

ANGISED™

Glyceryl trinitrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

ANGISED sublingual tablets contain 0.5 mg (500 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.

Treatment of acute attacks angina pectoris

When angina starts, 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 of angina pectoris

ANGISED one tablet may be used prior to activity which is likely to precipitate angina pectoris.

Treatment of 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 possible increased intracranial pressure (e.g. cerebral haemorrhage or head trauma).

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

ANGISED is contraindicated in patients taking soluble guanylate cyclase (sGC) stimulators, such as riociguat (*see Interactions*).

ANGISED is contraindicated in patients who are hypersensitive to the active substance, to other nitro compounds, or to any of the excipients.

Warnings and Precautions

ANGISED 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.

ANGISED should be used with caution in patients with severe hypotension (systolic blood pressure below 90 mm Hg).

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.

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*).

Interactions

The risk of hypotension and syncope with use of *ANGISED* may be enhanced by alcohol.

Treatment with other agents with hypotensive effects (e.g. antihypertensives including beta-blockers and calcium channel blockers, vasodilators, neuroleptics, and tricyclic antidepressants) may potentiate the hypotensive effect of *ANGISED*.

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, phosphodiesterase type 5 inhibitors (e.g. sildenafil, vardenafil and tadalafil) have been shown to potentiate the hypotensive effects of nitrates, and coadministration with *ANGISED* is therefore contraindicated (*see Contraindications*).

The use of *ANGISED* concomitantly in patients taking soluble guanylate cyclase (sGC) stimulators, such as riociguat is contraindicated. Concomitant use may result in severe hypotension, syncope, or myocardial ischemia (*see Contraindications*).

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

There is evidence that systemic nitrates may interfere with the anticoagulant effects of heparin. It is not known if this effect occurs following single sublingual nitroglycerin doses. Monitoring of anticoagulation is recommended when systemic nitrates and heparin are used in combination.

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, embryofetal development, parturition or postnatal development. However, the relevance of these animal findings to man is unknown. No data are available on the use of *ANGISED* during human pregnancy, hence 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.

Lactation

It is unknown if *ANGISED* 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 *ANGISED* therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

Glyceryl trinitrate is placed under the tongue and retained in the mouth. A local burning or tingling sensation may occur in the tongue or mouth.

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*, blood pressure decreased* 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 *ANGISED* 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 *ANGISED*, temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas.

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*). 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.

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 intravenous Methylene Blue over 5 minutes unless the patient is known to have G-6-PD deficiency.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

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 glyceryl trinitrate is principally through peripheral venodilatation, while higher doses increasingly cause arterial vasodilatation and high concentrations produce arteriolar relaxation.

Furthermore, glyceryl trinitrate causes redistribution of blood flow to the subendocardial regions of the heart when the coronary circulation is partially occluded by arteriosclerotic lesions. This last effect is likely to be due to a selective dilation of large coronary vessels. Nitrate-induced dilation of collateral arteries can improve the perfusion of poststenotic myocardium. Nitrates also dilate eccentric stenosis as they can counteract possible constricting factors acting on the residual arch of compliant smooth muscle at the site of the coronary narrowing. Furthermore, coronary spasms can be relaxed by nitrates.

Effects on other organ systems include a relaxation of the bronchial muscle, the muscles of the gastrointestinal, the biliary and the urinary tract. Relaxation of the uterine smooth muscle has been reported.

Like all organic nitrates, glyceryl trinitrate acts as a donor of nitric oxide (NO). NO causes a relaxation of vascular smooth muscle via the stimulation of guanylyl cyclase and the subsequent increase of intracellular cyclic guanosine monophosphate (cGMP) concentration. A cGMP-dependent protein kinase is thus stimulated, with resultant alteration of the phosphorylation of various proteins in the smooth muscle cell. This leads to the dephosphorylation of the light chain of myosin and the lowering of contractility.

Pharmacodynamic Effects

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.

Nitrates were shown to improve resting and exercise haemodynamics in patients suffering from congestive heart failure due to many of the beneficial mechanisms described above as well as improvement of valvular regurgitation.

Two of the major metabolites of glyceryl trinitrate, 1,2-glyceryl dinitrate and 1,3-glyceryl 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 min (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.

Plasma protein binding is about 60%.

Metabolism

Orally administered 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. The enzymes necessary for this process is glutathione-S-transferase. Evidence suggests that extra-hepatic metabolism occurs in the vasculature, and that systemic clearance is affected by cardiac output.

Glyceryl dinitrates and glyceryl mononitrates are also glucuronidised and excreted in the urine and, to a small extent, in the bile. Most of the metabolic data on glyceryl trinitrate have been obtained from animal studies. Mononitrates of glyceryl trinitrate have been detected in human urine.

There is no accumulation of glyceryl trinitrate or its metabolites (1,2-glyceryl dinitrate and 1,3-glyceryl dinitrate).

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction. Glyceryl trinitrate was weakly positive in strains 1535 and 1537 of a gene mutation test in *S. typhimurium* (Ames' test). These effects are not unexpected given the mode of action of glyceryl trinitrate as a therapeutic agent, releasing nitric oxide. Glyceryl trinitrate showed no mutagenic activity when tested for chromosome damage, either *in vitro* CHO cells or *in vivo* in rat bone marrow and was negative when tested for the induction of Unscheduled DNA Synthesis *in vitro* using rat hepatocytes.

PHARMACEUTICAL PARTICULARS

Shelf Life

The expiry date is indicated on the packaging.

24 months

Special Precautions for Storage

Store below 25°C. Protect from light.

ANGISED 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 snap-fitting plastic cap and containing no cotton wool wadding.

Instructions for Use/Handling

See Dosage and Administration.

Not all presentations are available in every country.

Version number: GDS 14/IPI 07

Date of issue: 08 August 2016

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