

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NITROLINGUAL® PUMPSPRAY safely and effectively. See full prescribing information for NITROLINGUAL PUMPSPRAY.

NITROLINGUAL® PUMPSPRAY (nitroglycerin) lingual spray

Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Nitrolingual Pumpspray is a nitrate vasodilator indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease (1).

DOSAGE AND ADMINISTRATION

- At the onset of an attack, administer onto or under the tongue. Repeat every 5 minutes as needed (2.1).
- Do up to three metered sprays within a 15-minute period. If chest pain persists, advise prompt medical attention (2.1).
- May be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack (2.1).

DOSAGE FORMS AND STRENGTHS

Lingual spray, 400 mcg per spray, available in 60 or 200 metered sprays per container (3).

CONTRAINDICATIONS

- Use of phosphodiesterase type 5 (PDE5) inhibitors,

- such as avanafil, sildenafil, tadalafil, or vardenafil, or soluble guanylate cyclase (sGC) stimulator (riociguat). (4.1)
- Severe anemia. (4.2)
- Increased intracranial pressure. (4.3)
- History of hypersensitivity to Nitrolingual Pumpspray or to other nitrates or nitrites or any excipient. (4.4)

WARNINGS AND PRECAUTIONS

Tolerance: Excessive use may lead to tolerance. (5.1)
Hypotension: Severe hypotension may occur. (5.2)

ADVERSE REACTIONS

Most common adverse reactions occurring at a frequency greater than 2% are headache, dizziness and paresthesia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Espero Pharmaceuticals, Inc. at 800-235-6520 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Antihypertensives: Possible additive hypotensive effects. (7.2)
- Ergotamine: increased bioavailability of ergotamine. Avoid concomitant use (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Nitrolingual Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended dosage

Instruct the patient to administer one or two metered sprays (400 mcg of nitroglycerin per spray) at the onset of an attack onto or under the tongue. A spray may be repeated approximately every five minutes as needed. No more than three metered sprays are recommended within a 15-minute period. If the chest pain persists after a total of three sprays, advise prompt medical attention. Nitrolingual Pumpspray may be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack.

2.2 Priming

The pump must be primed prior to the first use. Each metered spray of Nitrolingual Pumpspray delivers 48 mg of solution containing 400 mcg of nitroglycerin after an initial priming of five sprays. It will remain adequately primed for 6 weeks. If the product is not used within 6 weeks it can be adequately re-primed with one spray. If the product is not used within 3 months it can be adequately re-primed with up to five sprays. There are 60 or 200 metered sprays per bottle. The total number of available doses is dependent, however, on the number of sprays per use (1 or 2 sprays), and the frequency of priming.

2.3 Administration

Instruct patients that during administration, the patient should rest, ideally in the sitting position. Hold the container vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. Spray the dose preferably onto or under the tongue by pressing the grooved-button firmly and the mouth closed immediately after each dose.

THE SPRAY SHOULD NOT BE INHALED. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration. Instruct patients to familiarize themselves with the position of the spray orifice, which can be identified by the finger rest on top of the valve, in order to facilitate orientation for administration at night [see Patient Information (17)]. The amount of liquid remaining in the container should be checked periodically. The transparent container can be used for continuous monitoring of the consumption. With the container upright and level, check to be sure the end of the center tube extends below the level of the liquid. Once fluid falls below the level of the center tube, remaining sprays will not deliver intended dose.

3 DOSAGE FORMS AND STRENGTHS

Lingual spray, 400 mcg per spray available in either 60 or 200 metered sprays per container.

4 CONTRAINDICATIONS

4.1 PDE-5-Inhibitors and sGC-Stimulators

Do not use Nitrolingual Pumpspray in patients who are taking PDE-5 inhibitors, such as avanafil, sildenafil, tadalafil, or vardenafil. Concomitant use can cause severe hypotension, syncope, or myocardial ischemia [see Drug Interactions (7.1)].

Do not use Nitrolingual Pumpspray in patients who are taking the soluble guanylate cyclase (sGC) stimulator riociguat. Concomitant use can cause hypotension.

4.2 Severe Anemia

Nitrolingual Pumpspray is contraindicated in patients with severe anemia (large doses of nitroglycerin may cause oxidation of hemoglobin to methemoglobin and could exacerbate anemia).

4.3 Increased Intracranial Pressure

Nitrolingual Pumpspray may precipitate or aggravate increased intracranial pressure and thus should not be used in patients with possible increased intracranial pressure (e.g. cerebral hemorrhage or traumatic brain injury).

