial pressure (afterload). Dilation of the coronary arteries also occurs which is of importance in the treatment of coronary spasm.

Pharmacokinetic Properties

When a Minitran Transdermal Delivery System is applied to the skin, glyceryl trinitrate is absorbed continuously through the skin into the systemic circulation maintaining constant blood levels. In healthy volunteers, steady-state plasma concentrations of glyceryl trinitrate are reached by about two hours after application of a patch and are maintained for the duration of wearing the patch. Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

INDICATIONS

Prevention of chronic, stable angina pectoris due to coronary artery disease.

CONTRAINDICATIONS

Minitran is contraindicated in cases of:

- known hypersensitivity to organic nitrates or to the stated excipients including adhesive in the patch
- severe anaemia
- increased intra-ocular and intracranial pressure, and
- marked arterial hypotension or shock.

It is also contraindicated in acute myocardial insufficiency due to obstruction as in aortic or mitral stenosis or constrictive pericarditis.

Do not use Minitran in patients who are taking phosphodiesterase inhibitors (such as sildenafil, tadalafil, or vardenafil) for erectile dysfunction or pulmonary hypertension because concomitant use may amplify the vasodilatory effects of Minitran resulting in severe hypotension.

Do not use Minitran in patients who are taking the soluble guanylate cyclase stimulator riociguat. Concomitant use can cause hypotension.

PRECAUTIONS

Amplification of the vasodilatory effects of Minitran patch by phosphodiesterase inhibitors, e.g. sildenafil can result in severe hypotension.

Severe hypotension, particularly with upright posture, may occur with even small doses of glyceryl trinitrate, particularly in the elderly. Minitran should therefore be used with caution in elderly patients who may be volume depleted, are on multiple medications, or who, for whatever reason, are already hypotensive. Hypotension induced by glyceryl nitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Minitran is not indicated for the treatment of acute angina attacks requiring rapid relief. The benefits of transdermal glyceryl trinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use glyceryl trinitrate in these conditions, careful clinical or haemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

Minitran should be removed before attempting cardioversion or defibrillation. A cardiovertor/defibrillator should not be discharged through a paddle electrode that overlies a Minitran patch due to the risk of burns to the patient and damage to the paddle.

Minitran should be used with caution in patients with hypoxaemia or ventilation perfusion imbalance, as a decrease in available oxygen may diminish the anti-anginal effect of Minitran.

Nitrate therapy, including Minitran, may aggravate the angina caused by hypertrophic cardiomyopathy, particularly in the elderly.

The appearance of tolerance (the decline in, or loss of efficacy) to the preparation and of cross tolerance with other nitrates may occur with repeated or continuous administration of long-acting nitrates, including Minitran and other transdermal systems. This can be prevented by keeping plasma glyceryl trinitrate levels low for a certain period of the dosing interval and for this reason intermittent therapy is preferable (see **DOSAGE AND ADMINISTRATION**).

As all nitrate vasodilators can induce withdrawal reactions, abrupt withdrawal of Minitran should be avoided. It is advisable to gradually reduce the dosage over a period of 4 to 6 weeks to prevent a potential withdrawal reaction.

The use of products for topical application, especially if prolonged, may give rise to sensitisation phenomena, in which case treatment should be suspended and suitable therapeutic measures adopted.

Effects on Fertility

Lower doses of glyceryl trinitrate did not affect fertility in rats but doses up to 230 mg/kg/day caused moderate to severe testicular degeneration and/or atrophy with severe to complete aspermatogenesis.

Use in Pregnancy (Category B2)

The safety of Minitran in pregnancy has not been established. As with all drugs, Minitran should not be prescribed during pregnancy, particularly during the first trimester, unless there are compelling reasons for doing so. If Minitran is in regular use and pregnancy occurs, the physician should be notified immediately.

Use in Lactation

It is not known whether glyceryl trinitrate passes into the breast milk. The benefits for the mother must be weighed against the risks to the child.

Use in the Elderly

Elderly patients may be more susceptible to hypotension and may be at greater risk of falling at the therapeutic doses of glyceryl trinitrate.

Genotoxicity

No genotoxicity studies were undertaken with glyceryl trinitrate.

Carcinogenicity

Studies in animals have not been performed with Minitran patches to evaluate the carcinogenic and mutagenic potential. Glyceryl trinitrate, the active component of the Minitran patch, given in the diet to rats at doses up to 1% caused an increase in the incidence of hepatic cholangiofibrosis, hepatocellular carcinomas and/or neoplastic nodules and Leydig cell tumours in the testis.

The Minitran patch contains an acrylate-based polymer adhesive. One of the unpolymerised acrylate monomers has been characterised as a carcinogen in animals and has been shown to have genotoxic potential in animals and *in vitro* which appears more pronounced in germ cells as compared to somatic cells. However, the risk of the very low levels of unpolymerised monomer causing tumours in humans following dermal application of the Minitran patch is very minimal.

INTERACTIONS WITH OTHER MEDICINES

Concomitant use of alcohol may enhance the vascular effects of glyceryl trinitrate.

Concomitant use of Minitran and other vasodilatory agents, calcium antagonists, β -blockers, ACE inhibitors, neuroleptics, diuretics, antihypertensives, tricyclic antidepressants, sildenafil and alcohol may enhance the blood pressure lowering effects of glyceryl trinitrate.

