Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitrolingual Pumpspray 400 micrograms per metered dose, sublingual spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 400 micrograms glyceryl trinitrate.

Excipients: contains 9.6 mg anhydrous ethanol per metered dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual spray.
A clear colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment and prophylaxis of angina pectoris and the treatment of variant angina, and for the emergency treatment of pulmonary oedema secondary to acute left ventricular failure until appropriate intravenous therapy can be instituted.

4.2 Posology and method of administration

Posology

Adults including Older people
Angina
At the onset of an attack or prior to a precipitating event: one or two 400 microgram metered doses sprayed under the tongue. If symptoms do not resolve, this may be repeated at five minute intervals for a total of three doses. If symptoms have not resolved after a total of three doses, the patient should seek prompt medical 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.

Left ventricular failure
Two 400 microgram metered doses sprayed under the tongue, as quickly as possible.
This may be repeated as necessary.

Older people
Hypotension and syncope can be a particular problem with the use of nitrates in the older people.

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

Method of Administration
Precautions to be taken before handling or administering the medicinal product.
During application for angina the patient should rest, ideally in the sitting position because of the risk of symptomatic postural hypotension. During administration for left ventricular failure, the patient should be maintained in an upright position.
The bottle should be held vertically with the valve head uppermost. If the pump is new, or has not been used for a week or more, the first actuation should be released into the air.
The spray orifice should then be placed as close to the mouth as possible. The dose should be sprayed under the tongue and the mouth should be closed immediately after each dose. The spray should not be inhaled.
Patients should be instructed to familiarise themselves with the position of the spray orifice, which can be identified by the finger rest on the top of the valve, in order to facilitate orientation for administration at night.

4.3 Contraindications

Glyceryl trinitrate should not be used in patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- acute circulatory shock including hypovolaemic shock
- cardiogenic shock, unless a sufficiently high left ventricular enddiastolic pressure is assured by intraaortal counterpulsation or positive inotropic drugs
- severe hypotension (systolic blood pressure below 90 mm Hg)
- severe anaemia
- possible increased intracranial pressure (e.g. cerebral haemorrhage or head trauma)
- severe mitral stenosis
- arterial hypoxaemia
- angina caused by hypertrophic obstructive cardiomyopathy (as it may exaggerate outflow obstruction)
- concomitant administration of phosphodiesterase inhibitors used for the treatment of erectile dysfunction or pulmonary arterial hypertension, e.g, sildenafil, vardenafil, tadalafil (see section 4.5).

4.4 Special warnings and precautions for use

Particularly careful monitoring by a doctor is necessary in patients:
- in whom adequate preload is important for maintaining cardiac output (e.g. mitral stenosis, pericardial tamponade, constrictive pericarditis, orthostatic dysfunction) because administration of a vasodilator in these patients may worsen clinical status.
- with cerebrovascular disease since symptoms may be precipitated by hypotension.
- with lung disease or cor pulmonale because glyceryl trinitrate may worsen hypoxaemia
- with myocardial infarction since arterial hypotension with bradycardia may occur; this is thought to be reflexly mediated.

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.

As with all glyceryl trinitrate preparations, this medicinal product should be used with care in patients with incipient glaucoma (where there is raised pressure within the eye).

This medicinal product contains small amounts of ethanol (alcohol); less than 10mg per metered dose (puff)

4.5 Interaction with other medicinal products and other forms of interactions

Consistent with their known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, phosphodiesterase type 5 inhibitors (e.g. sildenafil, vardenafil and tadalafil) have been shown to potentiate the hypotensive effects of nitrates. A severe and possibly dangerous fall in blood pressure may occur. This can result in collapse, unconsciousness and paradoxical myocardial ischaemia and may be fatal. Such use is therefore contra-indicated (section 4.3) If a patient treated with these drugs for erectile dysfunction or pulmonary arterial hypertension needs a rapidly effective nitrate, he/she should be closely monitored.

Treatment with other agents with hypotensive effects (e.g. vasodilators, antihypertensives, diuretics, beta-blockers, calcium channel blockers and neuroleptics, tricyclic antidepressants and sapropterin) may potentiate the hypotensive effect of glyceryl trinitrate. In addition to these agents, the risk of hypotension and syncope with use of glyceryl trinitrate may be enhanced by alcohol.

N-acetylcysteine may potentiate the vasodilator effects of glyceryl trinitrate.

The possibility of tolerance to the effects of glyceryl trinitrate should be considered when used in conjunction with long-acting nitrate preparations.

There is evidence that systemic nitrates may interfere with the anticoagulant effects of heparin. Early and frequent monitoring of anticoagulation is recommended when systemic nitrates and heparin are used in combination.