4.4 Hypersensitivity

Nitrolingual Pumpspray is contraindicated in patients who are allergic to nitroglycerin, other nitrates or nitrites or any excipient.

4.5 Circulatory Failure and Shock

Nitrolingual Pumpspray is contraindicated in patients with acute circulatory failure or shock.

5 WARNINGS AND PRECAUTIONS

5.1 Tolerance

Excessive use may lead to the development of tolerance. Only the smallest number of doses required for effective relief of the acute angina attack should be used [see Dosage and Administration (2.1)].

5.2 Hypotension

Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin particularly in patients with constrictive pericarditis, aortic or mitral stenosis, patients who may be volume-depleted, or are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris. Symptoms of severe hypotension (nausea, vomiting, weakness, pallor, perspiration and collapse/syncope) may occur even with therapeutic doses.

5.3 Hypertrophic Obstructive Cardiomyopathy

Nitrate therapy may aggravate the angina caused by hypertrophic obstructive cardiomyopathy.

5.4 Headache

Nitroglycerin produces dose-related headaches, especially at the start of nitroglycerin therapy, which may be severe and persistent but usually subside with continued use.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Adverse reactions occurring at a frequency greater than 2% and greater than placebo included: headache, dizziness, and paresthesia.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Nitrolingual Pumpspray and other nitroglycerin drugs. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

Neurologic: weakness, drowsiness

Dermatologic: cutaneous vasodilation, flushing, drug rash, exfoliative dermatitis

Gastrointestinal: nausea, vomiting

Respiratory: transient hypoxemia

Cardiovascular: tachycardia

7 DRUG INTERACTIONS

7.1 PDE-5-Inhibitors and sGC-Stimulators

Nitrolingual Pumpspray is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). PDE5 inhibitors such as avanafil, sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates.

Do not use Nitrolingual Pumpspray in patients who are taking the soluble guanylate cyclase (sGC) stimulator riociguat. Concomitant use can cause hypotension.

The time course and dose dependence of these interactions have not been studied, and use within a few days of one another cannot be recommended. Appropriate supportive care for the severe hypotension 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.

Nitrolingual® Pumpspray

Instructions for Use

Nitrolingual® Pumpspray (nī-trō-ling' gwal)
(nitroglycerin)
lingual spray

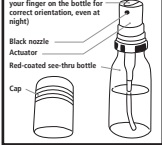
Read this Instructions for Use before you start using Nitrolingual Pumpspray and each time you get your prescription refilled. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Important information:

- Nitrolingual Pumpspray is for use onto or under the tongue.** Do not inhale Nitrolingual Pumpspray.
- A dose of Nitrolingual Pumpspray may be either 1 or 2 sprays. Follow your healthcare provider's instructions about how many sprays you should use for each dose. Doses should be separated by approximately 5 minutes.
- You should not use more than 3 sprays of Nitrolingual Pumpspray within 15 minutes.**
- Get emergency medical help right away if you still have chest pain after using a total of 3 sprays of Nitrolingual Pumpspray.**

Nitrolingual Pumpspray parts:

Figure A



How should I use Nitrolingual Pumpspray?

- It is best to use Nitrolingual Pumpspray while you are resting and in a sitting position.
- Do not shake the Nitrolingual Pumpspray container.**

INFORMATION FOR THE PATIENT

Priming Nitrolingual Pumpspray:

Before you use Nitrolingual Pumpspray for the first time, you must prime it. To prime your Nitrolingual Pumpspray, follow the steps below:

Step 1.

Remove the plastic cap from the container. (See Figure B)

Step 2.

Hold the container upright and facing away from yourself and others. Press down on the top of the grooved button 5 times. (See Figure C)

- Your Nitrolingual Pumpspray is now primed. You are ready to give your first dose.

- If you do not use your Nitrolingual Pumpspray within 6 weeks, you will need to prime it again by pressing down on the top of the grooved button 1 time.

- If you do not use your Nitrolingual Pumpspray within 3 months, you will need to re-prime it by pressing down on the top of the grooved button up to 5 times.

Figure B

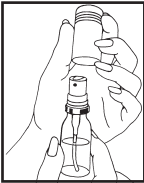
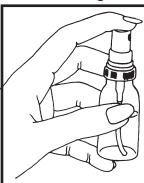


Figure C



7.2 Antihypertensives

Patients receiving antihypertensive drugs, beta-adrenergic blockers, and nitrates should be observed for possible additive hypotensive effects. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly.

