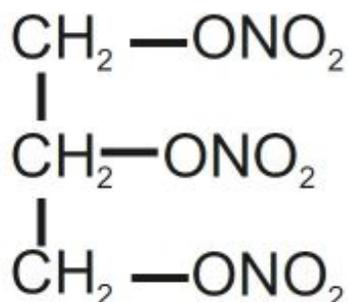


NITROGLYCERIN- nitroglycerin ointment
Encube Ethicals, Inc.

Nitroglycerin Ointment USP, 2%
FOR TOPICAL USE ONLY
Rx Only

DESCRIPTION

Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

Nitroglycerin ointment USP, 2% for topical use contains lactose and 2% nitroglycerin in a base of lanolin, white petrolatum and purified water. Each inch (2.5 cm), as squeezed from the tube, contains approximately 15 mg of nitroglycerin.

CLINICAL PHARMACOLOGY

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation 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). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

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 inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have

consistently failed. Only after nitrates had been absent from the body for several hours was their anti-anginal efficacy restored.

Pharmacokinetics: The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about three minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow; known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. The dinitrates are further metabolized to (non-vasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide.

To avoid development of tolerance to nitroglycerin, drug-free intervals of 10 - 12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was less than that exhibited by the parallel group receiving placebo.

Reliable assay techniques for plasma nitroglycerin levels have only recently become available, and studies using these techniques to define the pharmacokinetics of nitroglycerin ointment have not been reported. Published studies using older techniques provide results that often differ, in similar experimental settings, by an order of magnitude. The data are consistent, however, in suggesting that nitroglycerin levels rise to steady state within an hour or so of application of ointment, and that after removal of nitroglycerin ointment, levels wane with a half-life of about half an hour.

The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

The maximal achievable daily duration of anti-anginal activity provided by nitroglycerin ointment therapy has not been studied. Recent studies of other formulations of nitroglycerin suggest that the maximal achievable daily duration of antianginal effect from nitroglycerin ointment will be about 12 hours.

It is reasonable to believe that the rate and extent of nitroglycerin absorption from ointment may vary with the site and square measure of the skin over which a given dose of ointment is spread, but these relationships have not been adequately studied.

Clinical Trials: Controlled trials have demonstrated that nitroglycerin ointment can effectively reduce exercise-related angina for up to 7 hours after a single application. Doses used in clinical trials have ranged from 1/2 inch (1.3 cm; 7.5 mg) to 2 inches (5.1 cm; 30 mg), typically applied to 36 square inches (232 square centimeters) of truncal skin.

In some controlled trials of other organic nitrate formulations, efficacy has declined with time. Because controlled, long-term trials of nitroglycerin ointment have not been reported, it is not known how the efficacy of nitroglycerin ointment may vary during extended therapy.

INDICATIONS AND USAGE

Nitroglycerin ointment USP, 2% is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it.

WARNINGS

Amplification of the vasodilatory effects of nitroglycerin by sildenafil can result in severe hypotension. The time 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.

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pains, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Some clinical trials in angina patients have provided nitroglycerin for about 12 continuous hours of every 24-hour day. During the nitrate-free intervals in some of these trials, anginal attacks have been more easily provoked than before treatment, and patients have demonstrated hemodynamic rebound and decreased exercise tolerance. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is not known.

Information for Patients

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches are 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 is likely to 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. Patient instruction leaflet is included.

Drug Interactions

The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies to evaluate the carcinogenic or mutagenic potential of nitroglycerin have not been performed. Nitroglycerin's effect upon reproductive capacity is similarly unknown.

Pregnancy

Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. 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. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment see OVERDOSAGE.

Data are not available to allow estimation of the frequency of adverse reactions during treatment with nitroglycerin ointment.

OVERDOSAGE

Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is:

and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

Nitroglycerin ointment USP, 2% for topical use contains lactose and 2% nitroglycerin in a base of lanolin, white petrolatum and purified water. Each inch (2.5 cm), as squeezed from the tube, contains approximately 15 mg of nitroglycerin.

Hemodynamic Effects: The ill effects of nitroglycerin overdose are generally the results of nitroglycerin's capacity to induce vasodilation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial 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 diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, 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.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which—if any—of these substances can usefully be removed from the body by hemodialysis.

