Glyceryl Trinitrate

Glyceryl trinitrate

5 mg/ml Sterile Concentrate

Reference market: UK

AfME Markets using same as LPD: Saudi Arabia

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 of glyceryl trinitrate. Each 10 ml ampoule contains 50 mg glyceryl trinitrate.

Excipients with known effect:
Glyceryl Trinitrate 5 mg/ml Sterile Concentrate contains 5278.4 mg anhydrous ethanol in each 10 ml ampoule which is equivalent to 527.84 mg/ml (52.78% w/v).
This product also contains 447.2 mg propylene glycol in each 10 ml ampoule which is equivalent to 44.72 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, practically colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Surgery: Glyceryl trinitrate is indicated for:
1. the rapid control of hypertension during cardiac surgery.
2. reducing blood pressure and maintaining controlled hypotension during surgical procedures.
3. controlling myocardial ischaemia during and after cardiovascular surgery.

Unresponsive Congestive Heart Failure: Glyceryl trinitrate may be used to treat unresponsive congestive heart failure secondary to acute myocardial infarction.

Unstable Angina: Glyceryl trinitrate may be used to treat unstable angina that is refractory to treatment with beta-blockers and sublingual nitrates.

4.2 Posology and method of administration

Posology

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

Adults

The dose of glyceryl trinitrate should be adjusted to meet the individual needs of the patient. The recommended dose range is 10-200 microgram/min, although up to 400 microgram/min may be necessary during some surgical procedures.

Paediatric population

The use of glyceryl trinitrate in children is not recommended, as the safety and efficacy of glyceryl trinitrate has not yet been established in this population.

Elderly population

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

Hepatic/renal impairment

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

Surgery

A starting dose of 25 microgram/min is recommended for the control of hypertension, or to produce hypotension during surgery. This may be increased by increments of 25 microgram/min at 5 minute intervals until the blood pressure is stabilised. Doses between 10-200 microgram/min are usually sufficient during surgery, although doses of up to 400 microgram/min have been required in some cases. The treatment of perioperative myocardial ischaemia may be started with a dose of 15-20 microgram/min, with subsequent increments of 10-15 microgram/min until the required effect is obtained.

Unresponsive congestive heart failure

The recommended starting dose is 20-25 microgram/min. This may be decreased to 10 microgram/min, or increased in steps of 20-25 microgram/min every 15-30 minutes until the desired effect is achieved.

Unstable angina

An initial dose of 10 microgram/min is recommended with increments of 10 microgram/min being made at approximately 30 minute intervals according to the needs of the patient.

Method of administration

Not to be given by bolus injection.

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.

Prepared admixtures should be given by intravenous infusion or with the aid of a syringe pump to ensure a constant rate of infusion. For an example of an admixture preparation, see section 6.6.

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

For full details it is advisable to consult the following dosage chart.

Infusion Rate	**Dosage (micrograms/min) by concentration of admixture**

(ml/hour or microdrops/min)	**100 micrograms/ml (1 x 10 ml ampoule in 500 ml)**	**200 micrograms/ml (2 x 10 ml ampoules in 500 ml)**	**300 micrograms/ml (3 x 10 ml ampoules in 500 ml)**	**400 micrograms/ml (4 x 10 ml ampoules in 500 ml)**
6	10	20	30	40
12	20	40	60	80
18	30	60	90	120
24	40	80	120	160
30	50	100	150	200
36	60	120	180	240
42	70	140	210	280
48	80	160	240	320
54	90	180	270	360
60	100	200	300	400
66	110	220	330	440
72	120	240	360	480
78	130	260	390	520
84	140	280	420	560
90	150	300	450	600

1 ml = 60 paediatric microdrops = 20 standard drops

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 hypovolaemic
3. Increased intracranial pressure
4. Constrictive pericarditis and pericardial tamponade
5. Severe anaemia and arterial hypoxaemia
6. Taking sildenafil (Viagra) 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 contains propylene glycol which can lead to hyperosmolality, haemolysis, and lactic acidosis. It is recommended that the use of this preparation be restricted to not more than three successive days.

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.

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 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).

4.5 Interaction with other medicinal products and other forms of interaction

Phosphodiesterase inhibitors
Sildenafil (Viagra) and other phosphodiesterase inhibitors has known effects on the nitric oxide/cGMP pathway, and has 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).

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

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).

Heparin
Glyceryl trinitrate may interfere with the anticoagulant effect of heparin and can induce heparin resistance.

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

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. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

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

4.8 Undesirable effects

Undesirable effects frequencies are defined as: very common (≥1/10), common (≥1/100 <1/10), uncommon (≥1/1,000 <1/100), rare (≥1/10,000 <1/1,000) or very rare (<1/10,000), not known (cannot be estimated from the available data).

During administration of Glyceryl Trinitrate Sterile Concentrate, the following undesirable effects may be observed:

Nervous system disorders	
Very common	Headache
Common	Dizziness (including dizziness postural), somnolence
Cardiac disorders	
Common	Tachycardia
Uncommon	Enhanced angina pectoris symptoms
Not known	Bradycardia, palpitations
Vascular disorders:	
Common	Orthostatic hypotension
Uncommon	Circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope).
Not known	Hypotension, flushing
Gastrointestinal disorders:	
Uncommon	Nausea, vomiting
Very rare	Heartburn
Skin and subcutaneous tissue disorders:	
Uncommon	Allergic skin reactions (e.g. rash), allergic contact dermatitis
Not known	Dermatitis exfoliative, rash generalised
General disorders and administration site conditions	
Common	Asthenia
Uncommon	Pruritus, burning, erythema and irritation
Investigations	
Not known	Heart rate increase

Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor, and excessive perspiration.

During treatment with Glyceryl Trinitrate Sterile Concentrate, a temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas. Particularly in patients with coronary artery disease this may lead to a myocardial hypoxia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

To Report side effects

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC) • Call Center: 19999 • E-mail: npc.drug@sfda.gov.sa • Website: https://ade.sfda.gov.sa/

- **Other GCC States**

Please contact the relevant competent authority.

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 patient's 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

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 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

Glyceryl trinitrate is widely distributed in the body with an apparent volume of distribution of 200 L in adult male subjects, 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

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Propylene glycol
Water for injections

6.2 Incompatibilities

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

Glyceryl Trinitrate must not be used after the expiry date which is stated on the ampoule label and carton after 'EXP'. Where only a month and year is stated, the expiry date refers to the last day of that month.

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:

For single use. Discard any unused contents

Do not use if the solution is discoloured.

6.5 Nature and contents of container

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

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.

Admixtures are prepared by replacing a given volume of infusion vehicle with an equal volume of the product to produce the final infusion solution. For admixture storage, refer to section 6.4.

Example of admixture preparation
To obtain an admixture of glyceryl trinitrate at a concentration of 100 micrograms/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 micrograms/min can be obtained by giving 60 ml of this admixture per hour. This is equivalent to a drip rate of 20 standard drops per minute or 60 paediatric microdrops per minute. At this drip rate the mixture provides enough solution for an infusion time of 8 hours 20 minutes.

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.

For single use only.

Keep out of the sight and reach of children.

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

7. MARKETING AUTHORISATION HOLDER

Hospira UK Limited, United Kingdom

Manufacturer
Siegfried Hameln GmbH, Germany

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07-Apr-1998

9. DATE OF REVISION OF THE TEXT

May 2024