

# PRODUCT INFORMATION

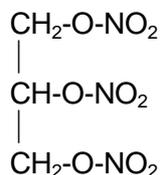
## NITROLINGUAL<sup>®</sup> Pumpspray

### NAME OF THE MEDICINE

#### Non-proprietary Name

Glyceryl trinitrate

#### Chemical Structure



#### CAS Number

55-63-0

### DESCRIPTION

Glyceryl trinitrate, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for glyceryl trinitrate is 1,2,3-propanetriol trinitrate (C<sub>3</sub>H<sub>5</sub>N<sub>3</sub>O<sub>9</sub>) and the compound has a molecular weight of 227.09.

Nitrolingual Pumpspray is a metered dose spray containing glyceryl trinitrate, fractionated coconut oil, glyceryl caprylate/caprates, ethanol and peppermint oil.

Each metered dose of Nitrolingual Pumpspray delivers 400µg of glyceryl trinitrate per spray emission. This product delivers glyceryl trinitrate in the form of spray droplets beneath the tongue.

### PHARMACOLOGY

#### Pharmacodynamics

The principal pharmacological action of glyceryl trinitrate 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 (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload).

The smaller ventricular radius and reduced systolic wall tension lower the myocardial energy and O<sub>2</sub> requirements. The reduction in cardiac filling pressures promotes perfusion of subendocardial wall layers threatened by ischemia.

On a molecular level, nitrates most likely act via formation of nitric oxide (NO) and cyclic guanosyl monophosphate (cGMP), which is thought to mediate relaxation.

Therapeutic doses of glyceryl trinitrate 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 glyceryl trinitrate 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.

### Pharmacokinetics

When administered sublingually, glyceryl trinitrate is rapidly absorbed from the mucosa of the mouth and reaches the vascular system, by-passing the liver. The systemic availability is subject to strong individual variations and is on average approximately 39%.

Glyceryl trinitrate is metabolized in the liver as well as in many other cells, including the erythrocytes, with cleavage of one or more nitrate groups. A liver reductase enzyme has primary importance in the formation of the 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.

After sublingual administration, a wide range of intra-individual and inter-individual variations are observed for the plasma concentration. In a study involving 21 healthy male subjects, a sublingual double dose totalling 800 micrograms resulted in the following pharmacokinetic parameter values: C<sub>max</sub> was 1.0 ng/mL, t<sub>max</sub> was 7.5 minutes and the plasma half-life was 5.5 minutes.

Plasma protein binding is approximately 60%.

Glyceryl trinitrate and its metabolites are principally renally eliminated and less than 1% is excreted unchanged.

## **INDICATIONS**

Treatment of acute angina pectoris.

As well as relieving the pain of an acute attack, Nitrolingual Pumpspray may be used prophylactically five to ten minutes prior to engaging in activities which may precipitate an acute attack.

## **CONTRAINDICATIONS**

Nitrolingual Pumpspray should not be used in the event of:

- known sensitivity to any of the ingredients in the product (see **DESCRIPTION**)
- idiosyncratic reaction to organic nitrates
- acute circulatory failure (shock, circulatory collapse)
- obstructive myocardial failure (aortic or mitral stenosis, compressive pericarditis, obstructive cardiomyopathy)
- acute inferior myocardial infarction with right ventricular involvement (see **PRECAUTIONS**)
- constrictive pericarditis and pericardial tamponade
- uncorrected hypovolaemia
- pronounced hypotension (systolic blood pressure below 90mm Hg)
- cardiogenic shock
- primary pulmonary hypertension, since hypoxaemia may occur due to a possible increase in blood flow to hypoventilated alveolar regions (pulmonary "shunt"-formation). This applies especially to patients with coronary artery disease.
- increased intracranial pressure (e.g. head trauma or cerebral haemorrhage)

- severe anaemia, arterial hypoxaemia
- concomitant use of phosphodiesterase 5 inhibitors (e.g. sildenafil, vardenafil, tadalafil): due to a considerable increase in the hypotensive effect and the resulting severe side effects (e.g. syncope, myocardial infarction), certain drugs (phosphodiesterase 5 inhibitors) for the treatment of erectile dysfunction or pulmonary arterial hypertension may not be given additionally to an existing therapy with nitric oxide donors (e.g. Nitrolingual Pumpspray).
- Concomitant use of nitrates in any form, with soluble guanylate cyclase stimulators, due to an increased risk of hypotension (see INTERACTIONS)

## PRECAUTIONS

### Use with caution in the following circumstances

The use of any form of glyceryl trinitrate during the early days of acute myocardial infarction requires particular attention to haemodynamic monitoring and clinical status. A reduction in systolic blood pressure below 90mmHg should be avoided.

