PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

NITRO-DUR® 0.2
NITRO-DUR® 0.4
NITRO-DUR® 0.6
NITRO-DUR® 0.8

Nitroglycerin Transdermal System

NITRO-DUR 0.2 (Rated release in vivo 0.2 mg/hour, 10 cm^2)
NITRO-DUR 0.4 (Rated release in vivo 0.4 mg/hour, 20 cm^2)
NITRO-DUR 0.6 (Rated release in vivo 0.6 mg/hour, 30 cm^2)
NITRO-DUR 0.8 (Rated release in vivo 0.8 mg/hour, 40 cm^2)

Antianginal Agent

DIN Owner:
USpharma Ltd.
13900 NW 57th Court
Miami Lakes, FL 33014, USA
Imported by:
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Mississauga, ON L4W 4Y1
CANADA

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Nitroglycerin Transdermal System

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Transdermal patch / 0.2 mg/hour; 0.4 mg/hour; 0.6 mg/hour 0.8 mg/hour	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NITRO-DUR (nitroglycerin) used intermittently 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.

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

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug, other nitrates or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Allergy to the adhesive used in nitroglycerin patches has been reported and constitutes a contraindication to the use of this product.
- Acute circulatory failure associated with marked hypotension (shock and states of collapse)
- Postural hypotension.

- Myocardial insufficiency due to obstruction (e.g. in the presence of aortic or mitral stenosis or of constrictive pericarditis).
- Increased intracranial pressure.
- Increased intraocular pressure.
- Severe anemia.
- Concomitant use of NITRO-DUR (nitroglycerin) either regularly and/or intermittently, with a phosphodiesterase inhibitor for erectile dysfunction (e.g. VIAGRA* (sildenafil citrate), CIALIS* (tadalafil), or LEVITRA* or STAXYN* (vardenafil) or for pulmonary arterial hypertension (e.g. REVATIO* (sildenafil citrate) or ADCIRCA* (tadalafil) is absolutely contraindicated. Concomitant use can cause severe drops in blood pressure.
- Do not use NITRO-DUR 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.

WARNINGS AND PRECAUTIONS

Cardiovascular

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 NITRO-DUR in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

NITRO-DUR 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.

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

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.

Tolerance to nitroglycerin with cross tolerance to other nitrates or nitrites may occur. 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.

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 dose of NITRO-DUR should be periodically reviewed in relation to continuing antianginal control.

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 NITRO-DUR can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Therefore, use NITRO-DUR 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 in children have not been established.

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 higher 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, 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.

Post-Market Adverse Drug Reactions

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 favor methemoglobin formation, even conventional doses of organic nitrates can produce harmful concentrations of methemoglobin.

Methemoglobinemia should be treated with methylene blue if the patient develops cardiac or CNS effects of hypoxia. The initial dose is 1-2 mg/kg infused intravenously over 5 minutes. Repeat methemoglobin levels should be obtained 30 minutes later and a repeat dose of 0.5-1.0 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 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.

DRUG INTERACTIONS

Drug-Drug Interactions

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquillizers may potentiate the blood pressure lowering effect of NITRO-DUR. Dose adjustment may be necessary.

Nitroglycerin 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.

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

Concomitant use of NITRO-DUR (nitroglycerin) with a phosphodiesterase inhibitor (e.g. VIAGRA* or REVATIO* (sildenafil citrate), CIALIS* or ADCIRCA* (tadalafil) or LEVITRA* or STAXYN* (vardenafil) can potentiate the hypotensive effect of NITRO-DUR (nitroglycerin). This could result in lifethreatening hypotension with syncope or myocardial infarction and death. Therefore, phosphodiesterase inhibitor drugs in any form are contraindicated in patients receiving NITRO-DUR therapy (see CONTRAINDICATIONS).

Concomitant use of NITRO-DUR with soluble guanylate cyclase stimulators such as ADEMPAS* (riociguat) is contraindicated (see CONTRAINDICATIONS).

