Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glytrin 400 micrograms per metered dose Sublingual Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose delivers 8.8 mg of solution containing 400 micrograms of glyceryl trinitrate

Excipient(s) with known effect
Ethanol (alcohol) – 7.5 mg per metered dose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual spray, solution
Pressurised metered dose aerosol canister containing a colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute angina pectoris.
Prevention of inducible angina (e.g. physical effort, emotional stress, exposure to cold).

4.2 Posology and method of administration

Posology
Sublingual Dosage

Adults including the Elderly
At the onset of an attack: one or two metered sprays (400 to 800 micrograms glyceryl trinitrate) to be sprayed under the tongue for the relief of anginal pain while the breath is held. If symptoms do not resolve, this may be repeated at five-minute intervals for a total of three sprays (maximum of 1.2mg taken within 15 minutes). If symptoms have not resolved after a total of three sprays, immediate medical attention should be sought.

For the prevention of inducible angina (e.g. due to physical effort, emotional stress, exposure to cold) one or two metered sprays (400 to 800 micrograms glyceryl trinitrate) to be sprayed under the tongue 2 to 3 minutes prior to activity likely to cause angina.

Paediatric population
Glytrin should not be used in children and adolescents under 18 years.

Method of administration
During application the patient should rest, ideally in the sitting position. The canister should be held vertically with the valve head uppermost and the spray orifice 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 top of the valve, in order to facilitate orientation for administration at night.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe hypotension (systolic blood pressure lower than 90mm Hg)
- Hypotensive shock
- Severe anaemia
- Constrictive pericarditis

- Extreme bradycardia
- Cerebral haemorrhage and brain trauma
- Aortic and/or mitral stenosis
- Angina caused by hypertrophic obstructive cardiomyopathy
- Circulatory collapse
- Cardiogenic shock, unless a sufficiently high left ventricular end diastolic pressure is assured by intra-aortic balloon pump counterpulsation therapy or positive inotropic drugs
- Toxic pulmonary oedema.
- Since Sildenafil has been shown to potentiate the hypotensive effects of nitrates, its co-administration with nitric oxide donors or nitrates (Glytrin) in any form is contra-indicated.
- Concomitant use with the soluble guanylate cyclase stimulator such as riociguat (see section 4.5).

4.4 Special warnings and precautions for use

Caution should be exercised in patients with arterial hypoxaemia due to severe anaemia (including G6PD deficiency induced forms).

Tolerance to this drug and cross-tolerance to other nitrates may occur.

Glytrin Spray should be administered with particular caution in:

- Pericardial tamponade.
- Low filling pressures (e.g. acute myocardial infarction, left ventricular failure).
- Tendency to dysregulation of orthostatic blood pressure.
- Diseases accompanied by an increased intracranial pressure (so far further pressure increase has been observed solely in high doses of glyceryl trinitrate).

Alcohol should be avoided because of the hypotensive effect and medical controls of the intraocular pressure of glaucoma-patients are advisable.

Particular caution should also be exercised when using Glytrin in patients with volume depletion from diuretic therapy, severe hepatic or renal impairment and hypothyroidism.

This medicine contains 7.5 mg of alcohol (ethanol) in each spray. The amount in one spray of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

- Alcohol may potentiate the hypotensive effect.
- Vasodilators, antihypertensives, beta-blockers, calcium antagonists, neuroleptics, tricyclic antidepressants and diuretics can increase nitrate induced hypotension.
- The hypotensive effects of nitrates are potentiated by the concurrent administration of sildenafil.
- The use of a soluble guanylate cyclase stimulator such as riociguat is contraindicated (see section 4.3) since concomitant use can cause hypotension.
- The bioavailability of dihydroergotamine may be increased by concomitant use of Glytrin which can result in vasoconstriction since dihydroergotamine can antagonise the effects of nitroglycerine. The concomitant administration of Glytrin and heparin can reduce the antithrombotic effect of heparin. Regular monitoring of coagulation parameters and adjustment of the heparin dose may be necessary.
- In patients pretreated with organic nitrates a higher dose of glyceryl trinitrate may be necessary to achieve the desired haemodynamic effect.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
The safety of glyceryl trinitrate in human pregnancy, especially during the first trimester has not been established.