Hypotension and reflex tachycardia may occur (see **ADVERSE EFFECTS**) and cause increased myocardial oxygen demand. These conditions may lead to cardiac arrhythmias such as ventricular fibrillation (sometimes fatal) mainly in patients with acute inferior myocardial infarction with right ventricular involvement (see **CONTRAINDICATIONS**).

Especially careful monitoring is necessary in aortic and/or mitral stenosis, and patients with congestive heart failure.

As Nitrolingual Pumpspray is more stable than glyceryl trinitrate tablets, it is possible that some patients transferred to the spray will receive a larger dose of the drug than usual. This may increase possible side effects e.g. headache (see **ADVERSE EFFECTS**).

Severe hypotension, particularly with upright posture, may occur even with small doses of glyceryl trinitrate. 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. Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In cases where cyanosis should develop during high dose treatment, work up must include search for methaemoglobinaemia (requiring specific treatment).

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 should be reduced.

### Tolerance

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.

Intermittent therapy, such as with Nitrolingual Pumpspray, will reduce the likelihood of tolerance developing to glyceryl trinitrate.

### Withdrawal

Various clinical trials in angina patients indicate that withdrawal of glyceryl trinitrate may cause rebound of haemodynamic effect and a more ready provocation of anginal attack. Sudden discontinuation should be avoided (see **ADVERSE EFFECTS**).

### Hypoxaemia

Arterial oxygen tension decreases after administration of glyceryl trinitrate in normal subjects and in patients with coronary artery disease.

Caution should be observed in patients with severe ischaemic heart disease as a decrease in available oxygen may oppose its antianginal effect.

### Methaemoglobinaemia

Methaemoglobinaemia has been reported in association with high doses of glyceryl trinitrate therapy. This may be clinically significant, especially in the presence of methaemoglobin reductase deficiencies or in congenital methaemoglobin variants.

Case reports of clinically significant methaemoglobinaemia are rare at conventional doses of organic nitrates. The formation of methaemoglobin is dose-related and in the case of genetic abnormalities of haemoglobin that favour methaemoglobin formation, even conventional doses of organic nitrates could produce harmful concentrations of methaemoglobin.

### Driving a vehicle or performing other 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.

### Use in pregnancy (Category B2)

The safety of glyceryl trinitrate administered to women who are or who may become pregnant has not been established. Therefore, Nitrolingual Pumpspray should not be given to pregnant women unless, in the judgement of the physician, the expected benefit outweighs any potential risk.

### Use in lactation

It is not known whether glyceryl trinitrate is excreted in human milk. Safety in breast-feeding women has not been established. Breast-feeding is therefore inadvisable for the duration of the treatment unless, in the judgement of the physician, the probable clinical benefits outweigh the possible risk to the child.

### Paediatric use

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

## **INTERACTIONS WITH OTHER MEDICINES**

Nitroglycerin should be used with care in combination with other medicines with blood-pressure lowering effect. Concomitant intake of vasodilators, antihypertensive drugs, diuretic substances,  $\beta$ -blockers, calcium channel blockers, hypotensive medicines (e.g. antipsychotics or tricyclic antidepressants) or alcohol may potentiate the antihypertensive effect of Nitrolingual Pumpspray.

Concomitant intake of nitric oxide donors (e.g. Nitrolingual Pumpspray) and certain drugs (phosphodiesterase 5 inhibitors) for the treatment of erectile dysfunction or pulmonary arterial hypertension enhances the hypotensive effect. Therefore the concomitant administration of nitric oxide donors, e.g. the active ingredient of Nitrolingual Pumpspray, and these drugs is contraindicated (see **CONTRAINDICATIONS**). If a patient treated with these drugs needs a rapidly effective nitrate (e.g. in case of an acute angina pectoris attack), he/she must be hospitalised immediately.

Agonists of soluble guanylate (sGC), which is the receptor for nitric oxide (NO), must not be used concomitantly with nitrates (see **CONTRAINDICATIONS**).

In patients previously treated with organic nitrates (e.g. isosorbide dinitrate, isosorbide-5-mononitrate) it may become necessary to increase the glyceryl trinitrate dose to achieve the desired haemodynamic effect.

