Glyceryl trinitrate

QUALITATIVE AND QUANTITATIVE COMPOSITION
ANGISED sublingual tablets contain either 0.5 mg (500 micrograms) or 0.6 mg (600 micrograms) glyceryl trinitrate.

PHARMACEUTICAL FORM
Sublingual tablets.

CLINICAL PARTICULARS
Indications
ANGISED is indicated for the treatment of acute attacks of angina pectoris including variant angina and for the prophylaxis of such attacks. ANGISED may be used for the emergency treatment of pulmonary oedema.

Dosage and Administration
ANGISED 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.

Treatment of acute attacks
When angina starts, 0.5 mg or 0.6 mg glyceryl trinitrate (one tablet) should be taken every 3 minutes until cessation of pain or limiting side effects, such as headache or light-headedness supervene. The patient should preferably rest in the sitting position because of the risk of symptomatic postural hypotension.

Prophylaxis
0.5 mg or 0.6 mg ANGISED (one tablet) may be used prior to activity which is likely to precipitate angina pectoris.

Pulmonary oedema
In the treatment of pulmonary oedema doses ranging between 0.8 mg and 2.4 mg of ANGISED has been used at intervals of 5 to 10 minutes.

• Children
No data are available on the use of ANGISED 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 ANGISED.

Contraindications
ANGISED is contraindicated in angina caused by hypertrophic obstructive cardiomyopathy as it may exaggerate outflow obstruction. ANGISED should not be used in patients with cerebral haemorrhage or head trauma. ANGISED is contraindicated in patients taking sildenafil (see Interactions).

Warnings and Precautions
ANGISED should be used with caution in patients with cerebrovascular disease since symptoms may be precipitated by hypotension. ANGISED 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 ANGISED 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 ANGISED. However it seems prudent to be cautious in treating ambulant patients with the combination of angina and moderate to severe valvular aortic stenosis.
Interactions
The risk of hypotension and syncope with use of ANGISED may be enhanced by alcohol.
The possibility of tolerance to the effects of ANGISED 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, sildenafil has been shown to potentiate the hypotensive effects of nitrates, and its coadministration with ANGISED is therefore contraindicated (see Contraindications).
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 ANGISED trinitrate may be decreased during concomitant administration and increased upon withdrawal of St John’s Wort.

Pregnancy and Lactation
In reproductive toxicity studies in animals, glyceryl trinitrate had no effects upon fertility, organogenesis or peri- and post-natal development. However, the administration of ANGISED during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.
No data are available on the excretion of glyceryl trinitrate or its metabolites in human breast milk.

Effects on Ability to Drive and Use Machines
Since dizziness and syncope have been reported following treatment with ANGISED, caution is recommended in patients performing skilled tasks.

Adverse Reactions
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:
Methaemoglobinemia

Psychiatric disorder:
Restlessness

Nervous system disorders:
Vascular headache, lightheadedness, dizziness, syncope, cerebral ischaemia
Headache and/or light-headedness persisting after relief of angina may be minimised by removing the ANGISED tablet before it has completely dissolved.

Cardiac disorders:
Bradycardia, tachycardia, cyanosis

Vascular disorders:
Hypotension, facial flushing

Respiratory, thoracic and mediastinal disorders:
Impairment of respiration

Gastrointestinal disorders:
Halitosis, vomiting

Skin and subcutaneous tissue disorders:
Drug rash
Large dose of ANGISED may cause vomiting, cyanosis, restlessness, methaemoglobinemia and impairment of respiration.
ANGISED-induced hypotension may cause cerebral ischaemia.

Overdose
In the case of ingestion, all that is usually required is supportive treatment of the cardiovascular and respiratory systems. The patient should be nursed head-down if hypotensive.
Arterial blood gas estimation should be performed and if there is acidosis or the patient is clinically cyanosed, then severe methaemoglobinemia must be assumed. Oxygen therapy should be given with 1 to 2 mg/kg bodyweight of intravenous Methylene Blue over 5 minutes.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Glyceryl trinitrate causes smooth muscle relaxation with a reduction in afterload, followed by a profound vasodilatation of arterial and venous beds. At low doses the action of ANGISED is principally through peripheral venodilatation, while higher doses increasingly cause arterial vasodilatation and high concentrations produce arteriolar relaxation.
The symptomatic relief of angina produced by glyceryl trinitrate results from a series of events. Initially, peripheral venodilatation redistributes circulating blood away from the lungs and heart, thus lowering left ventricular diastolic volume and pressure. The reduced filling pressure reduces myocardial wall stress and hence oxygen consumption, also causing a fall in left ventricular end diastolic pressure (preload). This in turn facilitates capillary blood flow to the ischaemic area. In addition, glyceryl trinitrate enhances sub-endocardial oxygenation, increases collateral flow and redistributes blood flow to ischaemic zones of the myocardium. Finally, glyceryl trinitrate causes dilatation of the large coronary arteries, a particularly important effect in variant angina where coronary spasm is the predominant mechanism.

Two of the major metabolites of glyceryl trinitrate, 1,2-ANGISED dinitrate and 1,3- ANGISED dinitrate, are also pharmacologically active. These function as vasodilators with a potency approximately 10-fold lower than that of the parent compound, thus contributing to the activity of the drug.

**Pharmacokinetics**

**Absorption**
Glyceryl trinitrate is readily absorbed from the buccal mucosa and gastrointestinal tract although average bioavailability is only 36%, with considerable interindividual variability (range 3 to 113%). Mean maximum plasma concentration following the administration of a 0.5 mg dose has been shown to be 1.97 nanograms/ml (range 0.57 to 4.33), the peak occurring 4.9 (range 3 to 7) post dosing. Following a 0.5 mg sublingual dose, peak serum concentrations of the active dinitrate metabolites are approximately 3.11 and 0.70 nanograms/ml with times to maximal concentration of 13.7 and 17.6 min, respectively.

**Distribution**
Sequential measurements of plasma levels of glyceryl trinitrate have indicated the volume of distribution to be 179.6 litres.

**Metabolism**
Glyceryl trinitrate undergoes extensive first pass metabolism and is rapidly metabolised to 1,2-glyceryl dinitrate, 1,3-glyceryl dinitrate and, to some extent, an intermediate product, glyceryl mononitrate. Evidence suggests that extra-hepatic metabolism occurs in the vasculature, and that systemic clearance is affected by cardiac output.

**Elimination**
Glyceryl trinitrate has a half-life of approximately three min, and only a small amount of intact drug is excreted. Mean clearance rate has been reported as between 14 and 28 l/min, exceeding hepatic blood flow and precluding the liver as the sole route of elimination. The half-life of both metabolites has been found to be within the range of 35 to 39 min.

**Pre-clinical Safety Data**
Findings from preclinical studies are not unexpected considering the mode of action of glyceryl trinitrate, releasing nitric oxide, and are highly unlikely to have any safety implications for the clinical use of glyceryl trinitrate at therapeutic doses.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**
As registered locally.

**Incompatibilities**
No data.

**Shelf Life**
The expiry date is indicated on the packaging.

**Special Precautions for Storage**
Glyceryl trinitrate tablets should be discarded after eight weeks in use.

**Nature and Contents of Container**
ANGISED tablets should be dispensed in glass containers of not more than 100 tablets, closed with a foil-lined cap and containing no cotton wool wadding.

**Instructions for Use/Handling**
See Dosage and Administration.
Not all presentations are available in every country.