New Zealand Data Sheet

1. PRODUCT NAME

Nitrolingual® Pumpspray 0.4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (one puff) contains 0.4 mg glyceryl trinitrate.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Oral spray

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

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

Dose

Adults

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

Elderly population

Hypotension and syncope can be a problem with use of nitrates in the elderly. Dose adjustment is not necessary.

Paediatric population

No data are available on the use of glyceryl trinitrate in children.

Method of Administration

During application 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.

There is no need to shake the canister. Spray under the tongue or onto the oral mucosa.

Patients should be instructed to familiarise themselves with the position of the spray opening for ease of use at night. The spray should not be inhaled.

4.3. Contraindications

- Known sensitivity to glyceryl trinitrate or idiosyncratic reaction to organic nitrates.
- Known sensitivity to any excipients (see Section 6.1).
- Acute circulatory failure (shock, circulatory collapse).
- Uncorrected hypovolaemia.
- Pronounced hypotension (systolic blood pressure below 90 mmHg).
- Increased intracranial pressure (eg. head trauma or cerebral haemorrhage).
- Severe anaemia or arterial hypoxaemia (see Section 4.4).
- Constrictive pericarditis and pericardial tamponade.
- Cardiogenic shock.

Concomitant administration of certain medicines (phosphodiesterase inhibitors, soluble guanylate cyclase stimulators) for the treatment of erectile dysfunction or pulmonary arterial hypertension and Nitrolingual is contraindicated due to an increase in the hypotensive effect of Nitrolingual. This may result in severe side effects such as syncope or myocardial infarction.

4.4. Special warnings and precautions for use

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.

Especially careful monitoring by a doctor is necessary in:

- patients with constrictive pericarditis, pericardial tamponade,
- acute myocardial infarction with low filling pressure, a reduction of the systolic blood pressure below 90 mmHg should be avoided,
- aortic and/or severe mitral stenosis,
- tendency to orthostatic disturbances of circulatory regulation,
- patients with cerebrovascular disease since symptoms may be precipitated by hypotension,
- patients with incipient glaucoma should be avoided.

Because 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 Section 4.8).

General

Severe hypotension, particularly with upright posture, may occur even with small doses of glyceryl trinitrate. Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate induced hypotension.

The use of glyceryl trinitrate could theoretically compromise myocardial blood supply in patients with left ventricular hypertrophy associated with aortic stenosis because of the detrimental effects of tachycardia and decreased aortic diastolic pressure.

Detailed haemodynamic studies in a small number of patients with valvular aortic stenosis with and without concomitant significant coronary artery disease studied in the supine position have not shown adverse effects with sublingual glyceryl trinitrate. However, it seems prudent to be cautious in treating ambulant patients with the combination of angina and moderate to severe valvular aortic stenosis.

Nitrolingual Pumpspray contains small amounts of ethanol (alcohol), less than 10 mg per spray dose.

Tolerance

Tolerance to this drug and cross tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal 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.

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.

Paediatric population

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

4.5. Interaction with other medicines and other forms of interaction

Concomitant intake of other vasodilatators, other antihypertensives (e.g. ß-blockers, calcium antagonists, ACE inhibitors, diuretics), neuroleptics or tricyclic antidepressants, alcohol and sapropterin may potentiate the antihypertensive effect of Nitrolingual Pumpspray.

N-acetylcysteine may potentiate the vasodilator effects of glyceryl trinitrate.
Concomitant use of Nitrolingual and certain medicines (phosphodiesterase inhibitors, soluble guanylate cyclase stimulators) for the treatment of erectile dysfunction or pulmonary arterial hypertension enhances the hypotensive effect. Therefore, the concomitant administration of Nitrolingual and these medicines is contraindicated (see Section 4.3). If a patient treated with these medicines for erectile dysfunction or pulmonary arterial hypertension needs a rapidly effective nitrate (e.g. in the case of an acute angina pectoris attack) he/she must be closely monitored.

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

If used concomitantly with dihydroergotamine, Nitrolingual Pumpspray may increase the DHE level and consequently enhance its hypertensive effect.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

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 judgment of the doctor, the expected benefit outweighs any potential risk. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Section 5.3).

Breast-feeding
It is unknown if glyceryl trinitrate or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue/abstain from breast-feeding or to discontinue/abstain from glyceryl trinitrate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.Fertility

Animal studies did not indicate harmful effects with respect to fertility.

4.7. Effects on ability to drive and use machines

Even when taken as directed, this drug may affect the ability to drive or operate machinery. It is recommended to the patient to wait at least five minutes after using the spray before driving or

using machinery. If the patient feels faint, dizzy or unwell, the patient should wait until he feels better. This can occur in particular at the beginning of the treatment, with an increase of the dosage, when changing the medicinal product or when used in combination with alcohol.

4.8. Undesirable effects

At the start of therapy, a nitrate-induced headache can occur very commonly, but usually subsides with continued use (overall common frequency).

Commonly a drop in blood pressure and/or orthostatic hypotension has been observed 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 (tachycardia), asthenia, drowsiness and dizziness.

Uncommonly, with a large drop in blood pressure angina pectoris symptoms may be intensified (paradoxical nitrate reaction).