Concurrent administration of NITRO-DUR 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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.

Recommended Dose and Dosage Adjustment
Starting dose is one NITRO-DUR 0.2 patch (10 cm^2), usually applied in the morning. If 0.2 mg/hour (10 cm^2) is well tolerated, the dose can be increased to 0.4 mg/hour (20 cm^2) if required. A maximum of 0.8 mg/hour (40 cm^2) may be used.

Administration
The NITRO-DUR Nitroglycerin Transdermal System may be applied to any convenient skin area; a recommended site of application is the arm or chest. Application sites should be rotated. A suitable area may be shaved if necessary. Do not apply NITRO-DUR to the distal part of the extremities. Hands should be washed thoroughly after application. Following use, the patch should be discarded in a manner that prevents accidental application or ingestion by curious children or others.

OVERDOSAGE

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, increased intracranial pressure with cerebral symptoms of confusion and moderate fever, paralysis, coma, clonic convulsions and death due to circulatory collapse.

The patch should be removed immediately and the underlying skin scrubbed thoroughly. No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in the central fluid volume. Specific elements of such therapy might include any or all of the following: elevation of the patient's legs, passive motion of the patient's extremities, and intravenous infusion of normal saline or similar fluid. In patients with renal disease or congestive heart failure, 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.

<u>Treatment of Overdosage</u>
Keep the patient recumbent in a shock position and comfortably warm. Remove the NITRO-DUR patch. Passive movement of the extremities may aid venous return. Administer oxygen and artificial ventilation if necessary. Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose; it and related compounds are contraindicated in this situation.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
The primary pharmacological effect of nitroglycerin is its smooth muscle relaxant effect. Therapeutic effectiveness depends on its actions on vascular smooth muscle.

Pharmacodynamics
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 roll in their metabolic activity, and caution should therefore be exercised in cases of anemia. In animal studies it has been found that extrahepatic vascular tissues (femoral vein, inferior vena 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.

STORAGE AND STABILITY
Store between 15 to 30°C. Do not refrigerate.

SPECIAL HANDLING INSTRUCTIONS
Not Applicable for present Product Monograph

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

NITRO-DUR System (Rated Release *In Vivo*)	Total Nitroglycerin Content	System Size	Package Size
NITRO-DUR 0.2 (0.2 mg/hour)	40 mg	10 cm^2	Retail until dose boxes of 30
NITRO-DUR 0.4 (0.4 mg/hour)	80 mg	20 cm^2	Retail unit dose boxes of 30
NITRO-DUR 0.6 (0.6 mg/hour)	120 mg	30 cm^2	Retail unit dose boxes of 30
NITRO-DUR 0.8 (0.8 mg/hour)	160 mg	40 cm^2	Retail unit dose boxes of 30

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

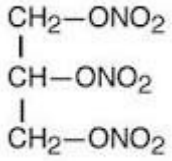
Drug Substance

Proper name: Nitroglycerin

Chemical name: 1,2,3-propanetriol trinitrate

Molecular formula and molecular mass: $C_3H_5(NO_3)_3$; 227.09

Structural formula:



Physicochemical properties: Milky white liquid

CLINICAL TRIALS

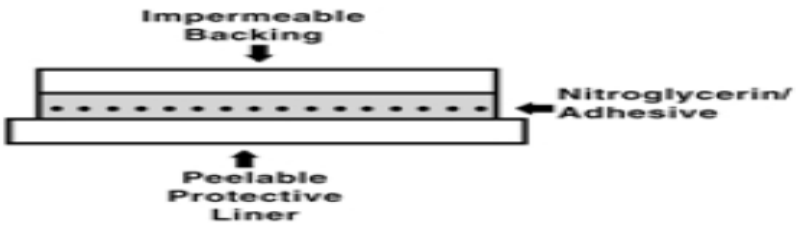
Not Applicable for present Product Monograph

DETAILED PHARMACOLOGY

The NITRO-DUR nitroglycerin transdermal system is a flat 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 0.02 mg of nitroglycerin per hour. Thus, the 10-, 20-, 30-, and 40-cm^2 systems deliver 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.

