NEW ZEALAND DATA SHEET
Glyceryl TRINITRATE Medicianz Solution for Injection

1. PRODUCT NAME

Glyceryl TRINITRATE Medicianz, Solution for injection, 50 mg/50 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of Glyceryl TRINITRATE Medicianz for Injection contains 5 milligrams of Glyceryl trinitrate, absolute ethanol and propylene glycol in Water for Injections. Glyceryl TRINITRATE Medicianz for Injection is available in ampoules in 50 mg Glyceryl trinitrate/50 mL.

Excipient(s) with known effect

- Propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glyceryl TRINITRATE Medicianz is indicated as follows:

1. Acute myocardial infarction with or without left ventricular failure.
2. Left heart failure associated with subacute and acute pulmonary oedema.
3. To reduce ventricular ectopic activity following myocardial infarction.
4. To reverse symptomatic coronary artery spasm following provocative testing in the diagnosis of variant angina.
5. Control of hypertension during surgical cardiovascular procedures and in the production of controlled hypotension during such procedures.
6. Treatment of angina pectoris in patients who have not responded to recommended doses of organic nitrates and/or a beta blocker.

4.2 Dose and method of administration

Dosage

Dosage is affected by the type of infusion set used (see below). Dosage recommendations represented as microgram Glyceryl trinitrate per minute can only be offered as a starting infusion rate. The correct dose for individual patients will be determined by the response to therapy. All patients should be on continuous cardiovascular monitoring during infusion therapy.

When non-absorbing tubing is used the dosage for Glyceryl TRINITRATE Medicianz for Injection infusion solution should be initially 5 microgram/minute delivered through an infusion pump capable of exact and constant medicine delivery. Increments should be cautious and adjusted to the clinical situation. Initially titration should be in 5 microgram/minute increments with increases each 3-5 minutes until some response is noted.

If there is no response at 20 microgram/minute, larger increments may be used, but once a blood pressure response is observed the increment should be reduced in magnitude and with longer intervals.

There is no fixed dose of Glyceryl TRINITRATE Medicianz for Injection. Each patient must be titrated to his/her individual needs. Continuous monitoring of physiological parameters (eg blood pressure, heart rate, and pulmonary capillary wedge pressure) must be performed to achieve the correct dose. Maintenance of adequate systemic blood pressure and coronary perfusion is essential.

The maximum dose is 8 (-10) mg per hour of Glyceryl trinitrate.

Method of Administration

ADMINISTRATION BY SMALL VOLUME INFUSION SYSTEMS
Glyceryl TRINITRATE Medicianz 50mg/50mL concentrated solution may be administered UNDILUTED by slow intravenous infusion using a syringe driver or small volume infusion pump ONLY.

Prior to activating the infusion pump, carefully check that the appropriate infusion rate has been set. During Glyceryl trinitrate administration there should be close haemodynamic monitoring of the patient.

ADMINISTRATION BY LARGE VOLUME INFUSION
Glyceryl TRINITRATE Medicianz 50mg/50mL concentrated solution may be administered by large volume infusion when DILUTED in 5% glucose or 0.9% sodium chloride prior to its infusion.

Initial dilution: To obtain a final concentration of 100 micrograms/mL Glyceryl trinitrate, aseptically transfer the contents of one Glyceryl TRINITRATE Medicianz 50 mg/50 mL ampoule into 450 mL of either 5% dextrose or 0.9% sodium chloride. Invert several times following admixture to ensure uniform dilution of Glyceryl trinitrate.

Maintenance dilution: It is important to consider the fluid requirements of the patient as well as

the expected duration of infusion in selecting the appropriate dilution of Glyceryl TRINITRATE Medicianz Injection.

After the initial dosage titration, the concentration of the admixture solution may be increased, if necessary, to limit fluids given to the patient. The Glyceryl trinitrate should not exceed 400 micrograms/mL.

If the Glyceryl trinitrate concentration is adjusted, it is imperative to flush or replace the infusion set before a new concentration is utilised. Depending on the infusion set used and the flow rate, it could take from 1 to 2 minutes to 3 hours for the new concentration to reach the patients if the infusion set is not flushed or replaced.

