GLICE

Glyceryl Trinitrate 1mg/ml Solution for Injection for Infusion

Composition:
Each ml of glyceryl trinitrate solution for injection for infusion:
50 mg diluted glyceryl trinitrate equivalent to glyceryl trinitrate 1 mg

Product Description:
Clear and colorless solution, odorless.
After dilution: Clear, colorless solution, free from foreign particles.

Pharmacodynamics:
Glyceryl trinitrate reduces the tone of vascular smooth muscle. This action is more marked on the venous capacitance vessels than the arterial vessels. There is a reduction in venous return to the heart and a lowering of elevated filling pressure. This lowering of filling pressure reduces the left ventricular end diastolic volume and preload. The net effect is a lowering of myocardial oxygen consumption. Systemic vascular resistance, pulmonary vascular pressure, and arterial pressure are also reduced by glyceryl trinitrate and there is a net reduction in the afterload. By reducing the preload and afterload, glyceryl trinitrate reduces the workload on the heart. Glyceryl trinitrate affects oxygen supply by redistributing blood flow along collateral channels from the epicardial to endocardial regions.

Pharmacokinetics:
Biotransformation
As with all commonly used organic nitrates the metabolic degradation of glyceryl trinitrate occurs via denitration and glucuronidation. The less active metabolites resulting from this biotransformation can be recovered from the urine within 24 hours.

Elimination
Glyceryl trinitrate is eliminated from plasma with a short half-life of about 2–3 minutes. This rapid disappearance from plasma is consistent with the high systemic clearance values for this drug (up to 3,270 l/hour).

Indications:
- Unresponsive congestive heart failure, including that secondary to acute myocardial infarction; acute left-sided heart failure and acute myocardial infarction.
- Refractory unstable angina pectoris and coronary insufficiency, including Prinzmetal's angina.
- Control of hypertensive episodes and/or myocardial ischemia during and after cardiac surgery.
- Induction of controlled hypotension for surgery.

Recommended Dose:
Adults
The dose of glyceryl trinitrate should be adjusted to meet the individual needs of the patient.
The recommended dosage range is 10–200 micrograms/minute but up to 400 micrograms/minute may be necessary during some surgical procedures.

Pediatric population
The safety and efficacy of glyceryl trinitrate has not yet been established in children.

Elderly population
There is no evidence that a dosage adjustment is required in the elderly.

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

Use in surgery
A starting dose of 25 micrograms/minute is recommended for the control of hypertension, or to produce hypotension during surgery. This may be increased by increments of 25 micrograms/minute at 5-minute

intervals until the blood pressure is stabilized. Doses between 10–200 micrograms/minute are usually sufficient during surgery, although doses of up to 400 micrograms/minute have been required in some cases.

Myocardial ischemia
The treatment of perioperative myocardial ischemia may be started with a dose of 15–20 micrograms/minute, with subsequent increments of 10–15 micrograms/minute until the required effect is obtained.

Unresponsive congestive heart failure
The recommended starting dose is 20–25 micrograms/minute. This may be decreased to 10 micrograms/minute or increased in steps of 20–25 micrograms/minute every 15–30 minutes until the desired effect is obtained.

Unstable angina
An initial dose of 10 micrograms/minute is recommended with increments of 10 micrograms/minute being made at approximately 30-minute intervals according to the needs of the patient.

Method of administration
For intravenous use. Glyceryl trinitrate should be administered by means of a microdrip set infusion pump or similar device which permits maintenance of constant infusion rate.
Glyceryl trinitrate can be administered undiluted by slow intravenous infusion using a syringe pump incorporating a glass or rigid plastic syringe. Alternatively, glyceryl trinitrate may be administered intravenously as an admixture using a suitable vehicle such as sodium chloride injection BP or dextrose injection BP. In case of dilution, glyceryl trinitrate must be mixed under aseptic conditions immediately after opening. For further instructions on dilution of the product before administration, see Instruction for use and handling. Prepared admixtures should be given by intravenous infusion or with the aid of a syringe pump to ensure a constant rate of infusion.
During glyceryl trinitrate administration, there should be close hemodynamic monitoring of the patient. The posology of glyceryl trinitrate IV should be adjusted to achieve the desired clinical response.

Example of admixture preparation:
To obtain an admixture of glyceryl trinitrate at a concentration of 100 micrograms/ml, add 50 ml glyceryl trinitrate solution (containing 50 mg glyceryl trinitrate) to 450 ml of infusion vehicle to give a final volume of 500 ml.
A dosage of 100 micrograms/minute can be obtained by giving 60 ml of the admixture per hour.

Contraindications:
Glyceryl trinitrate should not be used in the following cases:
- Hypersensitivity to the active substance, other nitrates, or any of the excipients.
- Severe anemia.
- Severe cerebral hemorrhage.
- Head trauma.
- Uncorrected hypovolemia and hypotensive shock.
- Arterial hypoxemia and angina caused by hypertrophic obstructive cardiomyopathy.
- Constrictive pericarditis.
- Pericardial tamponade.
- Toxic pulmonary edema.
- Acute circulatory failure (shock, collapse).
- Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures).
- During nitrate therapy, phosphodiesterase inhibitors type 5 (PDE5) (e. g. sildenafil, vardenafil, tadalafil) must not be used because PDE5 inhibitors may amplify the vasodilatory effects of glyceryl trinitrate resulting in severe hypotension.
- Conditions associated with an increased intracranial pressure.
- Myocardial insufficiency due to obstruction, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, or constrictive pericarditis.
- During nitrate therapy, the soluble guanylate cyclase stimulator riociguat must not be used.