Use of Minitran with phosphodiesterase inhibitors is contraindicated (see **CONTRAINDICATIONS**). Concomitant use of Minitran with riociguat, a soluble guanylate cyclase inhibitor, is contraindicated (see **CONTRAINDICATIONS**).

There is a risk of coronary artery constriction with concurrent administration of dihydroergotamine.

ADVERSE EFFECTS

Adverse reactions to glyceryl trinitrate are generally dose-related and almost all of these reactions are the result of its vasodilatory activity. Headache is the most frequently encountered adverse reaction, particularly when high doses are used. This usually regresses after a few days despite the continuation of therapy. However, if headache is persistent, it may be necessary to reduce the dose or interrupt treatment.

Reddening of the skin, with or without itching or a slight erythematous reaction, sometimes develops and generally disappears a few hours after removal of the patch without adopting other measures. The site of application should be altered daily to avoid local irritation.

Common ($\geq 1\%$):

Central Nervous System: Headache

Cardiovascular: Hypotension (postural), dizziness, lightheadedness, hot flushes

Dermatological: Application site reaction (redness)

Gastrointestinal: Nausea, vomiting

Uncommon ($\geq 0.1\%$ to $< 1\%$):

Cardiovascular: Palpitations, tachycardia, angina aggravated, fainting

Rare ($< 0.1\%$):

Cardiovascular: Rebound hypertension

Haematological: Methaemoglobinaemia

Hypersensitivity: Anaphylaxis, allergic contact dermatitis

DOSAGE AND ADMINISTRATION

The response to nitrates differs between individuals and the minimum effective dose should be prescribed in each case. It is, therefore, recommended that treatment is started with one Minitran 5 patch per day, with upward dosage titration when necessary.

Attenuation of effect has occurred in some patients being treated with sustained release nitrate preparations. To avoid the development of tolerance (loss of effect) with continuous application and on the basis of current clinical studies, it is recommended that Minitran should be applied daily with a patch free interval of 8-12 hours (usually at night).

Each Minitran patch is contained in a sealed pouch. The adhesive layer is covered by a protective film which should be removed before application. The Minitran patch should be applied to a clean, dry, healthy area of skin on the upper arm or chest and should not be applied to the distal parts of the extremities. Subsequent patches should not be applied to the same area of skin until several days have elapsed. Minitran patches adhere easily to the skin and also stay in place whilst bathing or during physical exercise.

Use in the Elderly

No specific information on use in the elderly is available.

Use in Children

The safety and efficacy of Minitran in children has yet to be established and, therefore, recommendations for its use cannot be made.

OVERDOSAGE

High doses of glyceryl trinitrate may induce rapid reduction in arterial pressure, causing collapse. Due to the controlled release of glyceryl trinitrate from Minitran, overdose is likely to be rare. In cases of suspected overdose, the Minitran patch should be removed and any reduction in arterial blood pressure and symptoms of collapse should be treated by appropriate measures.

Haemodynamic Effects: The adverse effects of glyceryl trinitrate overdose are generally the results of vasodilation, venous pooling, reduced cardiac output and hypotension. These haemodynamic changes may have protean manifestations, including increased intra-cranial pressure with any or all of persistent throbbing headache, confusion and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhoea); syncope (especially in the upright posture); air hunger and dyspnoea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Because the hypotension associated with glyceryl trinitrate overdose is the result of venodilation and arterial hypovolaemia, prudent therapy should be directed towards an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or a similar fluid may also be necessary. The use of adrenaline or other arterial vasoconstrictors in this setting is likely to do more harm than good. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of glyceryl trinitrate overdose in these patients may be subtle and difficult and invasive monitoring may be required.

Methaemoglobinaemia: Nitrate ions liberated during metabolism of glyceryl trinitrate can oxidise haemoglobin into methaemoglobin. Assuming that nitrate moieties of glyceryl trinitrate are quantitatively applied to the oxidation of haemoglobin, patients without cytochrome b₅ reductase activity would require about 1 mg/kg of glyceryl trinitrate before manifesting clinically significant ($\geq 10\%$) methaemoglobinaemia. Patients with normal reductase function would require even larger doses of glyceryl trinitrate before manifesting clinically significant methaemoglobinaemia. Continuous glyceryl trinitrate infusion at 3.1 to 4.0 mg/hr for 2-4 weeks in 36 patients resulted in an average methaemoglobin level of 0.2%, which was comparable to the level observed in patients receiving placebo. Nevertheless, there are case reports of significant methaemoglobinaemia in association with moderate overdoses of organic nitrates in patients who were thought not to be susceptible.

Methaemoglobin levels are available from most clinical laboratories. The diagnosis should be carried out in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO₂. Classically, methaemoglobinaemic blood is described as chocolate brown without colour change on exposure to air. When methaemoglobinaemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

PRESENTATION AND STORAGE CONDITIONS

MINITRAN 5: 1's[#], 3's[#], 30's; MINITRAN 10: 1's[#], 3's[#], 30's; MINITRAN 15: 1's[#], 3's[#], 30's.

Store below 25⁰C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

Prescription only Medicine

Date of First Inclusion on the Australian Register of Therapeutic Goods

27 July 1995

Date of most recent amendment: 30 October 2015

not marketed