SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glyceryl Trinitrate Tablets 500 micrograms

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms Glyceryl Trinitrate.
Excipients with known effect: Also contains lactose

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

Glyceryl trinitrate 500micrograms tablets are white, round, biconvex, and unscored.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a short-acting vasodilator

- Relief of angina pectoris
- Prophylaxis of angina pectoris
- Relief of acute spontaneous coronary artery spasm

4.2 Posology and method of administration

Posology

Glyceryl trinitrate must be placed under the tongue (administered sublingually) and retained in the mouth until dissolved or discarded. A local burning or tingling sensation may occur.

Populations

Adults

Treatment of acute attacks of Angina Pectoris

When angina starts, 0.5 mg glyceryl trinitrate (one tablet) should be taken and if symptoms do not resolve, 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.

The patient should preferably rest in the sitting position because of the risk of symptomatic postural hypotension.

Prophylaxis of Angina Pectoris

Glyceryl trinitrate, 0.5 mg (one tablet), may be used prior to activity which is likely to precipitate angina pectoris.

Children

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

Elderly

Hypotension and syncope can be a particular problem with use of nitrates in the elderly. Patients should be advised to sit down whenever possible when taking sublingual glyceryl trinitrate.

Method of administration

For sublingual administration

4.3 Contraindications

Hypersensitivity to the active substance, to other nitro compounds or to any of the excipients listed in section 6.1.

Glyceryl trinitrate is contraindicated in patients taking phosphodiesterase type 5 inhibitors (e.g. sildenafil, vardenafil, tadalafil) (*see Interactions*).

- Glyceryl trinitrate is contraindicated in angina caused by hypertrophic obstructive cardiomyopathy as it may exaggerate outflow obstruction.

- Glyceryl trinitrate should not be used in patients with possible increased intracranial pressure (e.g. cerebral haemorrhage or head trauma).

- Marked anaemia

- Closed angle glaucoma

4.4 Special warnings and precautions for use

Glyceryl trinitrate should be used with caution in patients in whom adequate preload is important for maintaining cardiac output (e.g. acute circulatory shock including hypovolemic shock or cardiogenic shock with inadequate diastolic filling pressures, severe 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 severe hypotension (systolic blood pressure below 90 mm Hg) and patients with cardiogenic shock, unless a sufficiently high left ventricular end diastolic pressure is assured by intra-aortal counter pulsation or positive inotropic drugs.

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.

Caution is necessary in patients with severe hepatic or renal impairment, hypothyroidism, hypoxaemia, hypothermia or a recent history of myocardial infaraction and malnutrition.

Sublingual tablets:

If angina symptoms have not resolved after a total of three doses, the patient should be instructed to seek prompt medical attention (*see Dosage and Administration*).

Important information regarding the ingredients of this medicine
These tablets contain lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Consistent with its 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, and coadministration with glyceryl trinitrate is therefore contraindicated *(see Contraindications).*

Treatment with other agents with hypotensive effects (e.g. vasodilators, antihypertensives, 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.

There is a potential for drugs that cause dry mouth (eg anticholinergic, antimuscarinics, tricyclic antidepressants) to reduce the effectiveness of sublingual nitrates.

An enhanced hypotensive effect with sublingual apomorphine may occur as a result of concomitant administration with glyceryl trinitrate.

Ergot alkaloids may oppose the coronary vasodilatation of nitrates. Ergot alkaloids can precipitate angina and glyceryl trinitrate can reduce the first pass hepatic metabolism of dihydroergotamine.

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.

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

As Glyceryl trinitrate can cause dizziness, patients should make sure they are not affected before driving or operating machinery. This effect appears to be accentuated by alcohol.

4.8 Undesirable effects

System Organ Class	*Very Common (≥ 1/10)*	*Common (≥ 1/100 < 1/10)*	*Uncommon (≥ 1/1000 <*	*Rare (≥ 1/10,000 <*	*Very Rare (< 1/10,00)*	*Frequency not known (cannot be estimated from the available*

			1/100)	*1/1000)*		*data)*
Blood and lymphatic system disorders					Methaemoglobinaemia	
Psychiatric disorder					Restlessness	
Nervous system disorders	Throbbing headache**	Vertigo**, Dizziness**, Drowsiness	Syncope		Cerebral ischaemia	
Eye disorders						Increased ocular pressure
Cardiac disorders		Tachycardia,		Enhanced angina, Pectoris symptoms, Bradycardia, Cyanosis		Hypoxaemia, palpitations
Vascular disorders		Orthostatic hypertension*,	Facial flushing, Circulatory collapse			
Gastrointestinal disorders			Nausea, Vomiting		Heartburn, Halitosis	
Respiratory, thorasic and					Impairment of respiration	

mediastinal disorders						
Skin and subcutaneous tissue disorders				Allergic skin reactions	Exfoliative dermatitis, Drug rash	
General disorders and administration site complications		Asthenia	Localised burning sensation Tongue blisters			weakness
Investigations		Blood pressure decreased *				

* Particularly upon initiation of therapy and following an increase in dose.

****** Headache and dizziness, persisting after relief of angina may be minimised by removing the glyceryl trinitrate tablet before it has completely dissolved. Glyceryl trinitrate-induced hypotension may cause cerebral ischaemia.

Large dose 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms and Signs

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*). 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

Pharmacotherapeutic Group: Organic nitrates

ATC code: C01D A02.

Glyceryl trinitrate is a vasodilator and is used for angina of effort. Vasodilation is achieved by the releasing of free radical nitric oxide which activates guanylate cyclase and increases synthesis of guanosine 3′ and 5′-monophosphate with resultant effects on the phosphorylation of proteins in smooth muscle. If taken in excess, its vasodilatory effect can cause headache.

5.2 Pharmacokinetic properties

Glyceryl Trinitrate is readily absorbed from the oral mucosa but rapidly metabolised so that it only has a fleeting duration of action..

Glyceryl Trinitrate is also readily absorbed from the gastro-intestinal tract but owing to extensive first pass metabolism in the liver, its bioavailability is reduced (short plasma half-life).

Glyceryl trinitrate is metabolised by hydrolysis to dinitrates and the mononitrate, which is the main urinary metabolite.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to that already included in other sections of SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Mannitol
Acacia Powdered Sieved
Stearic Acid Powder
Magnesium Stearate

6.2 Incompatibilities

None stated

6.3 Shelf life

36 months unopened

8 weeks opened

6.4 Special precautions for storage

Keep in the bottle with cap tight closed, in a dark place and protect from sunlight. Do not store above 25°C.

6.5 Nature and contents of container

3-RDM square amber-coloured glass bottle having a fin-plate screw cap fitted with a waxed aluminium-faced pulpboard liner.

Pack size: 100.

6.6 Special precautions for disposal

- If you do not use the tablets within 8 weeks of first opening the bottle obtain a fresh supply and return the old tablets to your pharmacist.
- In any event, do not use the tablets after expiry date stated on the bottle.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8. Marketing Authorisation Number(s)

PL 17907/0171

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/02/2005 / 17/03/2009

10 DATE OF REVISION OF THE TEXT

14/11/2016