The NITRO-DUR transdermal system contains nitroglycerin in acrylic-based polymer adhesives with a resinous cross-linking agent to provide a continuous source of active ingredient. Each unit is sealed in a paper polyethylene-foil pouch.

Cross section of the system:



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 systemic 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 NITRO-DUR 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, 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, steady-state plasma concentrations of nitroglycerin were reached within one half-hour after application of the patch and were maintained at the same level for the duration of the study (24 hours). Between 2 and 24 hours, the mean steady-state concentration was 0.224 ng/mL (20 cm^2 patch); the total amount of nitroglycerin delivered in 24 hours was 5.11 + 1.69 mg, 10.67 + 4.78 mg and 17.85 + 7.40 mg from 10 cm^2, 20 cm^2, and 40 cm^2 patches, respectively, indicating that the dose delivered is proportional to the surface area of the patch. Within one hour of removal of the patch, the plasma concentration declines to about 50% of steady-state concentration and to undetectable concentrations by two hours.

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 well-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, have 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. One controlled clinical trial suggested that the intermittent use of nitrates may be associated with a decreased, in comparison to placebo, exercise tolerance during the last part of the nitrate-free interval; 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 or severity of angina

during the nitrate-free interval should be considered.

MICROBIOLOGY
Not Applicable for present Product Monograph

TOXICOLOGY
Acute Toxicity
The intravenous lethal dose of nitroglycerin was found to be 45 mg/kg in the rabbit. The minimum lethal dose following intramuscular administration to rabbits was found to be 400-500 mg/kg and in the rat was 150-400 mg/kg. Orally, doses of 80 to 100 mg/kg were found to be lethal in the 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 dose 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 at post-mortem.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic effects of oral nitroglycerin at doses up to 1060 mg/kg/day for up to 2 years were studied in rats and mice. No carcinogenic effects were observed in mice; in rats, hepatocellular carcinomas were observed at the middle doses of 31.5 or 38.1 mg/kg/day and high doses of 363 or 434 mg/kg/day given for 2 years. The clinical relevance of these findings is unknown. The extensive use of nitroglycerin in man has not produced any evidence of carcinoma.

There were no apparent nitroglycerin-induced mutagenic effects in the cytogenetics analyses of bone marrow and kidney cells from dogs and rats fed nitroglycerin for 2 years and in the dominant lethal mutation study in rats.

A three generation reproduction study in rats found adverse effects on fertility in the high dose group (363 or 434 mg/kg/day) 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NITRO-DUR®

Nitroglycerin Transdermal System

Read this carefully before you start taking NITRO-DUR and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your prescribing physician about your medical condition and treatment and ask if there is any new information about NITRO-DUR.

What is NITRO-DUR used for?
NITRO-DUR is used in adults to prevent angina (chest pain).

NITRO-DUR is **NOT** intended to be used for acute angina attacks. Sublingual nitroglycerin medications should be used if you are having an acute angina attack**.**

How does NITRO-DUR work?
NITRO-DUR is a patch applied directly to the skin. The nitroglycerin passes from the adhesive surface through the skin - allowing medication to be absorbed directly into the bloodstream. 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.

The amount of NITRO-DUR you need will depend upon your body's needs. Observe the dosing instructions given to you by your prescribing physician and report to him/her if your condition changes.

What are the ingredients in NITRO-DUR?
Medicinal ingredients: Nitroglycerin
Non-medicinal ingredients: Polymers used mainly in the adhesive of the patch.

