PRODUCT MONOGRAPH

MYLAN-NITRO SUBLINGUAL SPRAY

Nitroglycerin Sublingual Spray

0.4 mg per metered dose

Anti-Anginal Agent

Mylan Pharmaceuticals ULC
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Date of Revision: September 8, 2017

Submission Control No.: 208308

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0.4 mg per metered dose

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral (sublingual)	spray, 0.4 mg per metered dose	ethanol, peppermint oil, propellant HFA 134a (1,1,1,2-tetrafluroethane)

INDICATIONS AND CLINICAL USE

MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) is indicated for:

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

CONTRAINDICATIONS

MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) 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 MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) either regularly and/or intermittently, with phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil and vardenafil is absolutely contraindicated, because PDE5 inhibitors amplify the vasodilatory effects of MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) which can lead

to severe hypotension.

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

WARNINGS AND PRECAUTIONS

General

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 MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) 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 MYLAN-NITRO SUBLINGUAL SPRAY 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 MYLAN-NITRO 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 nitroglycerin 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 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 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 Spray in Patients with Angina

System Organ Class Adverse Event	**Frequency** Nitroglycerin Spray 0.4 - 1.6 mg n=51	Placebo n=49
Gastrointestinal disorders		
Abdominal Pain	2 %	0 %
Stomatitis	0 %	2 %
General disorders and Administration Site Conditions		
Asthenia	2 %	0 %
Peripheral Edema	2 %	0 %
Infections and Infestations		
Pharyngitis	4 %	0 %
Rhinitis	2 %	2 %
Nervous System disorders		
Headache	16 %	0 %
Dizziness	6 %	2 %
Paresthesia	4 %	0 %
Respiratory, Thoracic and Mediastinal disorders		
Dyspnea	4 %	0 %
Vascular disorders		
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 MYLAN-NITRO 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

MYLAN-NITRO SUBLINGUAL SPRAY should be used with care in combination with other medicinal products with blood-pressure lowering effect including antihypertensive, diuretics, tricyclic antidepressants, neuroleptics, alcohol, sapropterin, 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
cGMP-specific Phosphodiesterase Type 5 (PDE5) Inhibitors: 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 MYLAN-NITRO SUBLINGUAL SPRAY could result in life-threatening hypotension with syncope or myocardial infarction and death. Concomitant administration of MYLAN-NITRO SUBLINGUAL SPRAY with PDE5 inhibitors is absolutely contraindicated (see **CONTRAINDICATIONS** 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+T	Severe Hypotension	A frequent and potentially serious side effect of TCA treatment is orthostatic hypotension. Therefore, a pharmacodynamic mechanism of a drug interaction is possible, as combined treatment may lead to augmentation of the hypotensive effect of nitrate derivatives. MYLAN-NITRO SUBLINGUAL SPRAY should be used with care in combination with tricyclic antidepressants as it may enhance sensitivity to the hypotensive effects of nitrates. If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.
Diuretics	T	Severe Hypotension	MYLAN-NITRO SUBLINGUAL SPRAY should be used with care in combination with diuretics as it may enhance sensitivity to the hypotensive effects of nitrates. If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.
Antihypertensives	T	Severe Hypotension	MYLAN-NITRO SUBLINGUAL SPRAY should be used with care in combination with antihypertensives as it may enhance sensitivity to the hypotensive effects of nitrates.