<u>Breastfeeding</u>

It is not known whether glyceryl trinitrate is excreted into human breast milk. Glytrin spray should be used only after weighing the benefit for the mother against possible risks for the child. Nursing should be discontinued during treatment with this product.

Fertility
Preclinical data reveal no special hazard for humans based on conventional studies of toxicity to reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

The ability to react may be diminished because of the side effects or interactions due to the nitrates. This effect is potentiated by alcohol consumption. Therefore, driving and/or using machines should be avoided during treatment with Glytrin Spray.

4.8 Undesirable effects

The following adverse reactions have been reported:

System Organ Class	**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)**
Nervous System Disorders	Headache	Vertigo Dizziness		Syncope	
Skin and Subcutaneous Tissue Disorders				Allergic dermatitis*	Exfoliative dermatitis
Vascular Disorders		Facial Flushing		Orthostatic hypotension Circulatory collapse	
General Disorders and Administration Site Conditions		Asthenia	Application site discomfort including Burning Sensation and Stinging		
Gastrointestinal Disorders		Nausea	Tongue blistering		
Cardiac Disorders				Tachycardia Bradycardia Angina pectoris aggravated	
Investigations				Blood pressure decreased	

*symptoms which are known in conjunction with hypersensitivity reactions

Tolerance development and the occurrence of crossed tolerance of other nitro compounds have been found in chronic, continuous treatment using high doses. To avoid a decrease in efficacy or a loss of efficacy high continuous doses should be avoided.

Use of Glytrin may give rise to transient hypoxaemia and, in patients with coronary heart disease, ischaemia as a result of a relative redistribution of the bloodstream which is to reach 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 to:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Signs and Symptoms
Flushing, severe headache, vertigo, tachycardia, a feeling of suffocation, hypotension, fainting 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.

Treatment
Recovery often occurs without special treatment. Hypotension may be corrected by elevation of the legs to promote venous return. If methaemoglobinaemia is suspected, it should be confirmed, assessed and treated in accordance with local guidance and best practice. Treatment includes supplemental oxygen and intravenous methylthioninium chloride, as indicated. Methylthioninium chloride must be used with caution in particular patients, including those with glucose-6-phosphate-dehydrogenase-deficiency. Symptomatic treatment should be given for respiratory and circulatory defects in more serious cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiac diseases, organic nitrates
ATC-Code: C01DA02.

Glyceryl trinitrate acts on vascular smooth muscles to produce arterial and venous vasodilation. The vasodilation results in a reduction of venous return and an improvement in myocardial perfusion with the result of a reduction in the work performed by the heart and hence reduced oxygen demand.

5.2 Pharmacokinetic properties

Glyceryl trinitrate is rapidly absorbed through the buccal and sublingual mucosa, and in man peak concentrations in plasma are observed within four minutes of sublingual administration. The absolute bioavailability after sublingual administration is approximately 39%. After sublingual administration the plasma levels have shown a wide range of intra and inter-individual variability. The compound is extensively metabolised by liver enzymes and has a plasma half life of 1-3 minutes. The principle mechanism of metabolism involves denitration.

5.3 Preclinical safety data

Reproductive toxicity
Animal studies conducted with various routes of administration have not shown teratogenicity, other embryotoxic effects or impairment of fertility with dosages inducing parental toxicity. Data from *in-vitro* mutagenicity testing as well as from studies in animals indicate that glyceryl trinitrate will not exert mutagenic or carcinogenic effects under conditions of clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Peppermint oil
Propellant HFC 134A (1,1,1,2 Tetrafluoroethane)
Ethanol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Warning. Pressurised container: May burst if heated.
Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. Do not pierce or burn, even after use.
Protect from sunlight. Do not expose to temperatures exceeding 50 °C
Do not store above 25ºC. Do not refrigerate or freeze.
Keep out of the sight and reach of children.

6.5 Nature and contents of container

Internally lacquered monobloc aluminium pressurised container (canister) sealed with a metered spray valve.
The product is presented in packs with one container.
Each container contains 1760.0 mg of solution (according to 11400.0 mg of solution and propellant) providing 200 single metered doses.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Evolan Pharma AB
PO Box 120
182 12 Danderyd
Sweden

8 MARKETING AUTHORISATION NUMBER

PA2262/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 November 1990

Date of last renewal: 29 November 2010

10 DATE OF REVISION OF THE TEXT

December 2024