NITRO-DUR comes in the following dosage forms:

Transdermal patch: 40 mg (0.2 mg/hour), 80 mg (0.4 mg/hour), 120 mg (0.6 mg/hour), 160 mg (0.8 mg/hour)

Do not use NITRO-DUR if you:

- are allergic to nitroglycerin, nitrates, or to any non-medicinal ingredient in the formulation.
- are taking medication for erectile dysfunction such as VIAGRA* (sildenafil citrate), CIALIS* (tadalafil), LEVITRA* or STAXYN* (vardenafil).
- are taking medications used to treat high blood pressure in your lungs such as ADEMPAS* (riociguat), REVATIO* (sildenafil citrate) or ADCIRCA* (tadalafil).
- have had a recent heart attack, or other serious heart problems, stroke, or head injury.
- experience lightheadedness, dizziness or fainting when going from lying or sitting to

standing up (postural hypotension).
- have severe anemia (low iron levels in your blood or low red blood cell count).
- have narrowing of the heart valves.
- have an eye disease called closed angle glaucoma or any other condition that increases the pressure in your eyes.

To help avoid side effects and ensure proper use, talk to your prescribing physician before you take NITRO-DUR. Talk about any health conditions or problems you may have, including if you:
- have heart failure
- have low blood pressure or take diuretics ("water pills")
- have lung disease
- Are breast feeding, pregnant or intend to become pregnant. Your healthcare professional will decide whether you should use NITRO-DUR and what extra care should be taken during its use
- are less than 18 years old

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

Tolerance to NITRO-DUR 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 NITRO-DUR. Talk to your prescribing physician if you wish to discontinue using NITRO-DUR.

Tell your prescribing physician about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NITRO-DUR:
- 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 NITRO-DUR.
- Do not use NITRO-DUR if you are taking drugs used to treat high blood pressure in your lungs such as ADEMPAS* (riociguat), REVATIO* (sildenafil citrate) or ADCIRCA* (tadalafil).
- Drugs used to treat high blood pressure.
- Diuretics ("water pills")
- Drugs used to treat depression called "tricyclic antidepressants".
- Tranquillizers.
- Other drugs that may have the same effect as NITRO-DUR.
- Alcohol.
- Drugs used to treat migraine headaches (such as dihydroergotamine).
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling (such

as ibuprofen, naproxen, and celecoxib).

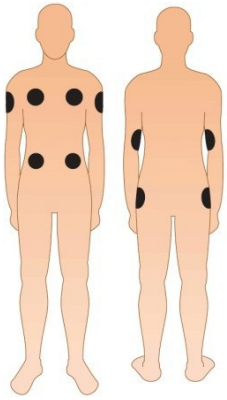
- Acetylsalicylic acid (Aspirin)

How to use NITRO-DUR:

1. Patches should be applied for 12 to 14 hrs, and taken off for 10 to 12 hrs.
2. Do not cut NITRO-DUR, use part patches or apply more than one patch at a time.
3. Do not reuse patch. Discard after first use in a safe manner.
4. Allow NITRO-DUR to stay in place as directed by your prescribing physician.
5. Showering is permitted with NITRO-DUR in place.
6. NITRO-DUR is packaged so that you have a 30-day supply. Be sure to check your supply periodically. Before it runs low, you should visit your pharmacist for a refill or ask your prescribing physician to renew your NITRO-DUR prescription.
7. It is important that you do not miss a day of your NITRO-DUR therapy. If your schedule needs to be changed, your prescribing physician will give you specific instructions.
8. NITRO-DUR has been prescribed for you. Do not give your medication to anyone else.
9. Notify your prescribing physician if your condition changes.

<u>Placement area</u>

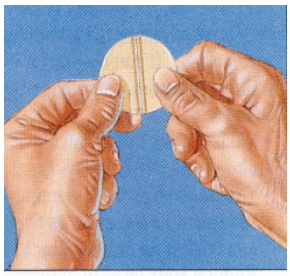
- Apply to clean, dry, hairless areas of the skin, each successive application to a different site. Select a reasonably hair-free application site. An appropriate application area can be shaved ifrequired
- Avoid extremities below the knee or elbow, skin folds, scar tissue, burned or irritated areas.