If used concomitantly with dihydroergotamine (DHE), glyceryl trinitrate may increase the DHE level and consequently enhance its hypertensive effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies did not indicate harmful effects with respect to pregnancy, embryofoetal development, parturition or postnatal development. However, the relevance of these animal findings to man is unknown. The administration of glyceryl trinitrate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

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. However, the relevance of these animal findings to man is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Since hypotension, dizziness and syncope have been reported following treatment with glyceryl trinitrate, caution is recommended in patients performing skilled tasks such as driving and operating machinery. It is recommended that patients wait at least five minutes after using the spray before driving and using machinery. If the patient feels faint, dizzy or unwell, the patient should wait until they feel 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

Undesirable effects are listed below by system organ class and frequency.
Frequencies are defined as follows: very common ≥1/10 (≥10%); common ≥1/100 and <1/10 (≥1% and <10%); uncommon ≥1/1000 and <1/100 (≥0.1% and <1%); rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%); very rare <1/10,000 (< 0.01%); not known (cannot be estimated from the available data).

The most serious, although uncommon, adverse reaction observed is a pronounced drop in blood pressure, in the worst case leading to circulatory collapse, occasionally accompanied by bradycardia. Headache occurs very commonly at the start of treatment but usually subsides with continued use.
The following table summarises adverse reactions by system organ class and frequency:

Blood and lymphatic system disorders	
Very rare	Methaemoglobinaemia
Psychiatric Disorders	
Very rare	Restlessness
Nervous System Disorders	
Very common	Headache
Common	Dizziness Drowsiness
Uncommon	Syncope
Very rare	Cerebral ischaemia
Cardiac disorders	
Common	Tachycardia
Uncommon	Enhanced angina pectoris symptoms

	Bradycardia Cyanosis
Vascular disorders	
Common	Orthostatic hypotension*
Uncommon	Facial flushing Circulatory collapse
Gastrointestinal disorders	
Uncommon	Nausea Vomiting
Not known (cannot be estimated from the available data)	Tongue swelling**
Respiratory, thoracic and mediastinal disorders	
Very rare	Impairment of respiration
Skin and subcutaneous tissue disorders	
Uncommon	Allergic dermatitis**
Very rare	Exfoliative dermatitis Drug rash
General disorders and administration site conditions	
Common	Asthenia
Not known	Drug tolerance Cross tolerance to other nitro compounds
Investigations	
Common	Blood pressure decreased*
*Particularly on initiation of therapy and following an increase in dose **Symptoms which are known in conjunction with hypersensitivity reactions	

Large doses of glyceryl trinitrate may cause vomiting, cyanosis, restlessness, methaemoglobinaemia and impairment of respiration.
During treatment with glyceryl trinitrate, temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

Signs and symptoms encountered with overdose are generally similar to those events
reported during treatment use although the magnitude and/or severity of the reactions may be more pronounced (see Adverse Reactions).
Flushing, severe headache, a feeling of suffocation, hypotension, fainting, restlessness, blurred vision, impairment of respiration, bradycardia and rarely, cyanosis and methaemoglobinaemia may occur. In a few patients there may be a reaction comparable to shock with nausea, vomiting, weakness, sweating and syncope.
At very high doses an increase in intracranial pressure with cerebral symptoms may occur. Additional gastrointestinal effects such as colicky pain and diarrhoea have also been reported.

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 glucose-**6**-phosphate dehydrogenase **deficiency**.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiac disease,
ATC code: C01DA02

Glyceryl trinitrate relieves angina pectoris by reduction of cardiac work and dilation of the coronary arteries. In this way, not only is there a lessening in arterial oxygen requirement but the amount of oxygenated blood reaching the ischaemic heart is increased.

5.2 Pharmacokinetic properties

The pharmacokinetics of glyceryl trinitrate are complex; venous plasma levels of the drug show wide and variable fluctuations and are not predictive of clinical effect. In a human pharmacodynamic study, pharmacological activity had commenced one minute after dosing and was obvious by two minutes.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium-chain triglycerides
Ethanol anhydrous
Medium-chain partial glycerides
Peppermint oil
Sodium (*S*)-lactate solution
(*S*)-Lactic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Glass bottle (colourless type III glass) whichmay be plastic-coated and pre-printed or labelled, fitted with meteringpump. Each bottle contains 6.3, 12.1, 13.2or 15.4 g solution (equivalent to about 75, 180, 200 or 250 doses).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

G Pohl-Boskamp GmbH & Co. KG
Kieler Strasse 11
25551 Hohenlockstedt
Germany

8 MARKETING AUTHORISATION NUMBER

PA2243/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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