

NITROSTAT

(Glyceryl trinitrate) sublingual tablet



1 NAME OF THE MEDICINE

Glyceryl trinitrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 300 micrograms or 400 micrograms of glyceryl trinitrate as the active ingredient.

Excipients with known effect: Lactose and sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

300 micrograms sublingual tablet:

Small, round, white, tablet debossed with “3” on one side and “N” on the other side

400 micrograms sublingual tablet:

Small, round, white, tablet debossed with “4” on one side and “N” on the other side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NITROSTAT is indicated for the acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administer one sublingual tablet under the tongue at the first sign of an acute anginal attack. Allow sublingual tablet to dissolve without swallowing. One additional sublingual tablet may be administered every 5 minutes until relief is obtained. No more than three sublingual tablets are recommended within a 15-minute period. If the pain persists after a total of 3 sublingual tablets in a 15-minute period, or if the pain is different than is typically experienced, seek prompt medical attention.

NITROSTAT may be used prophylactically 5 to 10 minutes prior to engaging in activities that might precipitate an acute attack.

For patients with xerostomia, a small sip of water prior to placing the sublingual tablet under the tongue may help maintain mucosal hydration and aid dissolution of the sublingual tablet.

Administer NITROSTAT at rest, preferably in the sitting position.

4.3 CONTRAINDICATIONS

PDE-5-Inhibitors and sGC-Stimulators

Do not use glyceryl trinitrate in patients who are taking PDE-5 Inhibitors, such as avanafil, sildenafil, tadalafil, vardenafil hydrochloride. Concomitant use can cause severe hypotension, syncope, or myocardial ischemia (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Do not use glyceryl trinitrate in patients who are taking the soluble guanylate cyclase stimulators, such as riociguat. Concomitant use can cause hypotension.

Severe Anemia

Glyceryl trinitrate is contraindicated in patients with severe anemia (large doses of glyceryl trinitrate may cause oxidation of hemoglobin to methemoglobin and could exacerbate anemia).

Increased Intracranial Pressure

Glyceryl trinitrate may precipitate or aggravate increased intracranial pressure and thus should not be used in patients with possible increased intracranial pressure (e.g., cerebral hemorrhage or traumatic brain injury).

Hypersensitivity

Glyceryl trinitrate is contraindicated in patients who are allergic to glyceryl trinitrate, other nitrates or nitrites or any excipient.

Circulatory Failure and Shock

Glyceryl trinitrate is contraindicated in patients with acute circulatory failure or shock.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Hemodynamic Effects**

The benefits of sublingual glyceryl trinitrate in patients with acute myocardial infarction (MI) or congestive heart failure (CHF) have not been established. If glyceryl trinitrate is used in these conditions, particular attention to hemodynamic monitoring and clinical status is required, because of the possibility of hypotension and tachycardia.

Severe hypotension, particularly with upright posture, may occur with small doses of glyceryl trinitrate particularly in patients with constrictive pericarditis, aortic or mitral stenosis, patients who may be volume-depleted, or are already hypotensive. Hypotension induced by glyceryl trinitrate may be accompanied by paradoxical bradycardia and increased angina pectoris. Symptoms of severe hypotension (nausea, vomiting, weakness, pallor, perspiration and collapse/syncope) may occur even with therapeutic doses.

Cardiac Effects

Nitrate therapy may aggravate angina caused by hypertrophic cardiomyopathy.

Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate-induced hypotension.

Tolerance

Tolerance to the vascular and anti-anginal effects of glyceryl trinitrate, and cross-tolerance to other nitrates and nitrites may occur. As tolerance to other forms of glyceryl trinitrate develops, the effects of sublingual glyceryl trinitrate on exercise tolerance, although still observable, are somewhat blunted. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance rarely occurs. Chest pain, acute MI, and even sudden deaths have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

General

Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. NITROSTAT tablets are intended for sublingual administration only and should not be swallowed (See section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL).

Glyceryl trinitrate should be discontinued if blurred vision or dry mouth occurs. Excessive dosages of glyceryl trinitrate may produce severe headaches.

Glyceryl trinitrate produces dose-related headaches, especially at the start of glyceryl trinitrate therapy, which may be severe and persist but usually subside with continued use.

