

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Glyceryl Trinitrate 5 mg/ml Sterile Concentrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5 mg glyceryl trinitrate. Each 5 ml and 10 ml ampoules contains 25 mg and 50 mg glyceryl trinitrate respectively.

Excipients with known effect:

Each 5 ml ampoule contains 2639.2 mg ethanol and 223.6 mg propylene glycol.

Each 10 ml ampoule contains 5278.4 mg ethanol and 447.2 mg propylene glycol.

Each ampoule contains 527.84 mg/ml of ethanol (52.78% w/v) and 44.72 mg/ml of propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (Sterile Concentrate).

Clear, practically colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Surgery: Glyceryl trinitrate is indicated for the prompt control of hypertension during cardiac surgery.

It may also be used for the production and maintenance of controlled hypotension during surgical procedures.

Glyceryl trinitrate may be given for the control of myocardial ischaemia both during and following cardiovascular surgery.

Unresponsive Congestive Cardiac Failure Secondary to Acute Myocardial Infarction:

Glyceryl trinitrate may be used in patients presenting with unresponsive congestive heart failure secondary to acute myocardial infarction.

Unstable Angina: Glyceryl trinitrate infusion may be used to reduce myocardial oxygen demand in proportion to the reduction in pre- and after-load. It may be indicated for the control of anginal episodes in patients with unstable angina who do not respond to standard treatment and/or beta-blockers.

4.2 Posology and method of administration

Posology

The posology of glyceryl trinitrate i.v. should be adjusted to achieve the desired clinical response.

Adults

The recommended dose range is 10-200 microgram/min, although larger doses than this have been used. During some surgical procedures, doses of up to 400 microgram/min may be required.

Elderly population

There is no evidence that a posology adjustment is required in the elderly.

Paediatric population

The use of glyceryl trinitrate in children is not recommended, as the safety and effectiveness of glyceryl trinitrate in children has not been established.

Hepatic / Renal Impairment

Additional dose adjustments in patients with severe hepatic insufficiency or severe renal failure may be necessary and require additional monitoring.

Surgery

For the control of hypertensive episodes or to produce hypotension during surgery the recommended starting dose is 25 microgram/min increasing in steps of 25 microgram/min at 5 minute intervals until the desired drop in blood pressure is achieved. Although most patients respond to doses between 10-200 microgram/min, doses up to 400 microgram/min have been required during some surgical procedures. In the treatment of perioperative myocardial ischaemia, the recommended starting dose is 15-20 microgram/min increasing in steps of 10-15 microgram/min until the desired effect is achieved.

Unresponsive Congestive Cardiac Failure Secondary to Acute Myocardial Infarction

The recommended starting dose is 20-25 microgram/min which can be decreased to 10 microgram/min or increased in steps of 20-25 microgram/min at 15-30 minute intervals until the desired effect is achieved.

Unstable Angina

The recommended starting dose is 10 microgram/min increasing in steps of 5-10 microgram/min at approximately 30 minute intervals according to the needs of the patient.

Method of administration

Not to be given by bolus injection.

Intravenous Infusion: Glyceryl Trinitrate Sterile Concentrate is a concentrated, potent drug which must be diluted prior to its infusion. .

During administration of glyceryl trinitrate there should be close haemodynamic monitoring of the patient.

4.3 Contraindications

To those who have or are:

1. Hypersensitive to glyceryl trinitrate and nitrates or to any of the excipients listed in section 6.1
2. Hypotensive shock or uncorrected hypovolaemia
3. Increased intracranial pressure
4. Constrictive pericarditis and pericardial tamponade

5. Severe anaemia and arterial hypoxaemia
6. Taking sildenafil or other phosphodiesterase inhibitors used for the treatment of erectile dysfunction or pulmonary arterial hypertension (see section 4.5).
7. Cerebral haemorrhage
8. Angina caused by hypertrophic obstructive cardiomyopathy
9. Concomitant administration of a soluble guanylate cyclase (GC) stimulator, such as riociguat due to potentiation of hypotensive effects (see section 4.5).

4.4 Special warnings and precautions for use

Not to be given by bolus injection.

