

**PRODUCT MONOGRAPH**

** APO-NITROGLYCERIN**

**Nitroglycerin**

**Sublingual Spray, 0.4 mg per metered dose**

**Apotex Standard**

**Anti-anginal Agent**


**APOTEX INC.  
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Toronto, Ontario  
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**DATE OF REVISION:  
September 21, 2016**

**Control Number: 198217**

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 **APO-NITROGLYCERIN**  
Nitroglycerin Sublingual Spray  
**Apotex Standard**

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Nonmedicinal Ingredients</b>
oral (sublingual)	spray, 0.4 mg per metered dose	dehydrated alcohol, medium chain monoglycerides, medium chain partial triglycerides, and peppermint oil.

**INDICATIONS AND CLINICAL USE**

APO-NITROGLYCERIN (nitroglycerin sublingual spray) is indicated for:

- The management and treatment of acute attacks of angina pectoris.

**CONTRAINDICATIONS**

APO-NITROGLYCERIN (nitroglycerin sublingual spray) is contraindicated in:

- Patients with known hypersensitivity to nitroglycerin or any of the excipients, or with previous idiosyncratic reaction to organic nitrates. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with severe anemia;
- Patients with closed angle glaucoma;
- Patients with increased intracranial pressure;
- Patients with myocardial infarction;
- Patients with acute circulatory failure (cardiogenic shock, severe hypovolemia or severe hypotension);
- Patients with heart failure (aortic or mitral stenosis, constrictive pericarditis or hypertrophic obstructive cardiomyopathy).

Concomitant use of APO-NITROGLYCERIN (nitroglycerin sublingual spray) either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA<sup>®</sup> (sildenafil), CIALIS<sup>®</sup> (tadalafil) and LEVITRA<sup>®</sup> (vardenafil) is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of nitroglycerin which can lead to severe hypotension.

Concomitant use of ADEMPAS (riociguat) with other drugs affecting the nitric oxide-soluble guanylate cyclase- cyclic guanosine monophosphate (NO-sGC-cGMP) pathway is contraindicated, due to the risk of developing potentially life-threatening episodes of hypotension or syncope.

## **WARNINGS AND PRECAUTIONS**

Headaches or symptoms of hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may be due to overdosage. When they occur, the dose or frequency of application of APO-NITROGLYCERIN (nitroglycerin sublingual spray) should be reduced.

In cases where cyanosis should develop during high-dose treatment, work-up must include search for methemoglobinemia.

### **Cardiovascular**

Nitroglycerin is a potent vasodilator and causes a slight decrease in mean blood pressure (approximately 10-15 mmHg) in some patients when used in therapeutic dosages. Caution should be exercised in using the drug in patients who are prone to, or who might be affected by hypotension.

Hypotension and reflex tachycardia or bradycardia may occur post APO-NITROGLYCERIN administration (see ADVERSE REACTIONS). These conditions may lead to fatal cardiac arrhythmias such as ventricular fibrillation or asystole, mainly in patients with acute inferior myocardial infarction particularly with right ventricular involvement.

### **Dependence/Tolerance**

Tolerance to this drug and cross-tolerance to other nitrates or nitrites may occur. Physical dependence has also been described. With the chronic use of nitrates, there have been reports of anginal attacks being more easily provoked as well as reports of rebound in hemodynamic effects, occurring soon after nitrate withdrawal. Sudden discontinuation of treatment should be avoided.

### **Driving a Vehicle or Performing on Hazardous Tasks**

Especially during treatment start, nitroglycerin may induce symptoms related to orthostatic hypotension such as dizziness, which can possibly impact the ability to drive or use machines (See ADVERSE REACTIONS).

### **Special Populations**

#### **Pregnant Women**

Animal reproduction studies have not been conducted with nitroglycerin. It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman. Therefore use APO-NITROGLYCERIN (nitroglycerin sublingual spray) only if the potential benefit justifies the risk to the fetus.

#### **Nursing Women**

It is not known whether nitroglycerin is excreted into breast milk. Safety in breast-feeding women has not been established. Breast-feeding is therefore inadvisable for the duration of treatment. Benefits to the mother must be weighed against the risks to the child.

#### **Pediatrics**

The safety and effectiveness of nitroglycerin in children have not been established.

#### **Geriatrics**

The safety and effectiveness of nitroglycerin in the elderly population have not been established.

