

New Zealand Data Sheet

LYCINATE™

Glyceryl trinitrate 600mcg Tablets

Presentation

LYCINATE Sublingual Tablets contain 0.6mg (600mcg) glyceryl trinitrate.

Uses

Actions

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 LYCINATE 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-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

Glyceryl trinitrate is readily absorbed from the buccal mucosa and gastrointestinal tract although average bioavailability is only 36%, with considerable interindividual variability (range 3-113%). Sequential measurements of plasma levels of glyceryl trinitrate have indicated the volume of distribution to be 179.6L.

Mean maximum plasma concentration following the administration of a 0.5mg dose has been shown to be 1.97ng/mL (range 0.57-4.33), the peak occurring 4.9 (range 3-7) minutes post dosing. Glyceryl trinitrate undergoes extensive first pass metabolism, with a half-life of approximately 3 minutes. Mean clearance rate has been reported as between 14 and 28L/min, exceeding hepatic blood flow and precluding the liver as the sole route of elimination. Evidence suggests that extra-hepatic metabolism occurs in the vasculature, and that systemic clearance is affected by cardiac output.

Only a small amount of intact drug is excreted, glyceryl trinitrate being rapidly metabolised to 1,2-glyceryl dinitrate, 1,3-glyceryl dinitrate and, to some extent, an intermediate product, glyceryl mononitrate. Following a 0.5mg sublingual dose peak serum concentrations of the active dinitrate metabolites are approximately 3.11 and 0.70ng/mL with times to maximal concentration of 13.7 and 17.6min respectively. The half-life of both metabolites has been found to be within the range of 35 to 39 minutes.

Indications

LYCINATE is indicated for the treatment of acute attacks of angina pectoris including variant angina and for the prophylaxis of such attacks.

Dosage and Administration

LYCINATE 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 0.6mg 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:

0.6mg glyceryl trinitrate (one tablet) may be used prior to activity which is likely to precipitate angina pectoris.

Children:

No data are available on the use of LYCINATE in children.

The 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 LYCINATE.

Contraindications

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

LYCINATE should not be used in patients with cerebral haemorrhage or head trauma.

LYCINATE is contraindicated in patients taking sildenafil (see Interaction with Other Medicinal Products and Other Forms of Interaction).

Warnings and Precautions

LYCINATE should be used with caution in patients with cerebrovascular disease since symptoms may be precipitated by hypotension.

LYCINATE 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 LYCINATE 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.

Use During 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 glyceryl trinitrate 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 LYCINATE 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 LYCINATE, caution is recommended in patients performing skilled tasks.

Adverse Effects

The dose of LYCINATE may be limited by vascular headaches.

Other side effects are facial flushing, tachycardia, light-headedness, dizziness, halitosis, hypotension, syncope and rarely bradycardia. Large doses may cause vomiting, cyanosis, restlessness, methaemoglobinaemia and impairment of respiration.

Headache and/or light-headedness persisting after relief of angina may be minimised by removing the LYCINATE Tablet before it has completely dissolved.

LYCINATE-induced hypotension may cause cerebral ischaemia.

LYCINATE occasionally causes a drug rash.

Interactions

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

The possibility of tolerance to the effects of LYCINATE 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 LYCINATE 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 glyceryl trinitrate may be decreased during concomitant administration and increased upon withdrawal of St John's Wort.

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 methaemoglobinaemia must be assumed. Oxygen therapy should be given with 1 to 2mg/kg bodyweight of intravenous Methylene Blue over 5 minutes.

Pharmaceutical Precautions

Shelf Life

LYCINATE tablets should be discarded after eight weeks in use.

Special Precautions for Storage

Store below 25°C.

Medicines Classification

Pharmacist Only Medicine

Package Quantities

100 Tablets.

Further information

Preclinical 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.

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