Glyceryl Trinitrate Sterile Concentrate should not be administered to patients known to be hypersensitive to organic nitrates, nor should it be given to patients with uncorrected hypovolaemia, severe anaemia or cerebral haemorrhage or hypotension.

Glyceryl trinitrate should be used with caution in patients presenting with malnutrition, hypothyroidism, severe hypothermia, or severe impairment of hepatic and/or renal function.

Severe hypotension may occur with even small doses of Glyceryl trinitrate.

Evidence is not available to demonstrate the safety of glyceryl trinitrate for intracoronary injection.

Caution should be exercised in patients with arterial hypoxaemia due to severe anaemia (including G6PD deficiency induced forms). Similarly, caution in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure.

Glyceryl Trinitrate Sterile Concentrate should be used with caution in patients predisposed to closed angle glaucoma.

Excipient Information

Glyceryl Trinitrate Sterile Concentrate contains propylene glycol and ethanol (see section 2).

Each 5 ml ampoule of Glyceryl Trinitrate Sterile Concentrate contains 2639.2 mg of anhydrous ethanol, which is equivalent to less than 66 ml of beer or 27 ml of wine. Each 10 ml ampoule of Glyceryl Trinitrate Concentrate contains 5278.4 mg of anhydrous ethanol which is equivalent to less than 132 ml of beer or 53 ml of wine. Administration of a 10 ml ampoule of Glyceryl Trinitrate Sterile Concentrate over 125 min (i.e. at an infusion rate of 400 microgram/min that is higher than normally recommended but may be necessary during some surgical procedures, see section 4.2) to an adult weighing 70 kg would result in exposure to 75.4 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 12.6 mg/100 ml. For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, particularly in young children with low or immature metabolic capacity. The ethanol content in this preparation is likely to affect children and neonates. These effects may include somnolence and changes in behaviour. The ethanol may also affect their ability to concentrate and take part in physical activities.

The ethanol content in this medicinal product should be carefully considered in the following patient groups who may be at higher risk of ethanol-related adverse effects:

- Pregnant or breast-feeding women (see section 4.6)
- Patients with liver disease
- Patients with epilepsy

- Patients suffering from alcoholism.

The amount of ethanol in this medicinal product may impair the ability to drive or use machines (see section 4.7). The amount of ethanol in this medicinal product may alter the effects of other medicines. The effects of ethanol may be reduced when the dose is administered more slowly using an infusion rate of 10-200 microgram/min (see section 4.2).

A 24 hour infusion of Glyceryl Trinitrate Sterile Concentrate at the maximum recommended infusion rate of 200 microgram/min administered to an adult weighing 70 kg would result in a propylene glycol exposure of 36.8 mg/kg/day. A propylene glycol exposure of ≥ 50 mg/kg/day might result in case of a 24 hour infusion at an infusion rate that is higher than the maximum recommended infusion rate (e.g. 300 microgram/min) or administration to a lower weight patient (e.g. 50 kg adult). Medical monitoring, including measurement of the osmolar and/or anion gap, is required in patients with impaired renal and/or hepatic function who receive ≥ 50 mg/kg/day of propylene glycol. Various adverse effects attributed to propylene glycol have been reported, such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. Prolonged administration of propylene glycol-containing products, as well as co-administration with other substrates of alcohol dehydrogenase (e.g. ethanol), increase the risk of propylene glycol accumulation and toxicity, especially in patients with liver or kidney impairment. Propylene glycol doses of ≥ 1 mg/kg/day may induce serious adverse effects in neonates, while doses of ≥ 50 mg/kg/day may induce adverse effects in children less than 5 years old. Administration of ≥ 50 mg/kg/day of propylene glycol to pregnant or lactating women should only be considered on a case by case basis (see section 4.6).

Glyceryl Trinitrate Sterile Concentrate contains propylene glycol which can lead to hyperosmolality, haemolysis, and lactic acidosis (see section 6.1). It is recommended that the use of this preparation be restricted to not more than three successive days.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-depressants: Glyceryl trinitrate may potentiate the hypotensive and anticholinergic effects of tricyclic anti-depressants.