To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the solution. Infusion should be completed within 24 hours and any residue discarded.

Due to the problem of Glyceryl trinitrate absorption by polyvinyl chloride (PVC) tubing, Glyceryl trinitrate Infusion should be used with the least absorptive infusion tubing (i.e. non-PVC tubing) available. Administration sets which incorporate polyethylene are recommended.

Dosage is affected by the type of containers and administration sets used (see **Section 4.4 Special warnings and precautions for use**).

Although the usual starting adult dose range reported in clinical studies was 25 micrograms/min or more, these studies used PVC ADMINISTRATION SETS. DOSES NEED TO BE REDUCED IF NON-ABSORBING TUBING IS USED.

Dosage Adjustments

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (eg angina patients without other complications) may be hypersensitive to the effects of Glyceryl trinitrate and may respond fully to doses as small as 5 micrograms/min. These patients require especially careful titration and monitoring.

The posology of intravenous Glyceryl trinitrate should be adjusted to achieve the desired clinical response. Additional dose adjustments in patients with severe hepatic insufficiency or severe renal failure may be necessary and require additional monitoring.

Paediatric Population*:*

Not recommended for use in children.

Elderly Population:

See **Section 4.4 Special warnings and precautions for use**.

4.3 Contraindications

Glyceryl trinitrate is contraindicated in the following cases:

- Hypersensitivity to Glyceryl trinitrate and nitrates, or any of the excipients of this product.
- Hypotensive shock, severe anemia, cerebral hemorrhage, increased intracranial pressure, arterial hypoxemia, uncorrected hypovolemia and angina caused by hypertrophic obstructive cardiomyopathy.
- Acute circulatory failure (shock, circulatory collapse).
- Pronounced hypotension (systolic blood pressure < 90 mmHg). Cardiogenic shock, in so far as sufficiently high left ventricular end-diastolic pressure is not ensured by intra-aortal counterpulsation or positive inotropic medicines.
- Concomitant administration of a soluble guanylate cyclase (GC) stimulator, such as riociguat due to potentiation of hypotensive effects.
- Constrictive pericarditis and pericardial tamponade.

For acute myocardial infarction with low filling pressures, Glyceryl trinitrate should only be used with caution. Administration of Glyceryl trinitrate for acute myocardial infarction should only be performed under a doctor's supervision. A drop in systolic pressure below 90 mmHg should be avoided.

Concomitant administration of phosphodiesterase inhibitors used for the treatment of erectile dysfunction or pulmonary arterial hypertension such as sildenafil and Glyceryl TRINITRATE Medicianz for Injection is contraindicated due to an increase in the hypotensive effect of Glyceryl TRINITRATE Medicianz for Injection. This may result in severe side effects such as syncope or myocardial infarction.

4.4 Special warnings and precautions for use

Warning: Intravenous Giving Sets

- Glyceryl trinitrate is readily absorbed onto certain plastics. The dilution and storage of Glyceryl trinitrate for i.v. infusion should only be in glass. Plastic parenteral solution containers should not be used.
- Some filters absorb Glyceryl trinitrate. Filters in the i.v. giving set should be avoided.

Adsorption is substantially less (5% or less) where polyethylene or polypropylene sets are utilised. Highest adsorption rates occur when the flow rates are low, Glyceryl trinitrate concentrations are high, and the tubing is long.

However, because the amount of vascular binding varies inter-individually there is no correlation between plasma level and the effect. Higher plasma levels can be measured in arterial than in venous blood. In patients showing a greater response to nitrates, lower plasma levels indicate a high vascular binding. Therefore, the dose is always chosen individually according to the prevailing haemodynamic parameters.

It is recommended that:

- That low adsorptive giving sets are utilised where possible.
- That dosage is individually titrated to patient needs by careful attention to dosage rates and response as documented by physiological monitoring.

In summary, the ideal giving set should be as short as possible, not include a blood filter or burette chamber and, if possible, be of different material than PVC.

Use with caution in the following circumstances

Severe hypotension may occur with even small doses of nitroglycerin.

