

# TOP NITRO\*

## Nitroglycerine Transdermal Therapeutic System

DESCRIPTION : TOP NITRO\* Nitroglycerine Transdermal Therapeutic System contains nitroglycerin in acrylic-based polymer adhesives with a resinous cross-linking agent to provide a continuous source of the active ingredient.

The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each  $\text{cm}^2$  of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Thus, the 10 and 20  $\text{cm}^2$  systems deliver approximately 0.02 and 0.4 mg of nitroglycerin per hour, respectively. The remainder of the nitroglycerin remains in the system and serves as the reservoir from which the drug is released in a controlled manner. The rated release of the drug is dependent upon the area of the system; approximately 0.5 mg nitroglycerin is released for every  $\text{cm}^2$  of system size per 24 hours.

Each unit is sealed in a paper-polyethylene-foil pouch.

ACTIONS : Nitroglycerin is a potent vascular dilator, which relaxes both peripheral arteries and veins (with more prominent effects on the latter) and thereby, reduces cardiac work and myocardial oxygen consumption. 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 (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload). Dilation of the coronary arteries also occurs and could be an important mechanism of action for those anginal syndromes not clearly related to increases in myocardial oxygen demand. The relative importance of preload reduction, afterload reduction and coronary dilation remains undefined.

Nitroglycerin is rapidly metabolized, principally by glucothionitrate reductase, to form glyceryl 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.

In healthy volunteers, detectable plasma concentration of nitroglycerin are reached one-half hour after application of TOP NITRO\* Nitroglycerine Transdermal Therapeutic System and are maintained for the duration of wearing the system. Upon removal of the system, the skin serves as a reservoir, and the plasma concentration declines to less than 50% of the steady-state concentration in approximately one-half hour and to undetectable concentrations by two hours.

Some well-controlled clinical trials using exercise-induced angina testing have shown maintenance of effectiveness when patches were worn continuously. The 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 (a dose far in excess of the acutely effective dose) were delivered continuously. The development of tolerance to nitroglycerin is not exclusive to transdermal delivery. It can also occur with oral organic nitrates when continuous blood levels are maintained.

Tolerance to organic nitrates can be prevented or attenuated by allowing a nitrate-free period of approximately 12 hours during each 24-hour cycle.

Since nitroglycerin metabolism is extremely rapid and because delivery from transdermal patches can be abruptly stopped by simple removal, it is relatively easier to produce a nitrate-free period with transdermal than with oral therapy.

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Therapeutic doses of nitroglycerin have been shown to reduce systolic and mean arterial blood pressures, especially when the patient assumes upright posture.

**INDICATIONS AND USAGE :** TOP NITRO\* Nitroglycerine Transdermal Therapeutic System is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

**DOSAGE AND ADMINISTRATION :** The recommended initial dose of TOP NITRO\* Nitroglycerine Transdermal Therapeutic System is between 10 cm<sup>2</sup> (0.2 mg/hr or 5 mg/24 hrs) to 20 cm<sup>2</sup> (0.4 mg/hr or 10 mg/24 hrs), applied for a period of 12 to 14 hours. Subsequently, the Nitroglycerine Transdermal Therapeutic System should be removed, allowing a 10- to 12- hour nitrate-free interval. Following this period, a fresh TOP NITRO\* Nitroglycerine Transdermal Therapeutic System is applied for another period of 12 to 14 hours. In some patients, it may be necessary to titrate to a higher dose to achieve optimum therapeutic effect. Dosage should be titrated while monitoring clinical response.

Doses between the 0.4 and 0.8 mg/hr have shown continued effectiveness for 10 to 12 hours daily for at least one month (the longest period studies) when administered on an intermittent regimen. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10 to 12 hours is sufficient. Thus to ensure maintenance of response TOP NITRO\* Nitroglycerine Transdermal Therapeutic System should be worn for 12 to 14 hours daily, providing a nitrate-free interval of 10 to 12 hours in any 24-hour cycle.

Patients currently maintained on continuous 24-hour therapy without clinical evidence of nitrate tolerance may continue the regimen as long as they show clinical benefit. Newly treated patients should be started on intermittent therapy.