Beta-adrenergic blockers blunt the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effects. If beta-blockers are used with nitroglycerin in patients with angina pectoris, additional hypotensive effects may occur.

7.3 Ergotamine

Oral administration of nitroglycerin markedly decreases the first-pass metabolism of dihydroergotamine and subsequently increases its oral bioavailability. Ergotamine is known to precipitate angina pectoris. Therefore, patients receiving sublingual nitroglycerin should avoid ergotamine and related drugs or be monitored for symptoms of ergotism if this is not possible.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C – Animal teratology studies have not been conducted with Nitroglycerin Pumpspray. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested.

A teratogenicity study was conducted in the third mating of F₂ generation female rats administered dietary nitroglycerin for gestation day 6 to day 15 at dose levels used in the 3-generation reproduction study. In offspring of the high-dose nitroglycerin group, increased incidence of diaphragmatic hernias and decreased hyoid bone ossification were seen. The latter finding probably reflects delayed development rather than a potential teratogenic effect, thus indicating no clear evidence of teratogenicity of nitroglycerin. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to pregnant women only if clearly needed.

8.3 Nursing mothers

It is not known whether nitroglycerin is excreted in human milk.

8.4 Pediatric use

Safety and effectiveness of nitroglycerin in pediatric patients have not been established.

8.5 Geriatric use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly (greater than or equal to 65 years) and younger (less than 65 years) patients. In general, dose selection for an elderly patient should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

10.1 Signs and symptoms, methemoglobinemia

Nitrate overdosage may result in: severe hypotension, persistent throbbing headache, vertigo, palpitation, visual disturbance, 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 and anorexia, 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 and coma followed by clonic convulsions, and possibly death due to circulatory collapse. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. 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 could produce harmful concentrations of methemoglobin.

10.2 Treatment of overdosage

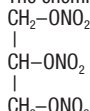
As hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. No specific antagonist to the vasodilator effects of nitroglycerin is known. Keep the patient recumbent in a shock position and comfortably warm. Passive movement of the extremities may aid venous return. Intravenous infusion of normal saline or similar fluid may also be necessary. Administer oxygen and artificial ventilation, if necessary. If methemoglobinemia is present, administration of methylene blue (1% solution), 1–2 mg per kilogram of body weight intravenously, may be required unless the patient is known to have G-6-PD deficiency. If an excessive quantity of Nitrolingual Pumpspray has been recently swallowed gastric lavage may be of use.

As epinephrine is ineffective in reversing the severe hypotensive events associated with overdosage, it is not recommended for resuscitation.

11 DESCRIPTION

Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate (C₃H₅N₃O₉). The compound has a molecular weight of 227.09.

The chemical structure is:



Nitrolingual Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue.

Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil, sodium lactate, lactic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Nitroglycerin forms free radical nitric oxide (NO), which activates guanylate cyclase, resulting in an increase of guanosine 3',5'-monophosphate (cyclic GMP) in smooth muscle and other tissues. This eventually leads to dephosphorylation of myosin light chains, which regulates the contractile state in smooth muscle and results in vasodilatation.

12.2 Pharmacodynamics

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle. Although venous effects predominate, nitroglycerin produces, in a dose-related manner, dilation of both arterial and venous beds. Dilation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood, decreases venous return to the heart, and

reduces left ventricular end-diastolic pressure (preload). Nitroglycerin also produces arteriolar relaxation, thereby reducing peripheral vascular resistance and arterial pressure (after load), and dilates large epicardial coronary arteries; however, the extent to which this latter effect contributes to the relief of exertional angina is unclear.

Therapeutic doses of nitroglycerin may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time. Elevated central venous and pulmonary capillary wedge pressures, and pulmonary and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased and a more favorable supply-demand ratio can be achieved. Patients with elevated left ventricular filling pressure and increased systemic vascular resistance in association with a depressed cardiac index are likely to experience an improvement in cardiac index. In contrast, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced following nitroglycerin administration.

12.3 Pharmacokinetics

A liver reductase enzyme is of primary importance in the metabolism of nitroglycerin to glycerol di- and mononitrate metabolites and ultimately to glycerol and organic nitrate. Known sites of extrahepatic metabolism include red blood cells and vascular walls. In addition to nitroglycerin, 2 major metabolites, 1,2- and 1,3-dinitroglycerin are found in plasma. The mean elimination half-life of both 1,2- and 1,3-dinitroglycerin is about 40 minutes. The 1,2- and 1,3-dinitroglycerin metabolites have been reported to possess some pharmacological activity, whereas the glycerol mononitrate metabolites of nitroglycerin are essentially inactive. Higher plasma concentrations of the dinitro metabolites, with their nearly 8-fold longer elimination half-lives, may contribute significantly to the duration of pharmacologic effect.