Phosphodiesterase inhibitors: Phosphodiesterase inhibitors (such as sildenafil) have known effects on the nitric oxide/cGMP pathway, and have been shown to potentiate the hypotensive effects of nitrates such as Glyceryl Trinitrate Sterile Concentrate. A severe and possibly dangerous fall in blood pressure may occur. This can result in collapse, unconsciousness and may be fatal. Such use, therefore, is contraindicated. 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).

Analgesics: Glyceryl trinitrate may slow the metabolism of morphine-like analgesics.

Other hypotensive drugs: Glyceryl trinitrate may potentiate the action of other hypotensive drugs.

Concurrent intake of drugs with blood pressure lowering properties, e.g. vasodilators etc. and/or alcohol may potentiate the hypotensive effect of Glyceryl trinitrate. This might also occur with neuroleptics.

ACE-inhibitors:	Concurrent intake of ACE-inhibitors may potentiate the hypotensive effect of Glyceryl trinitrate.
Diuretics:	Concurrent intake of diuretics may potentiate the hypotensive effect of Glyceryl trinitrate.
Dihydroergotamine:	Reports suggest that, when administered concomitantly, Glyceryl trinitrate may increase the blood level of dihydroergotamine and its effect. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonises the effect of nitroglycerin and may lead to coronary vasoconstriction.
Acetylsalicylic acid:	Concurrent administration of Glyceryl trinitrate with acetylsalicylic acid may potentiate the blood pressure lowering effects of glyceryl trinitrate.
Heparin	Glyceryl trinitrate may interfere with the anticoagulant effect of heparin and can induce heparin resistance.
Soluble guanylate cyclase (GC) stimulators:	Concurrent use of Glyceryl trinitrate and a soluble guanylate cyclase stimulator such as riociguat is contraindicated due to potentiation of hypotensive effects (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of glyceryl trinitrate during pregnancy has not been demonstrated and therefore it should not be used unless considered essential by the physician.

The ethanol and propylene glycol content of Glyceryl Trinitrate Sterile Concentrate should be taken into account for pregnant women (see section 4.4). Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it may reach the foetus. Administration of ≥ 50 mg/kg/day propylene glycol to pregnant women should only be considered on a case by case basis.

Breast-feeding

The safety of glyceryl trinitrate during lactation has not been demonstrated and therefore it should not be used unless considered essential by the physician.

The ethanol and propylene glycol content of Glyceryl Trinitrate Sterile Concentrate should be taken into account in women who are breast-feeding (see section 4.4). Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it has been found in milk and may be orally absorbed by a nursing infant. Administration of ≥ 50 mg/kg/day propylene glycol to lactating women should only be considered on a case by case basis.

4.7 Effects on ability to drive and use machines

There is no information available regarding the effects of glyceryl trinitrate on the ability to drive and operate machinery.

If dizziness, weakness or cardiac symptoms are experienced, the patient should be advised not to drive or use machinery.

The amount of ethanol in Glyceryl Trinitrate Sterile Concentrate may impair the ability to drive or use machines (see section 4.4).

4.8 Undesirable effects

In terms of frequency of classification of adverse effects the following convention was used: Very common $\geq 1/10$, common $\geq 1/100$ and $<1/10$, uncommon $\geq 1/1000$ and $<1/100$, rare $\geq 1/10,000$ and $<1/1000$, very rare $<1/10,000$. Not known: cannot be estimated from the data available.

Adverse reactions to organic nitrates which have been reported include:

Psychiatric disorders:	
Not known	Anxiety, restlessness
Nervous system disorders	
Not known	Headache, dizziness, syncope
Cardiac disorders	
Rare	Bradycardia (paradoxical)
Not known	Tachycardia, palpitations
Vascular disorders:	
Not known	Hypotension, flushing
Gastrointestinal disorders:	
Not known	Nausea, retching, abdominal pain
Skin and subcutaneous tissue disorders:	
Not known	Hyperhidrosis
Musculoskeletal and connective tissue disorders:	
Not known	Muscle twitching
General disorders and administration site conditions	
Not known	Chest discomfort

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Signs and Symptoms

Overdosage usually results in hypotension and tachycardia.