### **Monitoring and Laboratory Tests**

The use of nitroglycerin in patients with congestive heart failure requires careful clinical and/or hemodynamic monitoring.

## **ADVERSE REACTIONS**

### **Adverse Drug Reactions Overview**

Adverse reactions to APO-NITROGLYCERIN (nitroglycerin sublingual spray) are generally dose-related. In a clinical trial studying patients with chronic stable angina, the following adverse events were reported during the use of nitroglycerin sublingual spray: headache, dizziness, paresthesia and dyspnea. All adverse events were mild to moderate.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reactions rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The safety of nitroglycerin sublingual spray was assessed in a double-blind, randomized, single-dose, 5-period crossover study involving patients with chronic, stable angina pectoris, who were known to be acutely responsive to sublingual nitroglycerin. The effects of varying doses (0.2 mg, 0.4 mg 0.8 mg and 1.6 mg) were assessed. The following adverse effects have been observed: headache, which may be severe and persistent, is the most commonly reported side effect of nitroglycerin. Occasionally, an individual may exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, retrosternal discomfort, perspiration and collapse) may occur even with therapeutic doses (see Less Common Clinical Trial Adverse Drug Reactions).

Common adverse events considered related to the drug are shown in the table below.

**Table 1 – Common Adverse Drug Reactions to Nitroglycerin Sublingual Spray in Patients with Angina**

System Organ Class Adverse Event	Frequency	
	Nitroglycerin Sublingual Spray 0.4 – 1.6 mg n=51	Placebo n=49
<b>Gastrointestinal disorders</b>		
Abdominal Pain	2 %	0 %
Stomatitis	0 %	2 %
<b>General disorders and Administration Site Conditions</b>		
Asthenia	2 %	0 %
Peripheral Edema	2 %	0 %
<b>Infections and Infestations</b>		
Pharyngitis	4 %	0 %
Rhinitis	2 %	2 %
<b>Nervous System disorders</b>		
Headache	16 %	0 %
Dizziness	6 %	2 %
Paresthesia	4 %	0 %

<b>Respiratory, Thoracic and Mediastinal disorders</b> Dyspnea	4 %	0 %
<b>Vascular disorders</b> Vasodilatation	2 %	0 %

### **Less Common Clinical Trial Adverse Drug Reactions**

#### **Blood and Lymphatic System disorders:**

- Clinically significant methemoglobinemia is rare at conventional doses, but may occur, especially in patients with genetic hemoglobin abnormalities.

#### **Cardiac disorders:**

- Tachycardia

#### **Gastrointestinal disorders:**

- Nausea
- Vomiting

#### **General disorders and administration site conditions:**

- Retrosternal discomfort
- Weakness

#### **Psychiatric disorders:**

- Restlessness

#### **Skin and Subcutaneous Tissue disorders:**

- Exfoliative dermatitis
- Perspiration
- Rash

#### **Vascular disorders:**

- Collapse
- Flushing
- Pallor
- Postural hypotension

### **Post-Market Adverse Drug Reactions**

- allergic reactions: anaphylactic reactions, angioedema (swelling of the face, lips, and/or tongue), oedema of larynx, uvula, and bronchus, skin hives and dermatitis around the mouth area have been reported.
- hypotension, sometimes severe, including orthostatic (postural) hypotension, possibly associated with reflex tachycardia or paradoxical reflex bradycardia. The paradoxical reflex bradycardia may range in severity from simple sinus bradycardia to atrioventricular block, asystole and syncope.

## DRUG INTERACTIONS

### Serious Drug Interactions

**PDE5 Inhibitors:** Concomitant use of APO-NITROGLYCERIN (nitroglycerin sublingual spray) and sildenafil, tadalafil, vardenafil or any other cGMP-specific phosphodiesterase Type 5 (PDE5) inhibitor could result in life-threatening hypotension with syncope or myocardial infarction and death.

### Overview

APO-NITROGLYCERIN should be used with care in combination with other medicinal products with blood-pressure lowering effect including, antihypertensive, diuretics, tricyclic antidepressants, neuroleptics as well as alcohol, as it may enhance sensitivity to the hypotensive effects of nitrates.

### Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the unexpected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 2 – Established or Potential Drug-Drug Interactions**

Proper Name	Ref	Effect	Clinical comment
<b>CGMP-specific Phosphodiesterase Type 5 (PDE5) Inhibitors</b>			
Sildenafil citrate/ Tadalafil/ Vardenafil	CT	Severe Hypotension (with syncope or MI) death	The hypotensive effects of nitrates or nitric oxide donors are potentiated by PDE5 inhibitors. Concomitant use with nitroglycerin sublingual spray could result in life-threatening hypotension with syncope or myocardial infarction and death. Concomitant administration of nitroglycerin sublingual spray with PDE5 inhibitors is absolutely contraindicated (see <b>CONTRAINDICATIONS</b> section). If a patient treated with any PDE5 inhibitor needs a rapidly effective nitrate (e.g. in case of an acute angina pectoris attack), the patient must be hospitalized immediately.
Neuroleptics	C + T	Severe Hypotension, dizziness, syncope, orthostasis or tachycardia	A pharmacokinetic interaction between nitrate derivatives and neuroleptics is possible, whereby NO liberated from nitrate derivatives could down-regulate CYP enzyme expression, decreasing metabolic clearance, thus increasing exposure to neuroleptics, in particular benzamide and second generation neuroleptics. A pharmacodynamic interaction is also possible, as nitrate derivatives are vasodilators and neuroleptics bind to certain receptors leading to a vasodilatory effect. Combined treatment may lead to augmentation of the hypotensive effect of nitrate derivatives.  Caution is advised in case of concomitant use. If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.
Tricyclic antidepressants	C +	Severe Hypotension	A frequent and potentially serious side effect of TCA treatment is orthostatic hypotension. Therefore, a

	T		<p>pharmacodynamic mechanism of a drug interaction is possible, as combined treatment may lead to augmentation of the hypotensive effect of nitrate derivatives.</p> <p>APO-NITROGLYCERIN should be used with care in combination with tricyclic antidepressants as it may enhance sensitivity to the hypotensive effects of nitrates.</p> <p>If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.</p>
Diuretics	T	Severe Hypotension	<p>APO-NITROGLYCERIN should be used with care in combination with diuretics as it may enhance sensitivity to the hypotensive effects of nitrates.</p> <p>If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.</p>
Antihypertensives	T	Severe Hypotension	<p>APO-NITROGLYCERIN should be used with care in combination with antihypertensives as it may enhance sensitivity to the hypotensive effects of nitrates.</p> <p>If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.</p>
Calcium Channel Blockers	T	Severe Hypotension	<p>APO-NITROGLYCERIN should be used with care in combination with calcium channel blockers as it may enhance sensitivity to the hypotensive effects of nitrates.</p> <p>If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.</p>
Prilocaine / Lidocaine	T	formation of methemoglobin (MetHb)	<p>Prilocaine, accentuates the formation of methemoglobin (MetHb) by a mechanism involving metabolism of prilocaine to o-toluidine and subsequent oxidation of hemoglobin to MetHb.</p> <p>Patients treated concomitantly with prilocaine/lidocaine and nitroglycerin may present overt clinical signs of methemoglobinemia. Caution is advised.</p>
$\alpha$ 2-adrenergic agonists like Tizanidine (Zanaflex)	T	Severe Hypotension	<p>APO-NITROGLYCERIN should be used with care in combination with <math>\alpha</math>2-adrenergic agonists as it may enhance sensitivity to the hypotensive effects of nitrates.</p> <p>If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.</p>
Guanylate cyclase stimulators	T	Severe Hypotension	<p>Concomitant use of APO-NITROGLYCERIN with soluble guanylate cyclase stimulators such as ADEMPAS (riociguat) is contraindicated (see CONTRAINDICATIONS).</p>

C = Case Study; CT = Clinical trial, T = Theoretical

*Interactions with other drugs have not been established.*

### **Drug-Food Interactions**

Interaction with alcohol has been reported, namely an enhanced hypotensive effect. Avoid concomitant use of nitroglycerin and alcohol.



### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

### **Drug-Lifestyle Interactions**

Interactions with lifestyle have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- The spray should not be inhaled.
- The spray should be kept away from eyes.
- This spray formulation is intended to be applied and absorbed on or under the tongue.

### **Recommended Dose and Dosage Adjustment**

Upon initiating therapy with APO-NITROGLYCERIN (nitroglycerin sublingual spray), especially when changing from another form of nitroglycerin administration, patients should be followed closely by their physicians in order to determine the minimal effective dose for each patient.