Proper Name	Ref	Effect	Clinical comment
			If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.
Calcium Channel Blockers	T	Severe Hypotension	MYLAN-NITRO SUBLINGUAL SPRAY should be used with care in combination with calcium channel blockers as it may enhance sensitivity to the hypotensive effects of nitrates. If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.
Prilocaine / Lidocaine	T	Formation of methemoglobin (MetHb)	Prilocaine, accentuates the formation of methemoglobin (MetHb) by a mechanism involving metabolism of prilocaine to o-toluidine and subsequent oxidation of hemoglobin to MetHb. Patients treated concomitantly with prilocaine/lidocaine and nitroglycerin may present overt clinical signs of methemoglobinemia. Caution is advised.
α2-adrenergic agonists like Tizanidine	T	Severe Hypotension	MYLAN-NITRO SUBLINGUAL SPRAY should be used with care in combination with α2-adrenergic agonists as it may enhance sensitivity to the hypotensive effects of nitrates. If concomitant administration cannot be avoided, dose adjustment and safety monitoring are required.
Guanylate cyclase stimulators	T	Severe Hypotension	Concomitant use of MYLAN-NITRO SUBLINGUAL SPRAY with soluble guanylate cyclase stimulators such as riociguat is contraindicated (see CONTRAINDICATIONS).
Dihydroergotamine	T	Hypertensive effect	Concomitant use of MYLAN-NITRO SUBLINGUAL SPRAY with dihydroergotamine may increase the DHE level and consequently enhance its hypertensive effect.

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 MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin), 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 overdosage are primarily related to vasodilation, which 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 Immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The principal action of MYLAN-NITRO SUBLINGUAL SPRAY (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 (preload). 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 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

MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) should be stored at room temperature: 15°C to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Do not place MYLAN-NITRO 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability

MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) is supplied in aerosol bottles delivering 200 metered doses of 0.4 mg of nitroglycerin each.

Composition

Each MYLAN-NITRO SUBLINGUAL SPRAY contains 0.4 mg nitroglycerin per metered dose and the following non-medicinal ingredients: ethanol, peppermint oil, propellant HFA 134a (1,1,1,2-tetrafluroethane).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

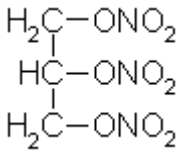
Proper name: Nitroglycerin

Chemical name: 1,2,3-propanetriol, trinitrate, glyceryl trinitrate

Molecular formula: $C_3H_5N_3O_9$

Molecular mass: 227.09 g/mol

Structural formula:



Physicochemical properties: A colorless, slightly volatile odorless oily liquid, with a sweet burning taste. It is soluble in alcohol, acetone, chloroform, ether and glacial acetic acid and sparingly soluble in glycerol and liquid petrolatum.

CLINICAL TRIALS

Pharmacodynamics:

A double blind randomized three-way, crossover study was conducted in 16 subjects with stable angina to assess the anti-anginal efficacy of MYLAN-NITRO SUBLINGUAL SPRAY 0.4 mg per metered dose and compare it with the reference brand Nitrolingual® Spray (nitroglycerin) 0.4 mg per metered dose and placebo.

A summary of the results is presented in the following table:

Time to onset of angina and time to moderate angina during exercise tolerance test following sublingual administration of nitroglycerin spray 0.4 mg or placebo.

Arithmetic Mean (CV%) [Least-Squares Means]				
Parameter	**Test***	**Reference†**	**Placebo Control**	**90% Confidence Interval Mean Ratios (Test/Reference)**
Time to onset of angina (seconds)	264.1 (36.5%) [261.2]	263.0 (34.9%) [261.5]	187.8 (37.3%) [187.1]	88.5 – 111.3 %
Time to moderate angina (seconds)	313.4 (31.5%) [308.4]	307.4 (29.1%) [307.3]	224.4 (28.7%) [225.7]	91.8 – 108.9 %

* MYLAN-NITRO SUBLINGUAL SPRAY 0.4 mg per metered dose
† Nitrolingual® Spray (nitroglycerin) 0.4 mg per metered dose

Pharmacokinetics:

In one study of healthy males (n=13), nitroglycerin was shown to have an apparent volume of distribution of approximately 250 litres. No statistically significant differences were demonstrated between the mean values of maximum plasma concentration (C_{max}) and time to achieve C_{max} (T_{max}) with equal doses (0.8 mg) of nitroglycerin spray and sublingual nitroglycerin tablets.

C_{max} after 0.8 mg of nitroglycerin by spray administration occurred on average within 5 minutes and the apparent plasma elimination half-life was approximately 5 minutes.