Glyceryl trinitrate should only be used in acute myocardial infarction for treating definite left ventricular failure. Careful haemodynamic monitoring must be observed during infusion of Glyceryl trinitrate in patients with acute myocardial infarction to avoid a sudden fall in arterial blood pressure and reflex tachycardia, which might reduce coronary perfusion and increase myocardial oxygen demand, thereby extending the area of ischaemic tissue injury.

Dosage must be carefully titrated to avoid the significant risk of a precipitous fall in blood pressure, particularly in patients with severe coronary or cerebral arteriosclerosis. Profound hypotension and bradycardia have been reported with sublingual, topical and intravenous Glyceryl trinitrate.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of the possible deleterious effects on the brain, heart, liver and kidney from impaired perfusion and the attendant risk of ischaemia, thrombosis and altered functions of these organs. Paradoxical bradycardia and increased angina pectoris may accompany Glyceryl trinitrate induced hypotension. Patients with low pulmonary wedge pressure are especially sensitive to the hypotensive effects of Glyceryl trinitrate. As a fall in pulmonary capillary wedge pressure precedes the onset of arterial hypotension, the pulmonary capillary wedge pressure is a useful guide to safe titration of Glyceryl trinitrate dosage.

Glyceryl trinitrate should be used with caution in patients predisposed to closed angle glaucoma.

Administration of vasodilators to hypertensive patients has been suspected of causing acute blindness. Long term or repeated administration of organic nitrates may induce tolerance or cross-tolerance to Glyceryl trinitrate or other organic nitrates. Larger doses of Glyceryl trinitrate may be required with chronic sublingual administration or when a patient is receiving oral nitrate vasodilators. Although clinical tolerance has not been observed during intravenous infusion of Glyceryl trinitrate, the possibility of this occurring should be kept in mind.

Nitrate dependence is a potentially serious problem. Death, myocardial infarction, coronary spasm and chest pain syndromes have been documented in industrial workers who leave the work environment for several days after exposure to Glyceryl trinitrate and nitroglycol. There is some clinical evidence of nitrate dependence in patients with both angina and congestive heart failure.

Although withdrawal syndromes have not been reported to occur following intravenous infusion of Glyceryl trinitrate for up to 9 days, it may be necessary to carefully taper therapy in patients with proven coronary arteriosclerosis who have received prolonged high dose infusions of the drug.

Arterial oxygen tension decreases after administration of Glyceryl trinitrate in normal subjects and in patients with coronary artery disease. Hypoxaemia occurs as a result of increased pulmonary ventilation-perfusion mismatch, but the clinical significance of this effect is dependent on the severity of the underlying pulmonary disease and pre-existing hypoxaemia. Caution should be observed in patients with severe ischaemic heart disease, as a decrease in available oxygen may oppose the antianginal effect of Glyceryl trinitrate. Glyceryl trinitrate may worsen hypoxaemia in patients with pulmonary disease or cor pulmonale.

Methaemoglobinaemia has been reported in association with Glyceryl trinitrate therapy. Methaemoglobinaemia may be clinically significant, especially in the presence of methaemoglobin reductase deficiencies or in congenital M haemoglobulin variants.

Glyceryl trinitrate should be used with caution in patients with malnutrition, hypothermia, hypothyroidism or hyperthyroidism.

Glyceryl trinitrate concentrate contains propylene glycol which can lead to hyperosmolality, haemolysis and lactic acidosis.

Use in hepatic/renal impairment

Glyceryl trinitrate should be used with caution in patients with severe liver or renal disease.

Use in the elderly

Elderly patients may be particularly sensitive to the side effects of Glyceryl trinitrate. If side effects occur, the dose should be reduced.

Paediatric use

The use of Glyceryl trinitrate in children is not recommended, as its safety and effectiveness in children 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.

Serum triglyceride assays that rely on glycerol oxidase may give falsely elevated serum triglyceride concentrations, as a result of the propylene glycol content of this product.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use with alcohol and levodopa may cause hypotension due to an enhanced vasodilatory effect of Glyceryl trinitrate. The risk of syncope may also be enhanced.

Information on potential interaction with other medicines is poorly documented. Caution

should be observed if other medicines are given concomitantly during infusion of Glyceryl trinitrate as an interaction may adversely affect the haemodynamic response to the drug. Careful haemodynamic monitoring is essential.