Each metered dose contains 0.4 mg nitroglycerin. With the onset of an acute attack of angina pectoris, 1 or 2 metered doses (0.4 or 0.8 mg of nitroglycerin), as determined by experience, may be administered onto or under the tongue, without inhaling. The optimal dose may be repeated twice at 5-10 minute intervals. Dosage must be individualized and should be sufficient to provide relief without producing untoward reactions.

### **Administration**

During administration the patient should be at rest, ideally in the sitting position, and the container kept vertical with the nozzle head up. The opening in the nozzle head should be kept as close to the mouth as possible. Patients should familiarize themselves with the position of the spray orifice, identified by the finger rest on top of the valve, in order to facilitate administration at night.

## **OVERDOSAGE**

*Symptoms:* Symptoms of overdose are primarily related to vasodilation, that could lead to severe hypotension and possible reflex tachycardia. These include cutaneous flushing, headache, nausea, dizziness, and hypotension. Methemoglobinemia has been reported in association with high dose of glyceryl nitrate therapy. This may possibly be clinically significant, especially in the context of hemoglobin reductase deficiencies or in congenital methemoglobin variants.

*Treatment:* No specific antidote is available. Treatment should be symptomatic and supportive.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The principal action of nitroglycerin is that of all nitrates, namely, relaxation of vascular smooth muscle. Nitrates act primarily by reducing myocardial oxygen demand rather than increasing its oxygen supply. This effect is thought to be brought about predominantly by peripheral action. Although venous effects predominate, nitroglycerin produces, in a dose-related manner, dilation of both arterial and venous beds. Dilation of the post capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load). Left ventricular end-diastolic pressure and volume are decreased, resulting in reduction of ventricular size and wall tension. The reduction in ventricular wall tension results in a net decrease in myocardial oxygen consumption and a favorable net balance between myocardial oxygen supply and demand.

### **Pharmacodynamics**

No data available.

### **Pharmacokinetics**

#### **Absorption**

In a pharmacokinetic study when a single 0.8 mg dose of nitroglycerin sublingual spray was administered to 24 healthy volunteers, the mean  $C_{max}$  and  $T_{max}$  were 1.04 ng/mL and 7.5 min, respectively. Additionally, in these subjects the mean AUC was 12.8 ng.min/mL.

#### **Distribution**

Nitroglycerin and its major metabolites are approximately 60% protein bound.

#### **Metabolism**

Nitroglycerin is rapidly metabolized in the liver by hepatic enzymes. The two active major metabolites are the hydrolysis products, 1,3- and 1,2-dinitro-glycerols. There are also two inactive minor metabolites, the 1- and 2- mononitroglycerols, which are considered biologically inactive.

#### **Excretion**

Nitroglycerin is excreted by the renal route primarily as the two dinitro-metabolites, which have an excretion half-life of approximately 3-4 hours.

## **STORAGE AND STABILITY**

APO-NITROGLYCERIN (nitroglycerin sublingual spray) should be stored at room temperature: 15°C - 30°C (59°F -86°F).

## **SPECIAL HANDLING INSTRUCTIONS**

Do not place APO-NITROGLYCERIN (nitroglycerin sublingual spray) in hot water or near radiators, stoves or other sources of heat. Do not open forcefully or incinerate container or expose to temperature over 40°C (104°F).

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Composition**

APO-NITROGLYCERIN (nitroglycerin sublingual spray) is a clear, slightly yellow oily solution.

Each metered dose of APO-NITROGLYCERIN contains 0.4 mg nitroglycerin.

Non-medicinal ingredients: dehydrated alcohol, medium chain monoglycerides, medium chain partial triglycerides, and peppermint oil.

### **Availability**

APO-NITROGLYCERIN (nitroglycerin sublingual spray) is supplied in orange-pink plastic coated glass vials with white spray pumps and white actuators delivering 200 metered doses of 0.4 mg nitroglycerin, in an aromatized oily solution.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

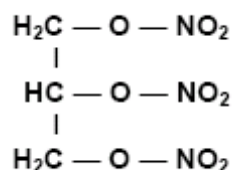
Proper name: Nitroglycerin

Chemical name: 1,2,3-Propanetriol trinitrate

Molecular formula:  $C_3H_5N_3O_9$

Molecular weight: 227.09 g/mol

Structural formula:



Physicochemical properties:

Description: A clear, colorless oily liquid.

