Medical Advisory Panel and
Pharmacy Benefits Management Strategic Healthcare Group
Drug Class Review
Transdermal Nitroglycerin Patches

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OBJECTIVE

1. To review the efficacy, safety, and administration of the currently available transdermal nitroglycerin patches in the prevention of angina pectoris due to coronary artery disease.

Brand Name:	Minitran	Nitro-Dur	Transderm-Nitro
Manufacturer:	3M Pharm	Key	Summit
Patch Sizes: (mg/hr)	0.1, 0.2, 0.4, 0.6	0.1, 0.2, 0.3, 0.4, 0.6, 0.8	0.1, 0.2, 0.4, 0.6, 0.8

2. To define the drug selection criteria for determining the formulary status of these products on the Veteran Health Administration National Drug Formulary.

I. PHARMACOLOGY[1-3]

Nitrates are converted in-vivo into nitric oxide, which is a potent vasodilator. Nitric oxide causes the relaxation of vascular smooth muscle through the stimulation of intracellular cyclic guanosine monophosphate (cGMP). The accumulation of intracellular cGMP leads to the relaxation of venular and arterial smooth muscle.

Nitrates tend to have more effect on the venous system, but the relaxation of arterial smooth muscle is also seen. Venodilation causes the venous pooling of blood and a reduction of venous return to the heart (preload). Arteriolar relaxation causes a decrease in systemic vascular resistance (afterload). The reduction of preload and afterload decreases cardiac workload and oxygen demand. In the coronary circulation, nitrates may redistribute blood flow to ischemic myocardium by increasing flow through collateral channels.

II. INDICATIONS[2]

Transdermal nitroglycerin patches are approved by the Food and Drug Administration (FDA) for the prevention of angina pectoris due to coronary artery disease.

III. PHARMACOKINETICS[2,4]

Absorption: Nitroglycerin is rapidly absorbed through the skin. The transdermal patch is designed to provide a continual release of nitroglycerin through the skin directly into the peripheral circulation, thus bypassing first pass hepatic metabolism. It accomplishes this through the use of a concentration gradient and a semi-permeable membrane. The total amount of active drug in the patch, the delivery system (semi-permeable membrane), and patch surface area differs from patch to patch. All patches are designed to deliver a constant amount of drug through the skin per hour (e.g. 0.2mg/hr, 0.4mg/hr, etc.). Physical activity and elevated ambient temperatures(e.g. sauna) may increase the rate of absorption. The onset of action for transdermal nitroglycerin patches is 30-60 minutes and duration of action is up to 24 hours, depending on the removal time of the patch.

Metabolism: Nitroglycerin is metabolized in the liver to 1,2 and 1,3 dinitroglycerols. These metabolites are active and may contribute to nitroglycerin's clinical efficacy.

IV. SAFETY AND ADMINISTRATION

A. Adverse effects:[1-3,7]

Transdermal nitroglycerin patches are generally well tolerated. Allergic reactions to the nitroglycerin molecule are rare. Patients may develop contact dermatitis from the patches' adhesives. The most common adverse effect is headache; this tends to subside with continued therapy. Hypotension and/or syncope and lightheadedness are less frequently reported.

B. Drug Interactions:

Precipitant Drug	Object Drug	Effect	Description
Alcohol	Nitrates	↑	Severe hypotension and cardiovascular collapse may occur
Aspirin	Nitrates	↑	Increased nitrate serum concentrations and actions may occur. This combination is commonly used together.
CCB	Nitrates	↑	Marked symptomatic orthostatic hypotension may occur. Dosage adjustment of either agent may be necessary.

Source adapted by Drugs Facts and Comparisons; 143c 1996
CCB = calcium channel blockers
↑ = object drug increased; ↓ = object drug decreased

C. Dosing:[1,2,6]

Starting dose: 0.2-0.4 mg/hr. Titration to the lowest dose that controls the symptoms of angina pectoris. Doses between 0.4 and 0.8mg/hr have been shown to be effective during 10-12 hour daily dosing for at least one month. Some controversy still exists over the need for a 10-12 hour nitrate free interval with the transdermal nitroglycerin patch. Patches should be applied to a hair-free area of intact shin and the application site should be rotated to prevent skin irritation. Patches should not be placed on extremities (below elbow or knee).