In a pharmacokinetic study when a single 0.8 mg dose of Nitrolingual Pumpspray was administered to healthy volunteers (n=24), the mean C_{max} and t_{max} were 1,041.0 pg/ml and 7.5 minutes, respectively. Additionally, in these subjects the mean area under the curve (AUC) was 12,769.5 pg/ml*min. The volume of distribution of nitroglycerin following intravenous administration is 3.3 L/kg.

Drug interactions

Aspirin: Coadministration of nitroglycerin with high dose aspirin (1000 mg) results in increased exposure to nitroglycerin. The vasodilatory and hemodynamic effects of nitroglycerin may be enhanced by concomitant administration of nitroglycerin with high dose aspirin.

Tissue-type plasminogen activator (t-PA): Concomitant administration of t-PA and intravenous nitroglycerin has been shown to reduce plasma levels of t-PA and its thrombolytic effect.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenesis studies with sublingual nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. There was no evidence of mutagenicity in an in vivo dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in in vitro cytogenic tests in rat and dog tissues and for chromosomal aberration in Chinese hamster ovary cells.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for six months prior to mating of the F₀ generation with treatment continuing through successive F₁ and F₂ generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F₀ generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

14 CLINICAL STUDIES

In a randomized, double-blind single-dose, 5-period cross-over study in 51 patients with exertional angina pectoris significant dose-related increases in exercise tolerance, time to onset of angina and ST-segment depression were seen following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pump-spray as compared to placebo. The drug showed a profile of mild to moderate adverse events.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each box of Nitrolingual Pumpspray contains one glass bottle coated with red transparent plastic which assists in containing the glass and medication should the bottle be shattered. Each bottle contains 4.9 g or 14.1 g (Net Contents) of nitroglycerin lingual spray which will deliver 60 or 200 metered sprays containing 400 mcg of nitroglycerin per spray after priming.

Nitrolingual Pumpspray is available as:

- 60-dose (4.9 g) single bottle NDC 70007-300-65
- 200-dose (14.1 g) single bottle NDC 70007-300-20

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Note: Nitrolingual Pumpspray contains 20% alcohol. Do not forcefully open or burn container after use.

Do not spray toward flames.

Rx Only.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use)

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U.S. Patent No. 7,872,049

Manufactured for
Espero Pharmaceuticals, Inc.
Jacksonville, FL 32250
by G. Pohl-Boskamp GmbH & Co. KG,
25551 Hohenlockstedt, Germany.

Giving a dose of Nitrolingual Pumpspray:

Step 3.

Hold your Nitrolingual Pumpspray container upright with your index finger on top of the grooved button.

Step 4.

Open your mouth and bring the Nitrolingual Pumpspray container as close to your mouth as possible.

Step 5.

Press down on the top of the grooved button firmly with your index finger to release the spray onto or under your tongue. (See Figure D). The grooved button can help you make sure the canister is turned to the correct position if you are administering the spray in the dark.

Figure D



Step 6.

Release the grooved button and close your mouth right away. Avoid swallowing right after using Nitrolingual Pumpspray. Do not spit out Nitrolingual Pumpspray or rinse your mouth for 5 to 10 minutes after using Nitrolingual Pumpspray.

Step 7.

If a second dose of Nitrolingual Pumpspray is needed, repeat Steps 3 through 6 above.

Step 8.

Replace the plastic cap.

Check the level of the fluid in your Nitrolingual Pumpspray container regularly.

- Check the container in an upright position.
- The end of the center tube should be covered by the fluid in the Nitrolingual Pumpspray container. If the level of the fluid falls below the end of the center tube, sprays will not provide enough Nitrolingual Pumpspray.
- Replace your Nitrolingual Pumpspray container before the fluid level falls below the end of the center tube.

How should I store Nitrolingual Pumpspray?

- Store Nitrolingual Pumpspray at room temperature 77°F (25°C); excursions permitted to 59–86°F (15–30°C).
- Do not forcefully open or burn the Nitrolingual Pumpspray container after use.
- Do not spray Nitrolingual Pumpspray toward flames.

Keep Nitrolingual Pumpspray and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for
Espero Pharmaceuticals, Inc.
Jacksonville, FL 32250
by G. Pohl-Boskamp GmbH & Co. KG,
25551 Hohenlockstedt, Germany.

Revised: 03/2016

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