1. Name of the medicinal product

NITROLINGUAL SPRAY

2. Qualitative and quantitative composition

Each metered dose contains 400 micrograms glyceryl trinitrate.

Excipients: contains 9.600 mg anhydrous ethanol per metered dose. For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sublingual spray.

4. Clinical particulars

4.1 Therapeutic indications

Relief of angina pectoris attacks, angina pectoris prophylaxis.

4.2 Posology and method of administration

Posology

Adults and older people:

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.

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:

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. During application the patient should rest, ideally in the sitting position because of the risk of symptomatic postural hypotension. Hypotension and syncope can be a particular problem with the use of nitrates in the elderly.

4.3 Contraindications

- Hypersensitivity to the active substance, other nitrates 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 end diastolic pressure is assured by intra-aortal counterpulsation or positive inotropic drugs.
- Severe hypotension (systolic blood pressure below 90 mm Hg).
- Severe anaemia, possible increased intracranial pressure (e.g. cerebral haemorrhage and head trauma), severe mitral stenosis and 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

- Any lack of effect may be an indicator of early myocardial infarction.
- As with all glyceryl trinitrate preparations, use in patients with incipient glaucoma should be avoided.
- Glyceryl trinitrate should be used with caution 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.
- Glyceryl trinitrate should be used with caution in patients with cerebrovascular disease since symptoms may be precipitated by hypotension.
- Glyceryl trinitrate may worsen hypoxaemia in patients with lung disease or cor pulmonale.
- Arterial hypotension with bradycardia may occur in patients with myocardial infarction; 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.
- Do not store or spray near inflammable material.

4.5 Interaction with other medicinal products and other forms of interaction

- 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.

  During the simultaneous use of dihydroergotamine, glyceryl trinitrate may lead to an increase in the DHE level and thus potentiate its hypertensive action.

4.6 Fertility, pregnancy and lactation

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*).

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.

Lactation

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.

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 or operating 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).	
Blood and lymphatic system disorders Very rare	Methaemoglobinaemia
Psychiatric disorders Very rare	Restlessness
Nervous system disorders Very common Common Uncommon Very rare	Headache Dizziness Drowsiness Syncope Cerebral ischaemias

Cardiac disorders Common Uncommon	 Tachycardia Enhanced angina pectoris symptoms Bradycardia Cyanosis
Vascular disorders Common Uncommon	 Orthostatic hypotension* Facial flushing Circulatory collapse
Gastrointestinal disorders Uncommon Not known	 Nausea Vomiting Tongue swelling** Tongue blistering
Respiratory, thoracic and mediastinal disorders Very Rare	 Impairment of respiration
Skin and subcutaneous tissue disorders Uncommon Very rare	 Allergic dermatitis** Exfoliative dermatitis Drug rash
General disorders and administration site conditions Common	 Asthenia
Investigations Common	 Blood pressure decreased*

*Particularly upon 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 suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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 G- 6-PD deficiency.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

medium-chain triglyceride, ethanol anhydrous, glycerol monocaprylocaprate, peppermint oil, sodium (S)-lactate solution 50%, (S)-lactic acid 90%, purified water

6.2 Incompatibilities

Not known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

20 ml colorless glass bottle coated with transparent red plastic (PVC) and pre-printed or labelled fitted with metering pump and a protecting cap. Each bottle contains 6.3 g, 13.2 g, 15.4 g solution (equivalent to about 75, 200 or 250 doses).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

See 'Administration' section.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Contains ethanol. Do not store or spray near flammable materials.

7. Manufacturer

G.Pohl-Boskamp GmbH & CO.
Kieler Str. 11,D-25551 Hohenlockstedt
Germany

8. Marketing authorisation holder

Megapharm Ltd.
Megapharm Ltd., 15 HaTidhar St., Ra'anana Israel

9. Marketing authorisation number

103-04-27820

10. Revised in November 2024 according to the Israeli Ministry of Health guideline

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