APPENDIX 1 - REVISED CORE SAFETY PROFILE

4.2 Posology and method of administration

Sublingual tablets:

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.

TREATMENT OF ACUTE CARDIOGENIC PULMONARY OEDEMA

In the treatment of non-hypotensive (i.e. systolic blood pressure > 100 mmHg) patients with acute cardiogenic pulmonary oedema, 0.5 mg of glyceryl trinitrate may be administered sublingually and repeated at intervals of 5 to 10 min while carefully monitoring the patients clinical status including blood pressure. Subsequently, patients may be switched to an intravenous formulation or to another vasodilating agent as appropriate depending upon the clinical response.

- **Children**
- **Elderly**

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

4.3 Contraindications

-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.

-Hypersensitivity to the active substance, to other nitro compounds, or to any of the excipients.

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

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 enddiastolic pressure is assured by intra-aortal counterpulsation 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.

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*).

The solution contains glucose; this should be taken into account in patients with diabetes mellitus.

4.5 Interactions 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.~~

~~*In vitro* data suggest that St John's Wort (*Hypericum perforatum*) may induce cytochrome P450 3A4. There is a theoretical possibility therefore, that plasma levels of glyceryl trinitrate may be decreased during concomitant administration and increased upon withdrawal of St John's Wort.~~

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

~~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).*~~

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.

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

~~*In vitro* data suggest that St John's Wort (*Hypericum perforatum*) may induce cytochrome P450 3A4. There is a theoretical possibility therefore, that plasma levels of glyceryl trinitrate may be decreased during concomitant administration and increased upon withdrawal of St John's Wort.~~

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 Non-Clinical Information*).

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 Ability to perform tasks that require judgement, motor or cognitive skills

Since dizziness and syncope have been reported following treatment with glyceryl trinitrate, caution is recommended in patients performing skilled tasks.

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%).

Blood and lymphatic system disorders	
Very rare	Methaemoglobinaemia
Psychiatric disorder	
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
Very Rare	Heartburn **** Halitosis ****
Respiratory, thoracic and mediastinal disorders	
Very rare	Impairment of respiration
Skin and subcutaneous tissue disorders	
Very rare	Exfoliative dermatitis Drug rash
for GTN patch only	
Uncommon	Allergic contact dermatitis Allergic skin reaction
General disorders and administration site conditions	
Common	Asthenia***
Investigations	
Common	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.

*** The original CCSI contained the LLT of feeling of weakness. GSK proposes the use of the preferred term asthenia.

**** only tablets

~~The frequency estimations for these adverse reactions are unknown due to a lack of robust clinical trial data to accurately determine frequency estimates.~~

~~**Blood and lymphatic system disorders:**~~
~~Methaemoglobinaemia~~

~~**Psychiatric disorder:**~~

~~Restlessness~~

~~**Nervous system disorders:**~~

~~Cerebral ischaemia, syncope, vascular headache, lightheadedness*, dizziness, drowsiness~~

~~Headache and/or light-headedness 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.~~

~~**Cardiac disorders:**~~

~~Enhanced angina pectoris symptoms, bradycardia, tachycardia, cyanosis~~

~~**Vascular disorders:**~~

~~Circulatory collapse, hypotension*, facial flushing~~

~~**Respiratory, thoracic and mediastinal disorders:**~~

~~Impairment of respiration~~

~~**Gastrointestinal disorders:**~~

~~Nausea, vomiting, heartburn, halitosis~~

~~**Skin and subcutaneous tissue disorders:**~~

~~Exfoliative dermatitis, drug rash~~

~~**General disorders and administration site conditions**~~

~~Asthenia~~

Large dose of glyceryl trinitrate may cause vomiting, cyanosis, restlessness, methaemoglobinaemia and impairment of respiration.

~~*Lightheadedness and hypotension may be exacerbated in an upright or standing position.~~

During treatment with glyceryl trinitrate, temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas.

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.