Infusion of Glyceryl trinitrate increases the duration of pancuronium induced neuromuscular blockade. This clinical observation has been supported by studies in the cat, however, Glyceryl trinitrate did not prolong neuromuscular blockade induced by succinylcholine and d-tubocurarine. The mechanism of the interaction between Glyceryl trinitrate and pancuronium is unknown.

Caution should be observed when morphine and Glyceryl trinitrate are administered concurrently. One patient who received four 3 milligram doses of intravenous morphine sulphate during a 24 hour period with intravenous Glyceryl trinitrate, became unarousable, eventually responding to nalorphine. The possibility that intravenous Glyceryl trinitrate slows morphine metabolism in this patient has been suggested.

As ergot alkaloids may precipitate angina, patients being treated with Glyceryl trinitrate for angina should avoid ergot alkaloids if at all possible.

Tricyclic antidepressants, anticholinergic agents, vasodilators such as hydralazine, minoxidil, prozosin and antihypertensive agents (including calcium antagonists, beta-blockers, diuretics and ACE inhibitors), major tranquillisers and opioid analgesics may potentiate the hypotensive effect of Glyceryl trinitrate. Caution should therefore be observed when any of these medicines are given concomitantly with Glyceryl trinitrate. Dosage adjustment may be required in these circumstances.

Glyceryl trinitrate may potentiate the action of other hypotensive drugs, and the hypotensive and anticholinergic effects of tricyclic anti-depressants.

Concomitant use of posphodiesterase inhibitors used for the treatment of erectile dysfunction or pulmonary arterial hypertension, such as sildenafil with Glyceryl trinitrate is contraindicated. A severe and possibly dangerous fall in blood pressure may occur. This can result in collapse, unconsciousness and may be fatal. If a patient treated with these drugs for erectile dysfunction or pulmonary arterial hypertension needs a rapidly effective nitrate, he/she should be closely monitored (see **Section 4.3 Contraindications**).

Concomitant use of a soluble guanylate cyclase (GC) stimulator, such as riociguat with Glyceryl trinitrate is contraindicated due to potentiation of hypotensive effect (see **Section 4.3 Contraindications**)

Aspirin and other non-steroidal anti-inflammatory drugs may diminish the therapeutic response to Glyceryl trinitrate.

The effects of noradrenaline may be decreased when it is used concurrently with Glyceryl trinitrate.

Concurrent use of sympathomimetics may reduce the antianginal effects of nitrates. Nitrates may counteract the pressor effects of sympathomimetics, possibly resulting in hypotension.

The anticoagulant effect of heparin may be decreased in patients receiving intravenous Glyceryl trinitrate. The solvent, propylene glycol, may be responsible for this effect. Patients should therefore be monitored to avoid inadequate anticoagulation. If intravenous Glyceryl trinitrate therapy is discontinued in patients receiving heparin, a reduction in heparin dosage

may be necessary.

4.6 Fertility, pregnancy and lactation

Fertility

Lower doses of Glyceryl trinitrate did not affect fertility in rats, but doses up to 230 milligrams/kg/day caused moderate to severe testicular degeneration and/or atrophy, with severe to complete aspermatogenesis.

Pregnancy

Pregnancy Category: B2.

Animal reproduction studies have not been conducted with Glyceryl trinitrate. It is also not known whether Glyceryl trinitrate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Glyceryl trinitrate should be given to a pregnant woman only if clearly needed.

Lactation

It is not known whether Glyceryl trinitrate or its metabolites are excreted into breast milk. Caution should be exercised if there is a need to administer Glyceryl trinitrate to a breast-feeding woman.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 Undesirable effects

Adverse reactions to Glyceryl trinitrate are generally dose-related; almost all the reported reactions are the result of its vasodilatory activity.

The most frequent adverse reaction in patients treated with Glyceryl trinitrate is headache, which occurs in approximately 2% of patients, and is dose dependent. Other adverse reactions, occurring in less than 1% of patients, are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain. Hypotension and bradycardia (see **Section 4.4 Special warnings and precautions for use**) have been reported with intravenous Glyceryl trinitrate. Decreased arterial oxygen tension has also been reported.

