AUSTRALIAN PRODUCT INFORMATION - NITROLINGUAL® (GLYCERYL TRINITRATE) PUMPSPRAY

1 NAME OF THE MEDICINE

Glyceryl trinitrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

Spray solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

When initiating therapy, especially when changing from another form of glyceryl trinitrate administration, patients should be followed closely in order to determine the minimal effective dose for each patient.

Reserved for use in adults. Tachyphylaxis (tolerance to treatment) may occur with chronic administration (prophylactic treatment of acute angina pectoris). Except in cases where the transdermal route is used as a follow-on treatment after another (e.g. intravenous) pharmaceutical form of nitrate treatment, the effective dosage should be attained gradually, because of the risk of orthostatic hypotension and/or violent headache in certain subjects.

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 patient's full medical history.

Method of administration

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.

4.3 CONTRAINDICATIONS

Nitrolingual Pumpspray should not be used in the event of:

- known sensitivity to any of the ingredients in the product (see 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and 6.1 LIST OF EXCIPIENTS)
- idiosyncratic reaction to organic nitrates
- acute circulatory failure (shock, circulatory collapse)
- cardiogenic shock
- obstructive myocardial failure (aortic or mitral stenosis, compressive pericarditis, obstructive cardiomyopathy)
- acute inferior myocardial infarction with right ventricular involvement (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- constrictive pericarditis and pericardial tamponade
- uncorrected hypovolaemia
- pronounced hypotension (systolic blood pressure below 90mm Hg)
- 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). See 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.
- concomitant use of nitrates in any form, with soluble guanylate cyclase stimulators, due to an increased risk of hypotension (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 4.8 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 4.3 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 4.8 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

Reserved for use in adults. Tachyphylaxis (tolerance to treatment) may occur with chronic administration (prophylactic treatment of acute angina pectoris). Except in cases where the transdermal route is used as a follow-on treatment after another (e.g. intravenous)

pharmaceutical form of nitrate treatment, the effective dosage should be attained gradually, because of the risk of orthostatic hypotension and/or violent headache in certain subjects.

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 4.8 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.

Paediatric use

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

Use in the elderly

No data available

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Glyceryl trinitrate should be used with care in combination with other medicines with blood-pressure lowering effect. Concomitant intake of vasodilators, antihypertensive drugs, diuretic substances, β-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 4.3 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 cyclase (sGC), which is the receptor for nitric oxide (NO), must not be used concomitantly with nitrates (see 4.3 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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.

Effects of fertility

No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Especially during treatment start, glyceryl trinitrate may induce symptoms related to orthostatic hypotension such as dizziness which can possibly impact the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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. Migraine has been reported.

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

Symptoms

The clinical picture depends on the extent of overdosage 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 glyceryl trinitrate therapy (see 4.4 SPECIAL WARNINGS AND

PRECAUTIONS FOR USE). This is possibly clinically significant, especially in the context of methaemoglobin reductase deficiencies or in congenital methaemoglobin variants.

Treatment

In cases of overdose, symptoms must be treated rapidly by discontinuing treatment and administering symptomatic treatment as necessary.

Keep the patient recumbent and comfortably warm. Hypotension and reflex tachycardia caused by overdosage can be treated by elevating the legs. Since the duration of the haemodynamic effects following overdosage 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 general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vasodilators used in cardiac diseases, organic nitrates

ATC code: C01DA02

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 ($C_3H_5N_3O_9$) and the compound has a molecular weight of 227.09.

Mechanism of action

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 O2 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.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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%.

Metabolism

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: Cmax was 1.0 ng/mL, tmax was 7.5 minutes and the plasma half life was 5.5 minutes.

Plasma protein binding is approximately 60%.

Excretion

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Nitrolingual Pumpspray contains the following excipients, fractionated coconut oil, glyceryl caprylate/caprate, ethanol, peppermint oil, sodium-lactate, (S)-lactic acid and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Plastic bottle with actuator with finger rest, snap on cap, pump body, dip tube with notch and gasket.

Metered dose pump spray containing 5.5 mL of solution (60 doses)* or 13.9 mL of solution (200 doses).

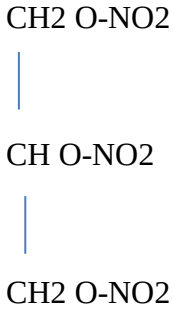
*not marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

55-63-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacist Only Medicine (S3)

8 SPONSOR

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Macquarie Park NSW 2113
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Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

19 October 2018

10 DATE OF REVISION

09 December 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2, 4.2, 4.3, 4.5, 4.8, 5.1, 5.3	Minor editorial changes
4.5, 4.7, 4.9, 6.1	Update ingredients to Australian Approved Names
4.2	Added new information on dose and method of administration.
4.4	Added new information on tolerance to the Warning and Precautions section
4.8	Migraine added to the section on Adverse Effects
4.9	Update to the treatment of overdose
6.5	Update to the description of the container to align to the ARTG record
8	Addition of Medical Information contact number
9	Revision to Date of First Approval