ANGININE
PRODUCT INFORMATION

NAME OF THE MEDICINE

ANGININE tablets contain glyceryl trinitrate.

DESCRIPTION

Glyceryl trinitrate is a white to pale yellow, thick, flammable, explosive liquid. It is slightly soluble in water (0.1% to 1% w/v) and soluble in acetone, alcohol, and ether. Glyceryl trinitrate has the following chemical structure:

![Chemical Structure of Glyceryl Trinitrate]

The molecular formula of Glyceryl Trinitrate is C₃H₅(O.NO₂)₃ and it has a molecular mass of 227.1 (CAS – 55 – 63 – 0)

Excipients: lactose, dextrin, maize starch, mannitol, glycerol, and magnesium stearate.

PHARMACOLOGY

ACTIONS

ANGININE is a vasodilator which relieves angina pectoris. Pain in angina pectoris is believed to be the result of myocardial ischaemia secondary to coronary artery disease. In the relief of acute anginal pain the effect is apparent after 2 to 3 minutes and lasts for up to 20 or 30 minutes.

ANGININE redistributes blood flow along collateral channels and from epicardial to endocardial regions and thus may increase blood flow to ischaemic areas. ANGININE also reduces oxygen demand by increasing venous capacitance causing pooling of blood in the peripheral veins and thereby reducing ventricular volume. Furthermore, the fall in arterial pressure will also reduce myocardial oxygen demand, although this may be offset by a reflex tachycardia. The beneficial effects of nitrates in pulmonary oedema depend on venous dilation and reduction of pre-load. ANGININE causes coronary vasodilation in coronary arteries that are in spasm, and may relieve pain in variant angina by this mechanism.

ANGININE is thought to exert its vasodilator effect through the activation of guanylate cyclase in vascular smooth muscle cells by nitric oxide; this results in an increased synthesis of cyclic guanosine monophosphate, which leads to smooth muscle relaxation.
PHARMACOKINETICS

Absorption:
Glyceryl trinitrate is readily absorbed through the buccal mucosa but is rapidly metabolised so it has a fleeting duration of action. Peak plasma levels of glyceryl trinitrate given sublingually appear within 4 minutes.

Distribution:
Glyceryl trinitrate has a volume of distribution of about 3 L/kg. It is taken up by vascular smooth muscle cells.

Metabolism:
In smooth muscle cells the nitrate group is cleaved to inorganic nitrite and then to nitric oxide (thought to be responsible for Glyceryl trinitrate’s vasodilatatory effect). Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly hydrolysed in the liver by glutathione-organic nitrate reductase to dinitrates and mononitrates. At least half of the intact glyceryl trinitrate is cleared from the blood in 1 to 3 minutes.

Excretion:
The main urinary metabolite of glyceryl trinitrate is the mononitrate.

INDICATIONS

Treatment of acute angina pectoris. As well as relieving the pain of an acute attack, it may be used prophylactically before physical exertion or mental stress which would be expected to produce an anginal attack.

CONTRAINDICATIONS

ANGININE is contraindicated, except for diagnostic purposes, in angina caused by hypertrophic obstructive cardiomyopathy as it may exaggerate outflow obstruction. ANGININE should not be used in patients with cerebral haemorrhage or head trauma. ANGININE is contraindicated in patients hypersensitive to glyceryl trinitrate. ANGININE is contraindicated in patients taking phosphodiesterase 5 inhibitors (see INTERACTIONS).

PRECAUTIONS

ANGININE should be used with caution in patients with the following conditions:

- **Anaemia**
- **Cerebral vascular disease:** Symptoms may be precipitated by hypotension.
- **Severe coronary atherosclerosis:** Arterial hypotension and reflex tachycardia associated with administration of ANGININE can be hazardous in these patients.
- **Glaucoma:** Nitrates may increase intraocular pressure.
- **Recent head trauma:** Nitrates may increase cerebrospinal fluid pressure.
- **Lung disease and cor pulmonale:** ANGININE may worsen hypoxaemia in these patients. Transient hypoxaemia may accompany the use of ANGININE and thereby cause a paradoxical response with further angina pectoris and electrocardiograph ST segment depression. This effect is thought to be due to pulmonary vascular shunting. Oxygen administration seems rational as adjunctive therapy in nitrate resistant angina, especially
in patients prone to hypoxaemia such as the elderly and patients with lung disease and left ventricular failure.

- **Severe hepatic function impairment:** Use of ANGININE may lead to increased risk of methaemoglobinaemia.
- **Hyperthyroidism**
- **Recent myocardial infarction:** There is a risk of hypotension and tachycardia, which may aggravate ischaemia.