Severe arterial hypotension with bradycardia has been reported in patients who received intravenous Glyceryl trinitrate within the first 24 hours after myocardial infarction; these effects were reversed by discontinuing the drug and elevating the lower extremities.

Adverse reactions to the solvents in Glyceryl TRINITRATE Medicianz Injection may occur.

Alcohol intoxication has been reported in patients receiving high dose intravenous infusions. The propylene glycol content may lead to hyperosmolarity.

The following additional adverse reactions have been reported with the oral and/or topical use of Glyceryl trinitrate: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis, hypertension, methaemoglobinaemia, postural hypotension and syncope on assuming upright posture, withdrawal syndrome, e.g. increased frequency of angina attack, blurred vision, cyanosis (rarely), fainting/lightheadedness and anaphylaxis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions**https://pophealth.my.site.com/carmreportnz/s/**.

4.9 Overdose

Symptoms

Glyceryl trinitrate is well tolerated and has a very wide safety margin. In the event of overdose a higher incidence of the known undesirable effects may occur, such as headaches, drop in blood pressure with orthostatic regulatory disorders and reflex tachycardia. At higher doses (> 20mcg/kg body weight) anticipate formation of methaemoglobin, cyanosis and tachypnoea resulting from nitrate ions formed during metabolism (degradation).

Treatment

Patients should be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilises. Since the duration of the haemodynamic effects following Glyceryl trinitrate administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (eg dopamine, methoxamine or phenylephrine) should be considered.

Methaemoglobinaemia may be treated with intravenous methylene blue at a dose of 1 to 2 milligrams/kg. Oxygen and assisted respiration may be required. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Glyceryl trinitrate, an organic nitrate, is a vasodilator. Its principal pharmacological action is the relaxation of vascular smooth muscle. Glyceryl trinitrate produces a dose related dilation

of both arterial and venous beds. Venous dilation predominates over dilation of the arterioles. 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 and pulmonary capillary wedge pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load). Glyceryl trinitrate also dilates the coronary arteries, although this effect is short lived.

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.

Therapeutic doses of intravenous Glyceryl trinitrate 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 an increased heart rate decreases diastolic filling time.

Glyceryl trinitrate reduces elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance. 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. Alternatively, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced by intravenous Glyceryl trinitrate.

5.2 Pharmacokinetic properties

Distribution

Glyceryl trinitrate is widely distributed in the body, with an apparent volume of distribution of 200 litres in adult male subjects. 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 vasodilator effect).

Metabolism

Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly hydrolysed in the liver by glutathione-organic nitrate reductase to dinitrates and mononitrates. It is also metabolised by enzymes in the blood.

Glyceryl trinitrate has a short half-life, estimated at 1 to 4 minutes. This results in a low plasma concentration after intravenous infusion. A therapeutic effect is apparent within 1 to 2 minutes of intravenous administration, while the duration of action following a single intravenous dose of Glyceryl trinitrate is about 3 to 5 minutes.

At plasma concentrations of between 50 and 500 nanograms/mL, Glyceryl trinitrate is approximately 60% bound to plasma proteins, while its metabolites, 1,3-glyceryl dinitrate and 1,2-glyceryl dinitrate, are approximately 60% and 30% bound respectively. The activity and half-life of the dinitrate metabolites are not well characterised. However, in animal studies, the vasodilator effects of Glyceryl trinitrate were 10 to 14 times greater than those of its dinitrate metabolites. Glyceryl mononitrate, the principal metabolite, is inactive. The dinitrates are

metabolised further to inactive mononitrates, and are metabolised ultimately to glycerol and carbon dioxide.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Glyceryl trinitrate, given in the diet to rats at doses up to 1% caused an increase in the incidence of hepatic cholangiofibrosis, hepatocellular carcinomas and/or neoplastic nodules and Leydig cell tumours in the testis.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- Dextrose monohydrate
- Propylene glycol
- Water for injection

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Glyceryl TRINITRATE Medicianz 50 mL glass vials are supplied in boxes each containing 1 x 50mL vials.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

NA

Summary table of changes

Section changed	Summary of new information