Solubility: It is soluble 1 in 800 of water, 1 in 4 of ethanol, 1 in 120 of carbon disulphide, and 1 in 6 of almond oil; miscible with acetone, chloroform, ether and glacial acetic acid and sparingly soluble in glycerine and light petroleum.

Chirality: The molecule does not present chiral centres.

Acidity: NMT 0.002% expressed as  $H_2SO_4$

Alkalinity: NMT 0.002% expressed as  $Na_2CO_3$

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioequivalence study, conducted under fasting conditions was performed on seventy-nine (79) healthy male and female volunteers. The rate and extent of absorption of nitroglycerin was measured and compared following two 0.4 mg metered doses of APO-NITROGLYCERIN (nitroglycerin) sublingual spray or NITROLINGUAL<sup>®</sup> PUMPSPRAY (nitroglycerin) sublingual spray. The results from measured data are summarized in the following table:

<b>Summary Table of the Comparative Bioavailability Data</b> Nitroglycerin (A single 0.8 mg dose: 2 x 0.4 mg) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	APO– NITROGLYCERIN (Apotex Inc.)	NITROLINGUAL <sup>®</sup> PUMPSPRAY <sup>†</sup> (sanofi-aventis Canada Inc.)	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC <sub>(0-t)</sub> (pg•min/mL)	5605.3 8180.3 (84.4)	5415.7 7772.1 (81.0)	103.42	90.13 – 118.64
AUC <sub>RefTmax</sub> (pg•min/mL)	1626.2 2900.6 (96.5)	1655.3 2412.2 (82.3)	97.99	81.74 – 117.45
AUC <sub>(0-∞)</sub> (pg•min/mL)	5812.6 8474.2 (84.4)	5598.5 8056.7 (81.1)	103.28	89.20 – 119.58
C <sub>max</sub> (pg/mL)	723.3 1070.5 (81.5)	671.3 983.1 (78.6)	107.54	92.68 – 124.78
t <sub>max</sub> <sup>§</sup> (min)	7.1 (32.54)	7.2 (29.94)		
t <sub>½</sub> <sup>§</sup> (min)	3.81 (30.76)	3.77 (32.18)		
<sup>§</sup> Expressed as arithmetic means (CV%) only. <sup>†</sup> NITROLINGUAL <sup>®</sup> PUMPSPRAY (sanofi-aventis Canada Inc.) was purchased in Canada.				

## **DETAILED PHARMACOLOGY**

In both animals and humans, the primary pharmacological effect of nitroglycerin is its smooth muscle relaxant effect. Its therapeutic effectiveness depends on its actions on vascular smooth muscle. The effect on venous system is stronger than that on arterial circulation.

In coronary occluded dogs, nitroglycerin given intravenously (200-300 µg/min. for 8 hours) decreased S-T segment elevations accompanying myocardial ischemia. Coronary blood flow in the sub-endocardium of ischemic areas increased by 45% but prolonged i.v. administration of nitroglycerin did not decrease infarct size.

## **TOXICOLOGY**

### **Acute Toxicity**

The intravenous lethal dose of nitroglycerin was found to be 83.5 mg/kg in the guinea pig, while the intravenous LD<sub>50</sub> was 43 mg/kg in the rabbit. The lethal dose following intramuscular administration to rabbits, guinea pigs, rats and cats varied between 150 and 500 mg/kg. Orally, doses of 80 to 100 mg/kg were found to be lethal in the guinea pig and rat.

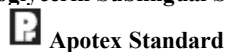
The signs and symptoms of nitroglycerin toxicity in these animals were usually circulatory collapse, convulsions and methemoglobinemia.

### **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.

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**PART III: CONSUMER INFORMATION****APO-NITROGLYCERIN  
(Nitroglycerin Sublingual Spray)**

This leaflet is part III of a three-part “Product Monograph” published for APO-NITROGLYCERIN (nitroglycerin sublingual spray) and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-NITROGLYCERIN. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

APO-NITROGLYCERIN (nitroglycerin sublingual spray) is used in adults for the treatment of acute attacks of angina pectoris – chest pain which occurs when the heart muscle does not get as much blood (hence as much oxygen) as it needs.

**What it does:**

APO-NITROGLYCERIN belongs to a group of drugs, which reduce the oxygen demand of the heart.