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 venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or the 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 nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₅ reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2 to 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

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 pO₂. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

As noted above (**CLINICAL PHARMACOLOGY**), controlled trials have demonstrated that nitroglycerin ointment can effectively reduce exercise-related angina for up to 7 hours after a single application. Doses used in clinical trials have ranged from 1/2 inch (1.3 cm; 7.5 mg) to 2 inches (5.1 cm; 30 mg), typically applied to 36 square inches (232 square centimeters) of truncal skin.

It is reasonable to believe that the rate and extent of nitroglycerin absorption from ointment may vary with the site and square measure of the skin over which a given dose of ointment is spread, but these relationships have not been adequately studied.

Controlled trials with other formulations of nitroglycerin have demonstrated that if plasma levels are maintained continuously, all anti-anginal efficacy is lost within 24 hours. This tolerance cannot be overcome by increasing the dose of nitroglycerin. As a result, any regimen of nitroglycerin ointment administration should include a daily nitrate-free interval. The minimum necessary length of such an interval has not been defined, but studies with other nitroglycerin formulations have shown that 10 to 12 hours is sufficient.

Thus, one appropriate dosing schedule for nitroglycerin ointment would begin with two daily 1/2- inch (7.5 mg) doses, one applied on rising in the morning and one applied six hours later. The dose could be doubled, and even doubled again, in patients tolerating this dose but failing to respond to it. The pouch is intended as a unit dose package only and is equivalent to approximately 1 inch as squeezed from the tube. Use entire

contents of pouch to obtain full dose and discard immediately after use.

Each tube of ointment and each box of pouchs is supplied with a pad of ruled, impermeable, paper applicators. These applicators allow ointment to be absorbed through a much smaller area of skin than that used in any of the reported clinical trials, and the significance of this difference is not known. To apply the ointment using one of the applicators, place the applicator on a flat surface, printed side down. Squeeze the necessary amount of ointment from the tube onto the applicator, place the applicator (ointment side down) on the desired area of the skin, and tape the applicator into place.

HOW SUPPLIED

Nitroglycerin ointment USP, 2%, is a pale yellow ointment. (Package includes a supply of ruled applicators for convenient application.)

NDC 21922-054-47 Carton for 48 x 1 gram pouch pack

NDC 21922-054-59 1 gram Pouch Pack

NDC 21922-054-05 30 gram Aluminum tubes.

Close tightly, immediately after each use. Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

To report SUSPECTED ADVERSE REACTIONS, contact Encube Ethical Private Limited at 1-833-285-4151, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:

Encube Ethicals Pvt. Ltd.

Plot No. C-1, Madkaim Industrial Estate,
Madkaim, Post: Mardol, Ponda, Goa - 403 404, India.

Distributed by:

Encube Ethicals, Inc. 200 Meredith Drive, Suite 202,
Durham, NC 27713 USA

Revised: 09/2024

PATIENT INSTRUCTIONS FOR APPLICATIONS

Nitroglycerin Ointment USP, 2%

PATIENT INSTRUCTIONS FOR APPLICATIONS

1. Measure desired dosage of nitroglycerin ointment 2% by means of the dose measuring applicator supplied with the tube. Place the applicator on a flat surface, printed side down. Squeeze the necessary amount of ointment from the tube onto the applicator, and place the applicator (ointment side down) on the desired area of the skin.
2. Spread the ointment using the dose measuring applicator lightly onto the chest or other areas of skin if preferred. Do not rub into the skin. Coverage of an area approximately the size of the dose measuring applicator (3 1/2" by 2 1/4") should be sufficient to obtain the desired clinical effects. A larger area may be used.

3. Tape the applicator into place.

NOTE: Nitroglycerin ointment can stain clothing. Care should be taken to completely cover the dose measuring applicator with a plastic kitchen wrap.

Dosage Instructions: Dosage instructions should be obtained from your physician. One appropriate dosing schedule for nitroglycerin ointment would begin with two daily 1/2 inch (7.5 mg) doses, one applied on rising in the morning and one applied six hours later. The dose could be doubled, and even doubled again, in patients tolerating this dose but failing to respond to it. The pouch is intended as a unit dose package only and is equivalent to approximately 1 inch as squeezed from the tube. Use entire contents of pouch to obtain full dose and discard immediately after use.