Vomiting, restlessness, syncope, cyanosis, coldness of the skin, impairment of respiration, bradycardia, psychosis and methaemoglobinaemia may also occur.

Treatment

The symptoms may be readily reversed by discontinuing treatment; if hypotension persists, raising the foot of the bed or compression bandaging of the patients' legs and the use of vasoconstrictors such as intravenous methoxamine or phenylephrine are recommended.

Methaemoglobinaemia should be treated by intravenous methylene blue. Oxygen and assisted respiration may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Organic nitrates, ATC code: C01DA02

Glyceryl trinitrate, an organic nitrate, is a vasodilator. The principal pharmacological action of glyceryl trinitrate is the relaxation of vascular smooth muscle. Glyceryl trinitrate produces, in a dose-related manner, dilation of both arterial and venous beds. Dilatation 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 (pre-load).

Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load). Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension time index and stroke work index) is decreased by both 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 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 slightly 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 and is rapidly metabolised to dinitrates and mononitrates, with a short half-life estimated at 1-4 minutes. This results in a low plasma concentration after intravenous infusion. Glyceryl trinitrate is also well absorbed from the gastro-intestinal tract, but it is not known if it is distributed into milk.

At plasma concentrations of between 50 and 500 ng/ml, the binding of glyceryl trinitrate to plasma proteins is approximately 60% and 30% respectively. The plasma half-life of glyceryl trinitrate is about 1-4 minutes. Glyceryl mononitrate which is inactive, is the principal metabolite.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Propylene glycol (E1520)
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Glyceryl Trinitrate Sterile Concentrate is incompatible with polyvinylchloride (PVC) and severe losses of glyceryl trinitrate (over 40%) may occur if this material is used. Contact with polyvinylchloride bags should be avoided. Polyurethane also induces a loss of the active ingredient. No other drug should be admixed with this medicinal product.

6.3 Shelf life

As packaged for sale: 3 years.

Once opened: see section 6.4.

6.4 Special precautions for storage

Prior to first use: Do not store above 25°C. Keep the ampoules in the outer carton in order to protect from light.

Open ampoules of glyceryl trinitrate should be used immediately and any unused portion discarded.

In use:

Following dilution in either 0.9% sodium chloride or 5% dextrose injection solutions in glass containers, chemical and physical in-use stability has been demonstrated for 7 days at both 18°C and 4°C.

Following dilution in 5% dextrose solution in polycarbonate or polypropylene syringes at concentrations of 1 mg or 4 mg per ml protected from light, chemical and physical in-use stability has been demonstrated for 72 hours at room temperature.

However, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use if the solution is discoloured.

6.5 Nature and contents of container

Clear, Type I glass ampoules – 5 ml and 10 ml in packs of 5 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Glyceryl Trinitrate Sterile Concentrate is a concentrated, potent drug which must be diluted in Dextrose (5%) Injection BP or Sodium Chloride (0.9%) Injection BP prior to its infusion.

Glyceryl Trinitrate Sterile Concentrate must be mixed under aseptic conditions immediately after opening.

Example of admixture preparation.

To obtain an admixture of GTN at a concentration of 100 microgram/ml add 10 ml (containing 50 mg glyceryl trinitrate) to 490 ml of infusion vehicle to give a final volume of 500 ml.

A dosage of 100 microgram/min can be obtained by giving 60 ml of the admixture per hour. This is equivalent to a drip rate of 20 standard drops per minute or 60 microdrops per minute. At this drop rate the mixture provides enough solution for an infusion time of 8 hours 20 minutes.

See section 4.2 for dosage instructions.

Compatible with commonly employed infusion solutions, Sodium Chloride (0.9%) Injection and Dextrose (5%) Injection.

Compatible with glass infusion bottles and rigid infusion packs made of polyethylene.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PA 0822/204/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 1987

Date of latest renewal: 1st October 2007

10. DATE OF REVISION OF THE TEXT

10/2024

Ref: gxGY 7_0