**When it should not be used:**

Do not use APO-NITROGLYCERIN if you:

- Are allergic to nitroglycerin or any of the non-medicinal ingredients in the formulation or to any other medication of the same group of medicines called nitrates
- Have an eye disease called closed angle glaucoma
- Are having a heart attack (myocardial infarction)
- Have low iron levels in your blood or low red blood cell count (severe anemia)
- Have low blood pressure (hypotension) or a diagnosis of heart failure
- Have a condition caused by an increase in normal brain pressure (increased intracranial pressure)
- Are taking CIALIS<sup>®</sup> (tadalafil), LEVITRA<sup>®</sup> (vardenafil), VIAGRA<sup>®</sup> (sildenafil citrate) or any similar medication for impotence (erectile dysfunction).
- Are taking ADEMPAS<sup>®</sup> (riociguat) for high blood pressure in your lungs (chronic thromboembolic pulmonary hypertension (CTEPH) or pulmonary arterial hypertension (PAH))

**What the medicinal ingredient is:**

Nitroglycerin

**What the nonmedicinal ingredients are:**

Dehydrated alcohol, medium chain monoglycerides, medium chain partial triglycerides, and peppermint oil

**What dosage forms it comes in:**

APO-NITROGLYCERIN is supplied in spray bottles delivering 200 metered doses of 0.4 mg nitroglycerin per spray emission.

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

**Headaches or symptoms of low blood pressure, such as weakness or dizziness, especially when you go from lying/sitting to standing up, may be due to taking too much APO-NITROGLYCERIN. You may also notice a bluish discolouration to your skin, especially around your lips and mouth. If these symptoms occur, talk to your doctor, nurse, or pharmacist as your dose of APO-NITROGLYCERIN may need to be reduced.**

BEFORE you use APO-NITROGLYCERIN talk to your doctor, nurse or pharmacist if you:

- are currently taking any other medications, whether on prescription or otherwise (see Interactions with this Medication section below).
- have headaches, weakness or dizziness especially when getting up suddenly from a laying down or sitting position, or symptoms of low blood pressure (hypotension).
- are breast feeding, pregnant, or think you might be pregnant.
- had a heart attack.
- Are less than 18 years old

Tolerance to APO-NITROGLYCERIN 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 APO-NITROGLYCERIN. Talk to your doctor if you wish to discontinue using APO-NITROGLYCERIN.

**Driving and using machines:** Temporary dizziness may be associated with the use of APO-NITROGLYCERIN. Make sure you know how you react to this medicine before you drive, operate machinery, or do anything requiring you to be alert.

Avoid alcoholic beverages until you have discussed their use with your doctor.

The spray should be kept away from the eyes and it should not be inhaled.

**INTERACTIONS WITH THIS MEDICATION**

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.



## IMPORTANT: PLEASE READ

### Serious Drug Interactions

**If you are currently taking medication for the treatment of impotence (erectile dysfunction) such as CIALIS<sup>®</sup> (tadalafil), LEVITRA<sup>®</sup> (vardenafil), VIAGRA<sup>®</sup> (sildenafil citrate) or any other similar medication (PDE5 inhibitors), the use of APO-NITROGLYCERIN (nitroglycerin sublingual spray) may lead to extreme low blood pressure resulting in fainting, heart attack and death.**

If you are being treated with any of these drugs and need **APO-NITROGLYCERIN** (e.g. in case of chest pain caused by an acute attack of angina pectoris) please seek emergency medical assistance immediately.

The following may interact with APO-NITROGLYCERIN:

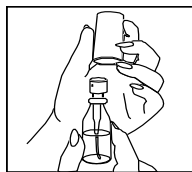
- Medications used to treat hypertension (high blood pressure) such as:
  - Diuretics (“water pills”)
  - Calcium Channel Blockers [medications used to treat conditions such as high blood pressure, angina (chest pain), and other heart conditions (e.g. diltiazem, nifedipine, verapamil)]
- Tricyclic antidepressants (e.g.: imipramine, amitriptyline, desipramine, nortriptyline)
- Antipsychotics (medications used to treat schizophrenia or bipolar depression)
- Medications used to relieve muscle spasms including tizanidine (e.g. Zanaflex)
- Alcoholic beverages (when combined with APO-NITROGLYCERIN it may cause your blood pressure to drop too low)
- Topical anesthetics prilocaine/lidocaine (e.g. EMLA<sup>®</sup>)
- Medication used to treat pulmonary hypertension such as riociguat (e.g. Adempas)

### PROPER USE OF THIS MEDICATION

Ideally, you should sit and rest while taking this medication.

