NITROLINGUAL- nitroglycerin spray
FIRST HORIZON PHARMACEUTICAL CORPORATION

Nitrolingual Pumpspray

Nitrolingual® Pumpspray
(nitroglycerin lingual spray)
400 mcg per spray, 60 or 200 Metered Sprays

Before using your Nitrolingual® Pumpspray (nitroglycerin lingual spray) 400 mcg per spray, 60 or 200 metered sprays, read carefully the following directions for use.

Nitrolingual® Pumpspray is a metered dose spray which delivers 48 mg of solution containing 400 mcg of nitroglycerin with each spray. Nitroglycerin is absorbed from the tongue and surrounding mucosa producing a prompt therapeutic effect. It is best to use Nitrolingual® Pumpspray in a sitting position.

INFORMATION FOR THE PATIENT

How to Use Nitrolingual Pumpspray

Before using this product for the first time, the pump must be sprayed 5 times into the air (this is known as priming). The pump should be primed every 6 weeks to remain ready for use. If the product has not been used for 6 weeks, a prime of 1 spray is necessary.

1. Remove the plastic cover.
2. **DO NOT SHAKE.**
3. Hold the container upright with forefinger on top of the grooved button.
4. Open the mouth and bring the container as close to it as possible.
5. Press the button firmly with the forefinger to release the spray onto or under the tongue. DO NOT INHALE THE SPRAY.
6. Release button and close mouth. Avoid swallowing immediately after administering the spray. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration.
7. If you require a second administration to obtain relief, repeat steps 4, 5, and 6.
8. Replace the plastic cover.

NOTE: To familiarize yourself with the product and while priming the container, actuate the spray into the air (away from yourself and others). Get the feel of your finger resting on the grooved button so that you can use the spray in the dark. **DO NOT SHAKE** the container before use. You may wish to keep additional pumpspray containers handy in convenient locations.

Dosage

During an anginal attack, one or two sprays should be administered into your mouth, preferably onto or under the tongue. Do not inhale spray. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration. A spray may be repeated approximately every 3-5 minutes as needed. No more than three metered sprays are recommended within a 15-minute period. If chest pain persists, prompt medical attention is recommended. Nitrolingual® Pumpspray may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack.

There are approximately 60 or 200 metered sprays of nitroglycerin per Nitrolingual® Pumpspray bottle. However, the number of times the medication may be used is dependent on the number of sprays per use (1 or 2 sprays), and frequency of repriming. Each metered spray of Nitrolingual® Pumpspray delivers 400 mcg of nitroglycerin after an initial priming of 5 sprays.The container will remain adequately primed for 6 weeks. If the medication is not used within 6 weeks, it can be adequately reprimed with 1 spray. Longer storage periods without use may require up to 5 repriming sprays.

Precaution

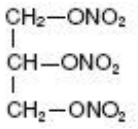
Your physician has determined that this product is likely to help your personal health.
USE THIS PRODUCT AS DIRECTED, BY YOUR PHYSICIAN.
If you have any questions about alternatives, consult with your physician.
Do not share or give your medication to others, particularly those who may appear to be having chest discomfort similar to yours.
Nitrolingual® Pumpspray should be used during an episode of chest pain or may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack.
Nitrolingual® Pumpspray is available in a clear glass bottle with a red plastic coating on the exterior. This plastic coating is designed to contain the glass and medication should the bottle be shattered. The transparent container can be used for continuous monitoring of the consumption. **The end of the pump should be covered by the fluid level**. Once fluid falls below the level of the center tube, sprays will not be adequate and the container should be replaced. As with all other sprays, there is a residual volume of fluid at the bottom of the bottle which cannot be used. Nitrolingual® Pumpspray contains 20% alcohol. Do not forcefully open or burn container. Do not spray toward flames. **Keep in a safe place and out of the reach of children.**

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

Manufactured for FIRST HORIZON PHARMACEUTICAL® CORPORATION, Alpharetta, GA 30005 by G. Pohl-Boskamp GmbH & Co., D-25551 Hohenlockstedt, Germany.

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 ($C_3H_5N_3O_9$). 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.

CLINICAL PHARMACOLOGY:

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on 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 (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load).

The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin and presumably, a more favorable supply-demand ratio is achieved.

While the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.
Nitroglycerin is rapidly metabolized *in vivo*, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolized to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.
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, pulmonary vascular resistance 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. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement

in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced.
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 1,041pg/mL • min and 7.5 minutes, respectively. Additionally, in these subjects the mean area-under-the-curve (AUC) was 12,769 pg/mL • min.
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 pumpspray as compared to placebo.
Additionally the drug was well tolerated as evidenced by a profile of generally mild to moderate adverse events.

INDICATIONS AND USAGE:

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

CONTRAINDICATIONS:

Allergic reactions to organic nitrates are rare. Nitroglycerin is contraindicated in patients who are allergic to it. Nitrolingual® Pumpspray is contraindicated in patients taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors), as their concomitant use can cause severe hypotension. The time course and dose-dependency of this interaction are not known.

WARNINGS:

Amplification of the vasodilatory effects of Nitrolingual® Pumpspray by certain drugs (phosphodiesterase inhibitors) used to treat erectile dysfunction 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 use of any form of nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status.

PRECAUTIONS:

General

Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drug, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g., below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and anti-anginal effects of nitrates has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory.