INFORMATION FOR PATIENTS: Your daily regimen of nitroglycerin ointment USP, 2% administration should include a nitrate-free period. Studies have shown 10-12 hours is sufficient. The most common side effect which is encountered is headache. Faintness, flushing and dizziness may occur, especially when suddenly arising from the recumbent (lying horizontal) position. If these latter symptoms do occur, it may warrant discontinuation of therapy, and your physician should be notified. For changes in dosage and frequency of application consult your physician.

TUBE: KEEP TUBE TIGHTLY CLOSED. Pouch: DISCARD IMMEDIATELY AFTER USE.

Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

To report SUSPECTED ADVERSE REACTIONS, contact Encube Ethical Private Limited at 1-833- 285-4151, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Revised: 09/2024

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

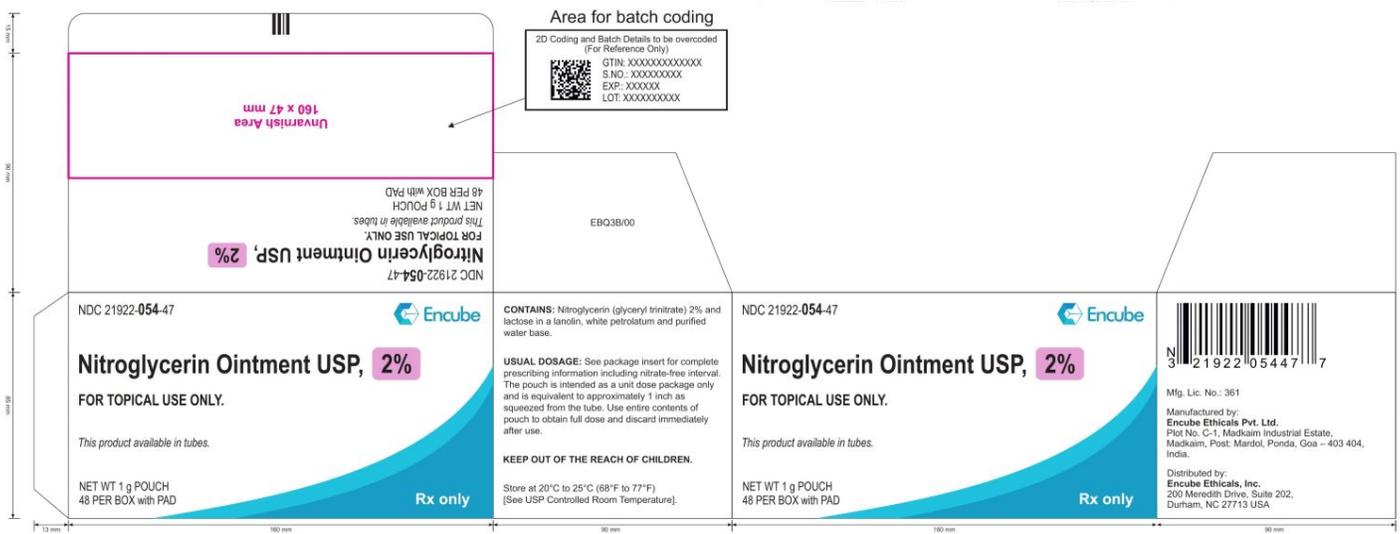
NDC 21922-054-47

Nitroglycerin Ointment USP, 2%

Pouch of 48 x 1 gram

Rx only

Carton Pouch Pack Label



NDC 21922-054-05

Nitroglycerin Ointment USP, 2%

30 gram

Rx only

Carton Label



NITROGLYCERIN

nitroglycerin ointment

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:21922-054
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NITROGLYCERIN (UNII: G59M7S0WS3) (NITROGLYCERIN - UNII:G59M7S0WS3)	NITROGLYCERIN	20 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
LANOLIN (UNII: 7EV65EAW6H)	
PETROLATUM (UNII: 4T6H12BN9U)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:21922-054-05	1 in 1 CARTON	04/16/2025	
1		30 g in 1 TUBE; Type 1: Convenience Kit of Co-Package		
2	NDC:21922-054-47	48 in 1 CARTON	04/16/2025	
2	NDC:21922-054-59	1 g in 1 POUCH; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA218235	04/16/2025	

Labeler - Encube Ethicals, Inc. (116982244)

Establishment

Name	Address	ID/FEI	Business Operations
Encube Ethicals Private Limited		725076298	ANALYSIS(21922-054) , LABEL(21922-054) , MANUFACTURE(21922-054) , PACK(21922-054)