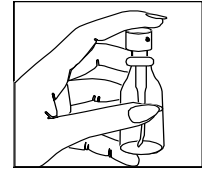
1. Holding container in upright position, remove the plastic cover.

**DO NOT SHAKE.**



2. The container must be primed prior to the first use. To prime, point away from face, press the button firmly with the forefinger to release one spray. Repeat this 3 times. Now your container is primed and ready for use.

Repriming is only necessary when the container has not been used for more than 14 days. To reprime, release 1 spray as directed previously. There is no need to reprime the container between more frequent usage.



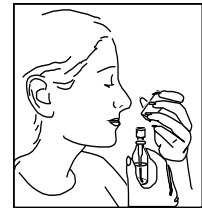
If the container has been maintained below freezing (0°C), warm the container in your hand for two minutes and prime 4 times prior to use

3. Hold the container upright with forefinger on top of the grooved button. There is no need to shake the container.
4. Open your 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.  
KEEP THE SPRAY AWAY FROM EYES.**

6. Release button and close mouth.
7. If you require a second dose, repeat steps 4, 5 and 6.
8. Replace the plastic cover.



When using this product for the first time, familiarize yourself with how to use it by testing the spray into the air (away from yourself and others). Get the feel of the finger resting on the groove button so that you can use the spray in the dark.

#### Usual adult dose:

APO-NITROGLYCERIN (nitroglycerin sublingual spray) should be taken as prescribed by your doctor.

During an anginal attack, one or two doses should be sprayed onto or under the tongue, **without inhaling**. Your doctor can help you to discover the exact dose which will be best for you. Administer at rest, ideally in the sitting position. A dose may be repeated twice at 5-10 minute intervals. If the pain persists, seek emergency medical assistance.

## IMPORTANT: PLEASE READ

**MAKE SURE THAT YOU HAVE A SPARE PUMPSPRAY READILY AVAILABLE (TO PREVENT RUNNING OUT WHEN NEEDED).**

**Overdose:**

Symptoms of overdosage may include: flushing, headache, nausea, dizziness, and hypotension.

If you think you have taken too much APO-NITROGLYCERIN Spray, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including APO-NITROGLYCERIN (nitroglycerin sublingual spray), may cause side effects. After you have started taking APO-NITROGLYCERIN, it is important that you tell your doctor at once about any unexplained symptom you might experience.

Side effects may include:

- Headache
- Sore throat and/or mouth, runny nose
- Restlessness

**If any of these affects you severely, tell your doctor, nurse or pharmacist.**

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Allergic reaction involving skin rash or swelling of the face, lips and/or tongue accompanied by difficulty breathing				√
Common	Severe, persistent headache		√	
	Dizziness		√	
	Weakness		√	
	Abdominal pain		√	
	Swelling of the ankles		√	
	Tingling or pins and needles of a limb		√	
	Shortness of breath		√	
Uncommon	Nausea		√	
	Sweating	√		
	Rash	√		
	Flushing		√	
	Chest pain		√	
	Racing heart rate		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
and/or palpitations (irregular heartbeat)			
Pallor		√	
Vomiting			√
Low blood pressure (hypotension). This can be severe, leading to slow or fast heartbeat, fainting or dizziness when you change from lying/sitting to standing up.			√
Fainting			√

*This is not a complete list of side effects. For any unexpected effects while taking APO-NITROGLYCERIN, contact your doctor, nurse or pharmacist.*

### HOW TO STORE IT

Contains alcohol. Do not open container forcefully or burn after use. Do not spray toward flames. Do not place APO-NITROGLYCERIN (nitroglycerin sublingual spray) in hot water or near radiators, stoves or other sources of heat. Do not expose to temperature over 40°C (104°F). Store at room temperature 15°C -30°C (59°F-86°F).

**Keep in a safe place and out of the reach and sight of children.**

**Reporting Side Effects**  
 You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report:**

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
 Health Canada, Postal Locator 0701E  
 Ottawa, ON  
 K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

**IMPORTANT: PLEASE READ**

*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.*

**MORE INFORMATION**

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service, at:

1-800-667-4708

This leaflet can also be found at:  
<http://www.apotex.ca/products>.

Manufactured by:	Manufactured for:
Groupe Parima	Apotex Inc.
Montreal, Quebec	Toronto, Ontario

Last revised: September 21, 2016

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