**Use in Children:**
The possible effects of ANGININE in children have not been studied.

**Use in the Elderly:**
The elderly may be particularly sensitive to the side effects of ANGININE. Starting at a reduced dose is recommended.

**Use in Pregnancy: (Category B2)**
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.

Data on the use of ANGININE during human pregnancy is not available.

**Use in Lactation:**
No data are available on the excretion of glyceryl trinitrate or its metabolites in human milk.

**Carcinogenicity, Mutagenicity, Impairment to Fertility:**
Studies have not been performed on the effects of glyceryl trinitrate on carcinogenicity, mutagenicity or effects on fertility.

**Effects on Ability to Drive and Operate Machinery:**
Since dizziness and syncope have been reported following treatment with ANGININE, caution is recommended in patients performing skilled tasks.

**INTERACTIONS WITH OTHER MEDICINES**

**Alcohol, Antihypertensives, tricyclic antidepressants, phenothiazines, levodopa, opioid analgesics, hydralazine, calcium channel blocking agents, minoxidil and prazosin:** The risk of orthostatic hypotension and syncope with the use of ANGININE may be enhanced by these medications.

**Sympathomimetics:** Concurrent use may reduce the anti-anginal effects of ANGININE, also ANGININE may counteract the pressor effect of sympathomimetics, possibly resulting in hypotension.

**Phosphodiesterase 5 inhibitors:** Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, these agents has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with ANGININE is therefore contraindicated (see CONTRAINDICATIONS).
ADVERSE EFFECTS

The dose of ANGININE may be limited by vascular headaches. Troublesome vascular side effects may be minimised by removing the tablet from the mouth before it is completely dissolved. Anginine-induced hypotension may cause cerebral ischaemia.

The adverse effects of ANGININE and their frequency are shown below:

**Rare**

(≥ 0.01% and < 0.1%)
- Blurred vision
- Dry mouth
- Severe and prolonged headache
- Skin rash
- Bradycardia

**Common**

(≥ 1% and < 10%)
- Flushing of face and neck
- Headache
- Dizziness
- Nausea or vomiting
- Orthostatic hypotension
- Syncope
- Restlessness
- Tachycardia

DOSAGE AND ADMINISTRATION

For acute angina attacks 600 to 900 microgram given as early in the attack as possible. Elderly patients are recommended to take a reduced dose of 300 microgram (half a tablet) as a starting dose. Glyceryl trinitrate is well absorbed through the buccal mucosa. It is therefore important that the tablets be placed under the tongue or in the cheek and allowed to dissolve rather than be swallowed. Repeated doses of glyceryl trinitrate may lead to tolerance, but cessation of the drug for a short period will re-establish its action.

Instructions to Patients: ANGININE should be taken at the first sign of an attack of angina. It is preferable to take it sitting down. The tablet should be placed beneath the tongue or in the cheek and allowed to dissolve. It should not be swallowed, as it is then ineffective. If two fresh tablets and rest in a chair do not relieve the chest pain within 10 minutes, a physician should be consulted.

Patients should be instructed on the storage conditions required to maintain the potency of ANGININE. The tablets should be stored only in the manufacturer’s bottle. No labels, other drugs, or any material apart from the manufacturer’s packing should be put in the bottle. The lid must always be kept tightly closed.

ANGININE should be stored in a cool place. It should not be carried close to the body and should be kept out of direct sunlight.

An unopened bottle has a shelf life of 2 years if stored below 25°C. However, tablets unused three months after first opening a bottle should be discarded and a fresh supply obtained.
OVERDOSAGE

**Signs and Symptoms:** Bluish-coloured lips, fingernails, or palms of hands; extreme dizziness or syncope; feeling of extreme pressure in head; shortness of breath; unusual tiredness or weakness; fast heartbeat; fever; convulsions.

Cyanosis may occur at blood methaemoglobin concentrations of 1.5 grams/100 mL. More pronounced signs of methaemoglobinemia (pressure in head, tiredness or weakness, shortness of breath) occur at concentrations of 20 to 50 grams/100 mL.

**Treatment:** Supportive therapy with particular attention being paid to the respiratory and cardiovascular systems is indicated. Hypotension and syncope should be treated by recumbency and elevation of legs to aid venous return. Methaemoglobin concentrations should be monitored and methaemoglobinemia treated by high-flow oxygen and intravenous methylene blue.

PRESENTATION AND STORAGE CONDITIONS

Tablets, 600 microgram (round white tablet scored on one face and plain on the other face): 100’s. Bottle.

**Storage**

Store below 25°C. Protect from light.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S3 (Pharmacist Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

19 February 2015.