V. CLINICAL TRIALS

After an extensive literature search, only a few relevant studies were available for review. The transdermal nitroglycerin patches are FDA approved to deliver a specified milligram dosage per hour. The FDA has not given a bioequivalence rating for any of these products.[5]

A. Deponit vs. Transderm-Nitro

Valle'-Jones C, et al.[7] This was the only trial found that compared the efficacy of transdermal nitroglycerin patches. It was a randomized, unblinded, two-period crossover trial that evaluated the number of angina attacks/week and number of doses of sub-lingual nitroglycerin used by patients/week on either the Duponit or Transderm-Nitro patch. Forty-seven patients were studied using a crossover method (therefore all subjects were evaluated on both patches). The study showed that both patches significantly decreased the primary endpoints vs. the placebo (baseline washout period). The study also showed that the Duponit patch decreased the two primary endpoints to a statistically greater degree than the Transderm-Nitro patch.

This study has several problems with its conclusions. First, no nitrate-free interval was used. Though not without controversy, most experts agree that a daily nitrate-free interval is necessary to prevent drug tolerance. Second, the study was unblinded and therefore patient and researcher bias may have affected the results. Lastly, the difference between the two patches was statistically significant but probably not clinically significant. Patients on Duponit had 0.4 less angina attacks/week and used 0.6 less doses of sub-lingual nitroglycerin/week. No definite conclusions can be made on the superiority of either patch based on this study.

B. Pharmacokinetic and Bioavailability Study

Sun J, et al.[4] This was a pharmacokinetic and bioavailability study that compared the plasma nitroglycerin concentrations of three commercial patches in 18 healthy males. The results showed that the plasma concentration profiles of nitroglycerin and its metabolites were similar for the three patches (Transderm-Nitro, Nitrodisc, and Nitro-Dur II). No statistical differences were demonstrated.

C. Patient and Physician Preference between Patches

Riley S, et al.[8] Two transdermal nitroglycerin patches were worn simultaneously and patients rated the adhesive properties and comfort of the patches. Sixty-four patients were placed on both the Transderm-Nitro and the Nitro-Dur patches. Patients preferred Transderm-Nitro patches (with statistical significance) for adhesive properties and comfort over the Nitro-Dur patches.

Clin Ther. 1991;13:545-9.[9] This study compared the Transderm-Nitro and Nitro-Dur patches in 72 patients who wore both patches simultaneously. The patients and physicians compared the two patches based on eight characteristics: size, color, comfort, ease of application, adhesiveness, ease of removal, appearance, and associated redness/irritation. In this study, patients and

physicians preferred Nitro-Dur patches (with statistical significance) in respect to the eight characteristics over the Transderm-Nitro patches.

Chinoy DA, et al.[10] One hundred forty-two patients compared the adhesiveness and comfort of two transdermal nitroglycerin patches worn simultaneously (Transderm-Nitro and Duponit patches).Patients preferred the Transderm-Nitro patches (with statistical significance) over the Duponit patch.

VI. CRITERIA FOR SELECTION OF FORMULARY AGENTS

Due to the lack of properly designed clinical trials that support the clinical superiority of any transdermal nitroglycerin patch, selection of the formulary product should be based on drug product cost and patient acceptance. Several "patient acceptance" studies have been performed all giving conflicting results indicating that there is a wide patient to patient variation in patch preference.

VII. RECOMMENDATIONS

Based on present VA usage, the following transdermal nitroglycerin patch product strengths should be contracted: 0.1, 0.2, 0.4, 0.6 mg/hr. Only one manufacturer's transdermal nitroglycerin patch is required to provide adequate anginal relief for VA patients. All products have shown to be effective in the prevention pectoris due to coronary artery disease. Because no one product has demonstrated superiority over another, selection of a product should first be based on quality of the product and then cost of the drug.

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