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_{50} 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

MYLAN-NITRO SUBLINGUAL SPRAY

Nitroglycerin Sublingual Spray

0.4 mg per metered dose

This leaflet is part III of a three-part "Product Monograph" published for MYLAN-NITRO SUBLINGUAL SPRAY and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about for MYLAN-NITRO SUBLINGUAL SPRAY. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MYLAN-NITRO 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:
MYLAN-NITRO SUBLINGUAL SPRAY belongs to a group of drugs, which reduce the oxygen demand of the heart.

When it should not be used:
Do not use MYLAN-NITRO SUBLINGUAL SPRAY 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 tadalafil, vardenafil, sildenafil citrate or any similar medication for impotence (erectile dysfunction).
- Are taking 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:
Ethanol, peppermint oil, propellant HFA 134a (1,1,1,2-tetrafluroethane).

What dosage forms it comes in:
MYLAN-NITRO SUBLINGUAL SPRAY (nitroglycerin) is supplied in aerosol bottles delivering 200 metered doses of 0.4 mg of nitroglycerin each.

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 MYLAN-NITRO SUBLINGUAL SPRAY.
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 pharmacists as your dose of MYLAN-NITRO SUBLINGUAL SPRAY may need to be reduced.

BEFORE you use MYLAN-NITRO SUBLINGUAL SPRAY 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 MYLAN-NITRO SUBLINGUAL SPRAY 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 MYLAN-NITRO SUBLINGUAL SPRAY. Talk to your doctor if you wish to discontinue using MYLAN-NITRO SUBLINGUAL SPRAY.

Driving and using machines: Temporary dizziness may be associated with the use of MYLAN-NITRO SUBLINGUAL SPRAY. 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.

Serious Drug Interactions

If you are currently taking medication for the treatment of impotence (erectile dysfunction) such as tadalafil, vardenafil, sildenafil citrate or any other similar medication (PDE5 inhibitors), the use of MYLAN-NITRO SUBLINGUAL SPRAY may lead to extreme low blood pressure resulting in fainting, heart attack and death.

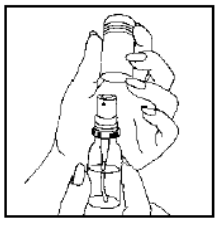
If you are being treated with any of these drugs and need MYLAN-NITRO SUBLINGUAL SPRAY (e.g. in case of chest pain caused by an acute attack of angina pectoris) please seek emergency medical assistance immediately.

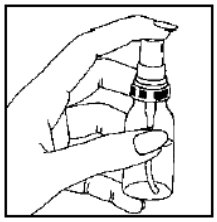
The following may interact with MYLAN-NITRO SUBLINGUAL SPRAY:

- 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
- Alcoholic beverages (when combined with MYLAN-NITRO SUBLINGUAL SPRAY it may cause your blood pressure to drop too low)
- Topical aesthetics prilocaine/lidocaine
- Medication used to treat pulmonary hypertension such as riociguat
- Sapropterin (a medication used to treat a disease called hyperphenylalaninemia)
- Dihydroergotamine (a medication used to treat migraine)

PROPER USE OF THIS MEDICATION

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



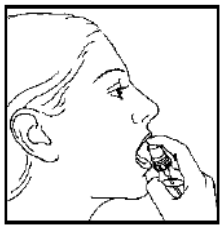


1. Holding container in upright position, remove the plastic cover.

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.



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:
MYLAN-NITRO 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.

MAKE SURE THAT YOU HAVE A SPARE MYLAN-NITRO SUBLINGUAL SPRAY 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 MYLAN-NITRO SUBLINGUAL SPRAY contact your doctor, nurse, pharmacist, 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 MYLAN-NITRO SUBLINGUAL SPRAY, may cause side effects. After you have started taking MYLAN-NITRO SUBLINGUAL SPRAY, 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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate emergency medical attention
		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 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 MYLAN-NITRO SUBLINGUAL SPRAY, 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 MYLAN-NITRO SUBLINGUAL SPRAY in hot water or near radiators, stoves or other sources of heat. Do not expose to temperature over 40°C.

Store at room temperature (15°C to 30ºC).

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

Reporting Side Effects

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

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

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

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-844-596-9526.

This leaflet was prepared by Mylan Pharmaceuticals ULC
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Revised On: September 8, 2017

Mylan

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