Uncommonly collapse states, occasionally with cardiac dysrhythmia with a slower pulse rate (bradicardial arrhythmia) and syncope (sudden loss of consciousness) are observed.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions are listed below in descending order by frequency of occurrence:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

<u>Immune system disorders</u>
Uncommon: hypersensitivity

<u>Psychiatric disorders</u>
Very rare: restlessness

<u>Nervous system disorders</u>
Common: headache, dizziness, drowsiness
Uncommon: syncope
Very rare: cerebral ischaemia

<u>Cardiac disorders</u>
Common: tachycardia
Uncommon: enhanced angina pectoris symptoms, bradycardia

Vascular disorders
Common: orthostatic hypotension
Uncommon: facial flushing, collapse cardiovascular

Respiratory, thoracic and mediastinal disorders
Very Rare: impairment of respiration

Gastrointestinal disorders
Uncommon: nausea, vomiting
Not known: tongue swelling*

Skin and subcutaneous tissue disorders
Uncommon: allergic dermatitis*
Very rare: exfoliative dermatitis

General disorders and administration site conditions
Common: asthenia
Not known: drug tolerance**

Investigations
Common: drop in blood pressure

Note
During the use of glyceryl trinitrate spray, a transient hypoxaemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar regions, and in patients with coronary heart disease it may lead to ischaemia.

* Uncommonly hypersensitivity reactions may occur and appear as e.g. allergic dermatitis or in isolated cases as tongue swelling.
** Tolerance development and the occurrence of cross tolerance to other nitro compounds have been described. In order to avoid an attenuation or loss of effect, high continuous dosage should be avoided.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms

Signs and symptoms of overdose are generally similar to the described adverse reactions: e.g. drop in blood pressure with orthostatic regulatory disturbances, reflex tachycardia and headaches, weakness, dizziness, flush, nausea, vomiting and diarrhoea may occur.

At high doses methaemoglobinemia, cyanosis, dyspnoea and tachypnoea must be anticipated owing to nitrite ions formed during the metabolism of glyceryl trinitrate.

At very high doses an increase in intracranial pressure with cerebral symptoms may occur.
At chronic overdosage increased methaemoglobin levels were measured of which the clinical relevance is controversial.

Treatment

In the case of overdose, the patient's clinical status including vital signs and mental status should be assessed and supportive treatment of the cardiovascular and respiratory systems provided as clinically indicated or as recommended by the national poisons centre, where available.

In the event of mild hypotension, passive elevation of the patient's legs and/or lowering of the head may be effective.

Arterial blood gas estimation should be performed and if there is acidosis or the patient is clinically cyanosed, then severe methaemoglobinaemia must be assumed.

Oxygen therapy should be given with 1 to 2 mg/kg bodyweight of i.v. Methylene Blue over five min unless the patient is known to have G-6-PD deficiency.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiac diseases, organic nitrates
ATC code: C01 DA 02

Mechanism of action

Glyceryl trinitrate, an organic nitrate, is a vasodilator, which has effects on both arteries and veins.

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. Dilatation of the postcapillary 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 mechanism by which glyceryl trinitrate relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of glyceryl trinitrate and presumably, a more favourable supply-demand ratio is achieved. While the large epicardial coronary arteries are also dilated by glyceryl trinitrate, the extent to which this action contributes to relief of exertional angina is unclear.

Pharmacodynamic effects

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.

5.2. Pharmacokinetic properties

Absorption

When administered sublingually, glyceryl trinitrate is rapidly absorbed from the mucosa of the mouth and reaches the vascular system, bypassing the liver. Maximum plasma concentration is reached approximately 4 minutes after administration.

Distribution

Plasma protein binding is approximately 60 %.

Biotransformation

Glyceryl trinitrate is rapidly metabolised *in vivo*, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolised to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.

Elimination

The plasma half-life following sublingual administration is 2½ to 4½ minutes. Glyceryl trinitrate is principally renally eliminated and less than 1 % is excreted unchanged.

5.3. Preclinical safety data

Tests with glyceryl trinitrate in cell cultures and in animal experiments showed no evidence of mutagenic or carcinogenic effects in the therapeutic dose range. Reproduction studies in animals were conducted with intravenous, intraperitoneal and dermal application. In studies on embyotoxicity and fertility no evidence for an influence on the embryo or evidence of fertility disorders were found in a dose range up to one which was toxic for the parent animals. In particular, there were no indications whatsoever pointing to any possible teratogenic properties. Doses above 1 mg/kg/day (i.p.) and 28 mg/kg/day (dermal) showed foetotoxic effects (reduced birthweights) after application during foetal development in pregnant rats. No data from investigations to determine the concentration of active ingredient in breast milk are on file.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Peppermint oil, Ethanol, Medium-chain triglycerides, Medium-chain partial glycerides, Sodium (*S*)-lactate solution, (*S*)-Lactic acid and Purified water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at temperature below 25°C.
Protect from frost, heat and sunlight.

6.5. Nature and contents of container

Pumpspray containing either 75, 200 or 250 metered doses per bottle.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Do not puncture or break even when empty.
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Pharmacist only medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

Under licence from G. Pohl Boskamp GmbH and Co. KG, Germany.

9. DATE OF FIRST APPROVAL

9 March 1995

10. DATE OF REVISION OF THE TEXT

12 June 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformat to SPC style.
4.3, 4.4	Clarified warning on concomitant use with medicines for treatment of erectile dysfunction or pulmonary arterial hypertension.
4.4, 4.5, 4.6, 4.8, 4.9	Safety information updated against master SmPC.
6.1	Added new excipients.