Glyceryl trinitrate may produce a burning or tingling sensation when administered sublingually; however, the ability to produce a burning or tingling sensation should not be considered a reliable method for determining the potency of the sublingual tablets.

Use in Renal Impairment

No dosage adjustment is required in patients with renal failure.

Use in the Elderly

Clinical studies did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this patient population.

Paediatric Use

The safety and effectiveness of glyceryl trinitrate in pediatric patients have not been established.

Effects on Laboratory Tests

Nitrates may interfere with the Zlatkis-Zak colour reaction, causing a false report of decreased serum cholesterol.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

PDE5 Inhibitors and sGC-Stimulators

Glyceryl trinitrate is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5). PDE-5-Inhibitors such as avanafil, sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates. (See section 4.3. CONTRAINDICATIONS).

Glyceryl trinitrate is contraindicated in patients who are taking soluble guanylate cyclase (sGC) stimulators. Concomitant use can cause hypotension.

The time course and dose dependence of these interactions have not been studied, and use within a few days of one another is not recommended. Appropriate supportive care for the severe hypotension has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

Alcohol

Concomitant use of nitrates and alcohol may cause hypotension.

Hypotensive Agents

Patients receiving antihypertensive drugs, beta-adrenergic blockers, phenothiazines, or other drugs known to cause hypotension with nitrates should be observed for possible additive hypotensive effects. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly. Dose adjustment of either class of agent may be necessary.

Aspirin

Aspirin may decrease the clearance and enhance the hemodynamic effects of sublingual glyceryl trinitrate.

Nitrates

A decrease in the therapeutic effect of sublingual glyceryl trinitrate may result from the use of long-acting nitrates (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Alteplase

Intravenous administration of glyceryl trinitrate decreases the thrombolytic effect of alteplase, a tissue plasminogen activator (TPA). Therefore, caution should be exercised in patients receiving sublingual glyceryl trinitrate during alteplase therapy.

Heparin

Intravenous glyceryl trinitrate reduces the anticoagulant effect of heparin. Activated partial thromboplastin times (aPTTs) should be monitored in patients receiving heparin and intravenous glyceryl trinitrate. It is not known if this effect occurs following single sublingual glyceryl trinitrate doses.

Anticholinergic Agents

Anticholinergic agents and tricyclic antidepressants (e.g., amitriptyline, desipramine, doxepin) may be associated with dry mouth and diminished salivary secretions. This may make dissolution of sublingual glyceryl trinitrate difficult. Increasing salivation by chewing gum or using artificial saliva products may prove useful in aiding dissolution of sublingual glyceryl trinitrate.

Ergot Alkaloids

Oral administration of glyceryl trinitrate markedly decreases the first-pass metabolism of dihydroergotamine and subsequently increases its oral bioavailability. Ergotamine is known to precipitate angina pectoris. Therefore, patients receiving sublingual glyceryl trinitrate should avoid ergotamine and related drugs or be monitored for symptoms of ergotism if this is not possible.

Tissue-type plasminogen activator (t-PA)

Concomitant administration of t-PA and intravenous glyceryl trinitrate has been shown to reduce plasma levels of t-PA and its thrombolytic effect.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

See section 5.3 PRECLINICAL SAFETY DATA.

Use in Pregnancy

Category B2

Animal reproduction and teratogenicity studies have not been conducted with sublingual glyceryl trinitrate. No clear evidence of teratogenicity was noted in rodent studies using dietary glyceryl trinitrate. There are no adequate and well-controlled studies in pregnant women. Glyceryl trinitrate should be given to a pregnant woman only if the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Use in Lactation

It is not known whether glyceryl trinitrate is excreted in human milk. Safety in breast-feeding women has not been established. Breast-feeding is therefore inadvisable for the duration of the treatment unless, in the judgement of the physician, the probable clinical benefits outweigh the possible risk to the child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Glyceryl trinitrate may cause dizziness, vertigo, and syncope. Patients with marked sensitivity to the vasodilatory effects of glyceryl trinitrate should avoid potentially hazardous tasks such as driving or operating machinery unless it is known that this medication does not affect their ability to engage in these activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Nervous System Disorders

Headache, which may be severe and persistent may occur immediately after use; syncope due to nitrate vasodilation has been reported.