TOP NITRO\* Nitroglycerine Transdermal Therapeutic System may be applied to any convenient skin area; a recommended site of application is the upper arm or chest. Application sites should be rotated. Suitable areas should be shaved if necessary. Do not apply TOP NITRO\* Nitroglycerine Transdermal Therapeutic System to the distal part of the extremities.

To apply the TOP NITRO\* Transdermal Infusion System, tear open the printed pouch and remove the unit. With the clear side and brown liens facing you, bend the unit away from you to break upon the plastic cover along the brown line. Peel off one-half of the plastic cover. Use the other one-half of the plastic cover as a handle, and apply the sticky side of the patch to the upper arm or chest. Apply TOP NITRO\* Nitroglycerine Transdermal Therapeutic System firmly to the skin surface, while peeling off the remaining side of the plastic cover. Hands should be washed thoroughly after application.

A discarded patch should be disposed of appropriately to avoid accidental application or use.

**DRUG INTERACTIONS :** Nitroglycerine acts directly on vascular muscle. Therefore, any other agent that directly or indirectly acts on vascular smooth muscle may have decreased or increased effect depending upon the agent.

Concomitant use of nitrates and alcohol, antihypertensive agents, beta adrenergic blockers or phenothiazines cause additive hypotensive effects.

Use of sildenafil (VIAGRA) may cause severe lowering of blood pressure and serious complications.

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**ADVERSE REACTIONS :** Headache is the most common adverse reaction of TOP NITRO\* Transdermal Infusion System, especially with the administration, of higher dosages. Transient episodes of lightheadedness, occasionally related to blood pressure changes may also occur. Hypotension occurs infrequently but may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina and rebound hypotension have been reported but are uncommon. Application-site irritation may occur but is rarely severe.

**CONTRAINDICATIONS :** TOP NITRO\* Nitroglycerine Transdermal Therapeutic System is contraindicated in patients with known hypersensitivity to organic nitrate drugs and in patients with marked anemia.

**PRECAUTIONS :** TOP NITRO\* Nitroglycerine Transdermal Therapeutic System should be used only under careful clinical and / or hemodynamic monitoring in patients with acute myocardial infarction of congestive heart failure.

TOP NITRO\* Nitroglycerine Transdermal Therapeutic System should not be used for the immediate treatment of acute anginal attacks. Occasional use of sublingual nitroglycerin may be necessary for this purpose.

Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because the possibility of electrical arcing, a phenomenon associated with the use of defibrillators, is enhanced by their presence.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In some patients, severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. Thus, TOP NITRO\* Nitroglycerine Transdermal Therapeutic System should be used with caution in patients who may have volume depletion from diuretic therapy and in patients who have low systolic blood pressure (e.g. below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

In clinical trials of angina patients, there are rare 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 is not known, however.

Amplification of the vasodilatory effects of TOP NITRO\* Nitroglycerine Transdermal Therapeutic System by sildenafil can result in severe hypotension. The course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

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

**USAGE DURING PREGNANCY AND IN NURSING MOTHERS :** It is not known whether TOP NITRO\* Nitroglycerine Transdermal Therapeutic System can affect reproductive capacity or cause fetal harm. Thus, it should be administered to pregnant women only if the potential benefits to the mother clearly outweigh the potential hazard to the fetus.

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions from nitroglycerin in nursing infants, caution should be exercised when TOP NITRO\* Nitroglycerine Transdermal Therapeutic System is administered to a nursing woman.

#### OVERDOSAGE INFORMATION

Nitrate overdoses may result in severe hypotension, persistent throbbing headache, vertigo, palpitations, visual disturbances, flushing and perspiring skin (later becoming cold and cyanotic), nausea and vomiting (colic and bloody diarrhea), syncope (especially in the upright posture), methemoglobinemia with cyanosis and anorexia, initial hyperpnea, dyspnea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intra cranial pressure with cerebral symptoms of confusion and moderate fever, paralysis and coma followed by clonic convulsions and possibly death due to circulatory collapse.

HOW SUPPLIED : TOP NITRO\* 5/10 each packed in cartons containing 5 pouches.

Store in a cool place.

For additional information contact :



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