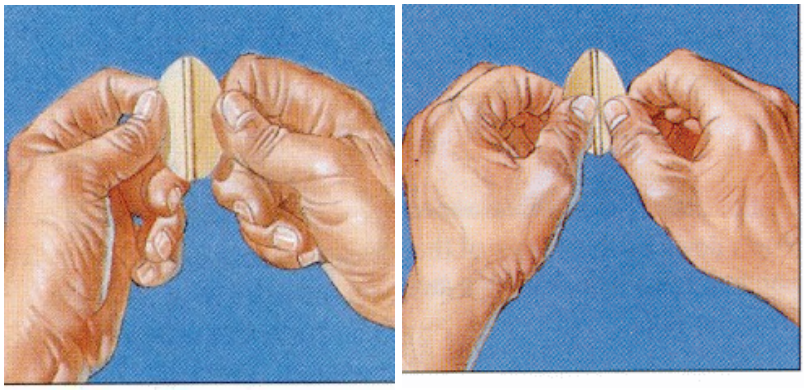
<u>Application</u>

- Wash hands before applying.

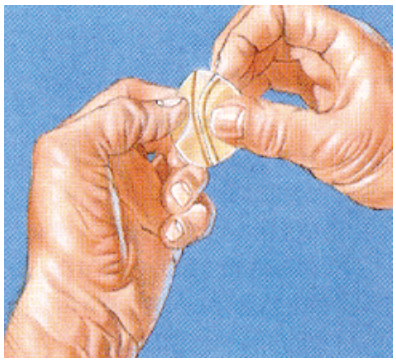
• Hold the unit with brown lines facing you, in an up and down position.



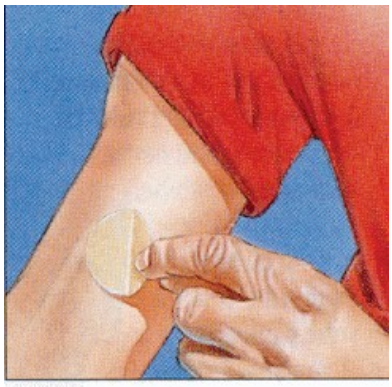
- Bend the sides of the unit away from you, then toward you until you hear a "SNAP".



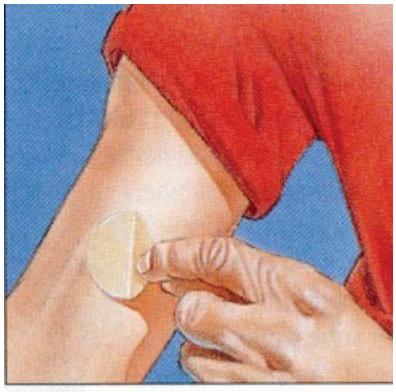
- Twist the patch gently to lift the plastic backing. Peel off one side of the plastic backing.



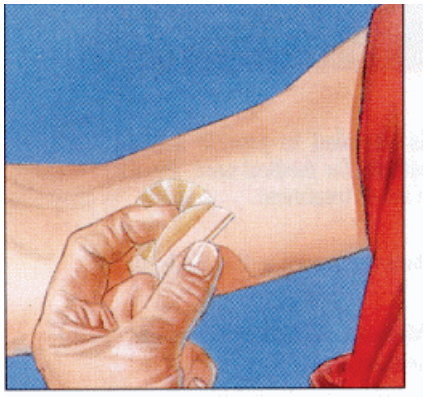
- Using the other half of the backing as a handle, apply the sticky side of the patch to the skin.



- Press the sticky side on the skin, and smooth down.