Cardiac Disorders

Paradoxical bradycardia and increased angina pectoris (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Vascular Disorders

Vertigo, dizziness, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients; marked sensitivity to the hypotensive effects of nitrates (manifested by nausea, vomiting, weakness, diaphoresis, pallor and collapse) may occur at therapeutic doses; flushing.

Skin and Subcutaneous Tissue Disorders

Drug rash, exfoliative dermatitis, urticaria.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Hemodynamic Effects

The effects of glyceryl trinitrate overdose are generally the results of glyceryl trinitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. Nitrate overdose may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, moderate fever, vertigo, palpitations, tachycardia, visual disturbances, nausea and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright posture), dyspnea, later followed by reduced ventilatory effort, diaphoresis, with the skin either flushed or cold and clammy, heart block and bradycardia, paralysis, coma, seizures, methemoglobinemia and death.

It is not known whether physiological maneuvers (e.g., maneuvers to change the pH of the urine) or hemodialysis accelerates elimination of glyceryl trinitrate and its active metabolites. No specific antagonist to the vasodilator effects of glyceryl trinitrate is known. Because the hypotension associated with glyceryl trinitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or CHF, therapy resulting in central volume expansion is not without hazard. Treatment of glyceryl trinitrate overdose in these patients may be subtle or difficult, and invasive monitoring may be required.

Methemoglobinemia

Methemoglobinemia should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial PO₂. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

If methemoglobinemia is present, intravenous administration of methylene blue (1-2 mg/kg of body weight) may be required.

Emesis and activated charcoal are of no value following sublingual administration of glyceryl trinitrate. Treatment is symptomatic and supportive and should be focused on hypotension and possible methemoglobinemia.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Relaxation of vascular smooth muscle is the principal pharmacological action of glyceryl trinitrate. Although venous effects predominate, glyceryl trinitrate produces, in a dose-related manner, dilation of both arterial and venous beds. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload). Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index and stroke-work index) is decreased by both the arterial and venous effects of glyceryl trinitrate, and a more favourable supply-demand ratio can be achieved.

Glyceryl trinitrate also dilates large epicardial coronary arteries; however, the extent to which this effect contributes to the relief of exertional angina is unclear.

Therapeutic doses of glyceryl trinitrate may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by glyceryl trinitrate therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced by intravenous glyceryl trinitrate.

Mechanism of Action

Glyceryl trinitrate forms free radical nitric oxide (NO), which activates GC, resulting in an increase of guanosine 3'5' monophosphate (cyclic GMP) in smooth muscle and other tissues. This eventually leads to dephosphorylation of the light chain of myosin, which regulates the contractile state in smooth muscle, resulting in vasodilatation.

Consistent with the symptomatic relief of angina, digital plethysmography indicates that the onset of the vasodilatory effect occurs approximately 1 to 3 minutes after sublingual administration of glyceryl trinitrate and reaches a maximum 5 minutes post-dose. Pharmacological effects are present for at least 25 minutes following sublingual administration of glyceryl trinitrate.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Glyceryl trinitrate is rapidly absorbed following sublingual administration. Mean peak glyceryl trinitrate plasma concentrations occur at a mean time of approximately 6 to 7 minutes post-dose (Table 1). Maximum plasma glyceryl trinitrate concentrations (C_{max}) and area under the curve (AUC) increase dose proportionately following 300 micrograms to 600 micrograms of glyceryl trinitrate. The absolute bioavailability of glyceryl

trinitrate sublingual tablets is approximately 40 %, but tends to be variable due to factors influencing drug absorption such as sublingual hydration and mucosal metabolism.

Table 1. Mean Glyceryl trinitrate (SD) Values		
	GLYCERYL TRINITRATE SUBLINGUAL TABLETS	
	2 x 300 micrograms sublingual tablets	1 x 600 micrograms sublingual tablet
C_{max}, ng/mL	2.3 (1.7)	2.1 (1.5)
t_{max}, min	6.4 (2.5)	7.2 (3.2)
AUC (0-∞), min	14.9 (8.2)	14.9 (11.4)
t ½, min	2.8 (1.1)	2.6 (0.6)

Distribution

The volume of distribution (V_{area}) following intravenous administration of glyceryl trinitrate is 3.3 L/kg. At plasma concentrations of between 50 ng/mL and 500 ng/mL, the binding of glyceryl trinitrate to plasma proteins is approximately 60 %, while that of 1,2-diglyceryl trinitrate and 1,3-diglyceryl trinitrate are 60 % and 30 %, respectively.