If used concomitantly with dihydroergotamine (DHE), Nitrolingual Pumpspray may increase the DHE level and consequently enhance its hypertensive effect. Concomitant use of nitrates and ergot alkaloids should be avoided.

Concomitant administration of heparin and glyceryl trinitrate weakens the effect of heparin.

Glyceryl trinitrate may also potentiate the anticholinergic effects of tricyclic antidepressants.

## **ADVERSE EFFECTS**

Adverse reactions to Nitrolingual Pumpspray, particularly headache and hypotension are generally dose related. Headache, is the most commonly reported side effect, but usually subsides with continued use. It may be severe and persistent.

Uncommon cases of hypotension, sometimes severe, and/or orthostatic hypotension, possibly associated with reflex tachycardia or paradoxical reflex bradycardia, have been reported when glyceryl trinitrate was used for the first time or the dose was increased. This may be accompanied by a reflex increase in heart rate, somnolence, dizziness and weakness especially on standing. In rare cases with a large drop in blood pressure angina pectoris symptoms may be intensified (paradoxical nitrate reaction). Less often states of collapse may occur, occasionally accompanied by bradyarrhythmias. Rarely nausea, vomiting, transient flushing, allergic skin reactions may occur.

Anaphylactic reactions, angioedema, lip and tongue swelling, urticaria have been reported.

Uncommon cases of asthenia have been reported.

Abrupt withdrawal may precipitate angina. Withdrawal may also exacerbate Raynaud's phenomenon in susceptible patients.

## **DOSAGE AND ADMINISTRATION**

The spray should not be inhaled.

At the onset of an attack, initially one metered dose (400 micrograms) should be sprayed under the tongue, followed by a second metered dose if pain relief has not occurred within 5 minutes. No more than two metered doses are recommended. If chest pain persists, seek prompt attention.

For the prevention of exercise induced angina or in other precipitating conditions: one or two 400 microgram metered doses sprayed under the tongue immediately prior to the event.

The maximum number of doses of Nitrolingual Pumpspray used per day should be determined by the prescribing physician after consideration of the severity of angina, concurrent medication and patients full medical history.

Nitrolingual Pumpspray should be primed before using it for the first time by pressing the nozzle five times.

If Nitrolingual Pumpspray has not been used for 7 days a priming of 1 spray will be necessary. If the product has not been used for more than 4 months it will need to be primed several times (max 5) until an even spray is obtained.

During administration the patient should rest in the sitting position. The bottle should be kept vertical with the nozzle head uppermost. Hold the opening in the nozzle head as close to the open mouth as possible. Close the mouth immediately after each dose.

Patients should be instructed to familiarise themselves with the position of the spray opening for ease of use at night.

## **OVERDOSAGE**

### Symptoms

The clinical picture depends on the extent of overdose and is characterized mainly by the following symptoms:

Drop in blood pressure with orthostatic regulatory disturbances, reflex tachycardia, persistent throbbing headaches, weakness, dizziness, somnolence, visual disturbances, flushing and perspiring skin (later becoming cold and cyanotic), nausea and vomiting (possibly with colic or bloody diarrhoea) may occur. Methaemoglobinemia has been reported in association with high doses of nitroglycerin therapy (see **PRECAUTIONS**). This is possibly clinically significant, especially in the context of methaemoglobin reductase deficiencies or in congenital methaemoglobin variants.

### Treatment

Keep the patient recumbent and comfortably warm. Hypotension and reflex tachycardia caused by overdose can be treated by elevating the legs. Since the duration of the haemodynamic effects following overdose with glyceryl trinitrate is quite short (because of its short half life) additional measures are usually not required.

Administer oxygen and artificial ventilation if necessary.

In cases of severe overdose apply the general guidelines for treating overdose and/or shock therapy. For pronounced hypotension and/or shock, volume expansion should be performed.

If further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g. metaraminol) should be considered.

### Warning

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

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

## **PRESENTATION AND STORAGE CONDITIONS**

Metered dose pump spray containing 4.5 mL of solution (60 doses)\* or 14.7mL of solution (200 doses).

Store below 25°C.

## **NAME AND ADDRESS OF THE SPONSOR**

sanofi-aventis australia pty ltd  
12-24 Talavera Road  
Macquarie Park NSW 2113  
Australia

## **POISON SCHEDULE OF THE MEDICINE**

Pharmacist Only Medicine (S3)

## **DATE OF FIRST INCLUSION IN THE ARTG**

4 July 1996

## **DATE OF MOST RECENT AMENDMENT**

15 October 2015

\* Not marketed in Australia.