In industrial workers continuously exposed to nitroglycerin, tolerance clearly occurs. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death

have occurred during temporary withdrawal of nitroglycerin from the workers. In various clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of nitroglycerin is not known.

PRECAUTIONS: (INFORMATION FOR PATIENTS)

Physicians should discuss with patients that Nitrolingual® Pumpspray should not be used with certain drugs taken for erectile dysfunction (phosphodiesterase inhibitors) because of the risk of lowering their blood pressure dangerously.

DRUG INTERACTIONS:

Alcohol may enhance sensitivity to the hypotensive effects of nitrates. Nitroglycerin acts directly on vascular muscle. Therefore, any other agents that depend on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending upon the agent.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and oral controlled-release nitroglycerin were used in combination. Dose adjustments of either class of agents may be necessary.

Concomitant use of nitric oxide donors (like Nitrolingual® Pumpspray) and certain drugs for the treatment of erectile dysfunction (phosphodiesterase inhibitors) can amplify their vasodilatory effects, resulting in severe hypotension. The concomitant use of these drugs is contraindicated (see **CONTRAINDICATIONS**) and alternative therapies should be used to treat acute angina episodes.

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. Nevertheless, 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.

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 F_0 generation with treatment continuing through successive F_1 and F_2 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 F_0 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.

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. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to pregnant women 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 Nitrolingual® Pumpspray is administered to a nursing woman.

PEDIATRIC USE:

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

ADVERSE REACTIONS:

Adverse reactions to oral nitroglycerin dosage forms, particularly headache and hypotension, are generally dose-related. In clinical trials at various doses of nitroglycerin, the following adverse effects have been observed:

Headache, which may be severe and persistent, is the most commonly reported side effect of nitroglycerin with an incidence on the order of about 50% in some studies. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop. Occasionally, an individual may exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) may occur even with therapeutic doses. Drug rash and/or exfoliative dermatitis have been reported in patients receiving nitrate therapy. Nausea and vomiting appear to be uncommon.

Nitrolingual® Pumpspray given to 51 chronic stable angina patients in single doses of 0.4, 0.8 and 1.6 mg as part of a double-blind, 5-period single-dose cross-over study exhibited an adverse event profile that was generally mild to moderate. Adverse events occurring at a frequency greater than 2% included: headache, dizziness, and paresthesia. Less frequently reported events in this trial included (≤2%): dyspnea, pharyngitis, rhinitis, vasodilation, peripheral edema, asthenia, and abdominal pain.

OVERDOSAGE:

Signs and Symptoms:

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.

Methemoglobinemia:

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.

Treatment of Overdosage:

Keep the patient recumbent in a shock position and comfortably warm. Passive movement of the extremities may aid venous return. 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. If an excessive quantity of Nitrolingual® Pumpspray has been recently swallowed gastric lavage may be of use.

WARNING:

Epinephrine is ineffective in reversing the severe hypotensive events associated with overdosage. It and related compounds are contraindicated in this situation.

DOSAGE AND ADMINISTRATION:

At the onset of an attack, one or two metered sprays should be administered onto or under the tongue. No more than three metered sprays are recommended within a 15-minute period. If the chest pain persists, prompt medical attention is recommended. Nitrolingual® Pumpspray may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

Each metered spray of Nitrolingual® Pumpspray delivers 48 mg of solution containing 400 mcg of nitroglycerin after an initial priming of 5 sprays. It will remain adequately primed for 6 weeks.If the product is not used within 6 weeks it can be adequately reprimed with 1 spray. Longer storage periods without use may require up to 5 repriming 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 repriming.

The transparent container can be used for continuous monitoring of the consumption. **The end of the pump should be covered by the fluid level**. Once fluid falls below the level of the center tube, sprays will not be adequate and the container should be replaced. As with all other sprays, there is a residual volume of fluid at the bottom of the bottle which cannot be used.

During application the patient should rest, ideally in the sitting position. The container should be held vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. The dose should preferably be sprayed onto the tongue by pressing the button firmly and the mouth should be 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. Patients should be instructed 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.

HOW SUPPLIED:

Each box of Nitrolingual® Pumpspray, contains one clear glass bottle coated with red transparent plastic which assists in containing the glass and medication should the bottle be shattered. Each unit contains 4.9 g (NDC 59630- 300-65) or 12 g (NDC 59630-300-20) (Net Content) of nitroglycerin lingual spray which will deliver 60 or 200 metered sprays containing 400 mcgs of nitroglycerin per spray after priming.

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.

Manufactured for FIRST HORIZON PHARMACEUTICAL® CORPORATION, Alpharetta, GA 30005 by G. Pohl-Boskamp GmbH & Co., D-25551 Hohenlockstedt, Germany.

NLPS-PI-2
Rev. 10/05

NITROLINGUAL

nitroglycerin spray

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59630-300
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
nitroglycerin (UNII: G59M7S0WS3) (nitroglycerin - UNII:G59M7S0WS3)		400 ug

Inactive Ingredients	
Ingredient Name	**Strength**
medium-chain triglycerides ()	
dehydrated alcohol ()	
medium-chain partial glycerides ()	
peppermint oil ()	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:59630-300-65	60 in 1 BOTTLE, GLASS		
2	NDC:59630-300-20	200 in 1 BOTTLE, GLASS		

Labeler - FIRST HORIZON PHARMACEUTICAL CORPORATION

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