Metabolism

Glyceryl trinitrate is rapidly metabolized with a short half-life, estimated at 1 to 4 minutes.

A liver reductase enzyme is of primary importance in the metabolism of glyceryl trinitrate to glycerol di- and mononitrate metabolites and ultimately to glycerol and organic nitrate. Known sites of extrahepatic metabolism include red blood cells and vascular walls. In addition to glyceryl trinitrate, two major metabolites 1,2- and 1,3-diglyceryl trinitrate, are found in plasma. Mean peak 1,2- and 1,3-diglyceryl trinitrate plasma concentrations occur at approximately 15 minutes post-dose. The elimination half-lives of 1,2- and 1,3-diglyceryl trinitrate are 36 and 32 minutes, respectively. The 1,2- and 1,3-diglyceryl trinitrate metabolites have been reported to possess approximately 2 % and 10 %, respectively, of the pharmacological activity of glyceryl trinitrate. Higher plasma concentrations of the diglyceryl trinitrate metabolites, along with their nearly 10-fold longer elimination half-lives, may contribute significantly to the duration of pharmacological effect. Glycerol mononitrate metabolites of glyceryl trinitrate are biologically inactive.

Excretion

Glyceryl trinitrate plasma concentrations decrease rapidly, with a mean elimination half-life range from 1.5 to 7.5 minutes. Clearance (13.6 L/min) greatly exceeds hepatic blood flow. Metabolism is the primary route of drug elimination.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Animal carcinogenesis studies with sublingually administered glyceryl trinitrate have not been performed.

Carcinogenicity potential of glyceryl trinitrate was evaluated in rats receiving up to 434 mg/kg/day of dietary glyceryl trinitrate for 2 years. Rats developed dose-related fibrotic and neoplastic changes in the liver, including carcinomas, and interstitial cell tumours in the testes. At high doses, the incidence of hepatocellular carcinomas in males was 48 % and in females was 33 % compared to 0 % in untreated controls. Incidences of testicular tumours were 52 % vs. 8 % in controls. Lifetime dietary administration up to 1058 mg/kg/day of glyceryl trinitrate was not tumorigenic in mice.

Mutagenesis

Glyceryl trinitrate was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an in vivo dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, PO, or in ex vivo cytogenetic tests in rat and dog tissues.

Reproductive Toxicity

Impairment of Fertility

In a three-generation reproduction study, rats received dietary glyceryl trinitrate at doses up to about 434 mg/kg/day for 6 months prior to mating of the F0 generation, with treatment continuing through successive F1 and F2 generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F0 generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males.

Teratogenicity

Animal reproduction and teratogenicity studies have not been conducted with sublingual glyceryl trinitrate. Teratology studies in rats and rabbits, however, were conducted with topically applied glyceryl trinitrate ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. In the three-generation study, there was no clear evidence of teratogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, glyceryl monostearate, pregelatinised starch, calcium stearate, and colloidal anhydrous silica.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Store in original container in order to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Amber glass bottles with metal closure.

Pack size:

300 microgram: 100 tablets are packed in a 7 mL bottle.

400 microgram: 100 tablets are packed in 4 x 3 mL bottles with 25 tablets in each bottle.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 438870 – NITROSTAT 300 micrograms sublingual tablets bottle

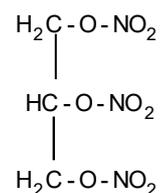
AUST R 438851 – NITROSTAT 400 micrograms sublingual tablets bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Glyceryl trinitrate, an organic nitrate, is a vasodilating agent. The chemical name for glyceryl trinitrate is 1,2,3 propanetriol trinitrate, the empirical formula is $\text{C}_3\text{H}_5\text{N}_3\text{O}_9$, and the compound has a molecular weight of 227.09.

CAS Number

55-63-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

Viatrix Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatrix.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

30/06/2025

10 DATE OF REVISION

N/A

Summary Table of Changes

Section Changed	Summary of New Information
All	New PI for registration

NITROSTAT_pi\Jun25/00 (CCDS ver5.0 2-Aug-2016)