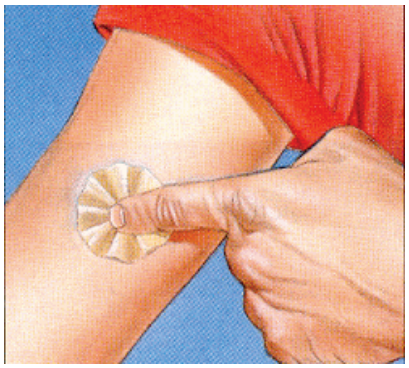
- Fold back the remaining side of the patch. Grasp the edge of the plastic applicator by the stripe, and pull it across the skin.



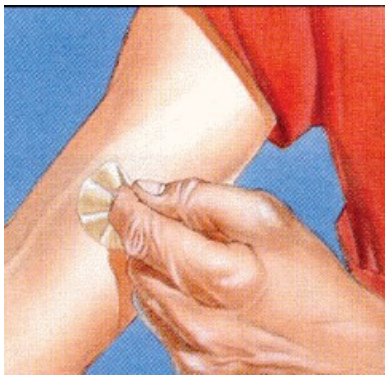
- Wash hands to remove any drug.

Removal

- Press down on the center of the system to raise its outer edge away from the skin.



- Grasp the edge gently, and slowly peel the patch away from the skin.



- Wash skin area with soap and water. Towel dry. Wash hands.
- After removal, the patch should be discarded in a manner that prevents accidental application or ingestion by children or pets.
- You should use a different application site every day.

Skin care

1. After you remove NITRO-DUR, your skin may feel warm and appear red. This is normal. The redness will disappear in a short time. If the area feels dry, you may apply a soothing lotion after washing.

2. Any redness or rash that does not disappear within a few hours should be called to your prescribing physician's attention.

Usual adult dose:

The starting dose is one NITRO-DUR 0.2 patch (10 cm^2), usually applied in the morning. If well tolerated and depending on response, dose may be increased to 0.4 mg/hr, maximum 0.8 mg/hr.

Patches should be applied for 12 to 14 hrs, and taken off for 10 to 12 hrs. Apply to clean, dry, hairless areas of the skin, each successive application to a different site.

Overdose:

The patch should be removed immediately and the underlying skin washed thoroughly.

If you think you have taken too much NITRO-DUR, contact your prescribing physician, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to apply NITRO-DUR at the scheduled time apply it as soon as you remember.

What are possible side effects from using NITRO-DUR ?

These are not all the possible side effects you may feel when taking NITRO-DUR. If you experience any side effects not listed here, contact your prescribing physician. Please also see Warnings and Precautions.

Side effects may include:

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

NITRO-DUR may also lower the blood pressure and cause dizziness, lightheadedness, or a fainting feeling, especially when you get up quickly from lying or sitting. Getting up slowly may help. If you feel dizzy, sit or lie down. You may be more likely to experience headaches, dizziness, or lightheadedness if you drink alcohol, stand for a long time, or if the weather is hot. While using NITRO-DUR, be careful about the amount of alcohol you drink. Also use extra care when exercising, standing for a long time, driving, or during hot weather.

Serious side effects and what to do about them			
Symptom / effect	Talk to your prescribing physician		Get 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.			√
COMMON **Low Blood Pressure:** dizziness, fainting, lightheadedness may occur when you go from lying or sitting to standing up.	√		
UNKNOWN **Increased levels of methemoglobin in the blood:** shortness of breath, blue or purple colouration of the lips, fingers and/or toes, headache, fatigue, dizziness, loss of consciousness.			√
UNKNOWN **Chest pain** (angina)	√		
UNKNOWN **Irregular, fast or slow heartbeat**		√	
UNKNOWN **Heart Attack:** crushing chest pain that radiates into the arm or jaw, shortness of breath, nausea, vomiting.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your prescribing physician.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15 to 30˚C. Do not refrigerate.
Keep out of reach and sight of children.

If you want more information about NITRO-DUR:

- Talk to your prescribing physician.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada.html https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; Questions/Concerns: 1-833-300-5309.

This leaflet was prepared by USpharma Ltd.

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