Warnings and Precautions:
- Caution should be exercised in patients with severe liver or renal disease, hypothermia, hypothyroidism.
- Glyceryl trinitrate should not be given by bolus injection.

- Glyceryl trinitrate must be used only with particular caution and under medical supervision in:
  - low filling pressures e.g., in acute myocardial infarction, impaired left ventricular function (left ventricular failure). Reducing systolic blood pressure below 90 mmHg must be avoided.
  - orthostatic dysfunction.
- The development of tolerance and cross tolerance to other nitro compounds has been described.
- Glyceryl trinitrate must not be used in patients known to be taking phosphodiesterase inhibitor-containing products (e.g., sildenafil, vardenafil, tadalafil) in the intervening 24 hours (48 hours for tadalafil). Patients who receive glyceryl trinitrate solution therapy must be warned not to take phosphodiesterase inhibitor-containing products.
- During treatment with glyceryl trinitrate, alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of glyceryl trinitrate.
- Materials made of polyethylene (PE), polypropylene (PP), or polytetrafluoroethylene (PTFE) have proven to be suitable for infusing glyceryl trinitrate solution. However, infusion material made of polyvinyl chloride (PVC) or polyurethane (PU) has been shown to induce a loss of the active substance due to adsorption. If these materials are used the dose must be adjusted to suit patient's needs.
- The solution contains glucose, this should be taken into account in patients with diabetes mellitus.
- Hypoxemia:
  Caution should be exercised in patients with arterial hypoxemia due to severe anemia (including G6PD deficiency induced forms), because in such patients, the biotransformation of glyceryl trinitrate is reduced.
  Similarly, caution is called for in patients with hypoxemia and ventilation/perfusion imbalance due to lung disease or ischemic heart failure.
  Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia).
  Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated region of the lung. As a potent vasodilator, glyceryl trinitrate could reverse this protective vasoconstriction and thus result in increased perfusion of poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.
- Methemoglobinemia
  Following treatment with glyceryl trinitrate, methemoglobinemia has been reported. Treatment of methemoglobinemia with methylene blue is contraindicated in patients with glucose-6-phosphate deficiency or methemoglobin-reductase deficiency.

Effects on ability to drive and use machines

Glyceryl trinitrate may affect the patient's reactivity to an extent that her/his ability to drive or to operate machinery is impaired. This effect is increased in combination with alcohol.

Interactions with Other Medicaments:

- Concomitant treatment with other vasodilators, calcium channel antagonists, ACE inhibitors, monoamine oxidase inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and neuroleptics, as well as the consumption of alcohol, may potentiate the hypotensive effect of the preparation.
- The blood pressure lowering effect of glyceryl trinitrate will be increased if used together with phosphodiesterase inhibitors (e.g., sildenafil, vardenafil, tadalafil) which are used for erectile dysfunction. This might lead to life threatening cardiovascular complications. Patients who have recently taken phosphodiesterase inhibitors therefore must not be treated with glyceryl trinitrate in the intervening 24 hours (48 hours for tadalafil). Patients who are on nitrate therapy must not use phosphodiesterase inhibitors.
- The use of glyceryl trinitrate with riociguat, a soluble guanylate cyclase stimulator, is contraindicated since concomitant use can cause hypotension.
- Simultaneous intravenous infusion of tissue plasminogen activator (tPA) and glyceryl trinitrate may accelerate plasma clearance of tPA by increasing hepatic blood flow.
- 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 antagonizes the effect of glyceryl trinitrate and may lead to coronary vasoconstriction.
- The use of heparin and glyceryl trinitrate solution can lead to a partial loss of action of heparin when both drugs are given simultaneously by intravenous route.
- Concurrent administration of glyceryl trinitrate with acetyl salicylic acid may potentiate the blood pressure lowering effects of glyceryl trinitrate.
- The nonsteroidal anti-inflammatory drugs except acetyl salicylic acid may diminish the therapeutic response of glyceryl trinitrate.

- Sapropterine (tetrahydrobiopterine, BH4) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterine-containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g., glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), isosorbide 5-mononitrate (5-ISMN), and others).

Pregnancy and Lactation:

Pregnancy

Developmental toxicity studies performed in rats and rabbits using various routes of administration did not reveal any effect on the embryos, fetuses, or the young animals even at toxic doses for the dam.

Lactation

Available evidence is inconclusive or inadequate for determining infant risk when used during breastfeeding. There is data that nitrates are excreted in breast milk and may cause methemoglobinemia in infants. The extent of excretion of nitroglycerin in human breast milk has not been determined. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from glyceryl trinitrate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Reproduction toxicity studies performed in rats and rabbits using various routes of administration did not reveal any effect on mating, fertility, and general reproductive parameters. There is no data available on the effect of glyceryl trinitrate on fertility in humans.

Adverse 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).

During administration of glyceryl trinitrate, the following undesirable effects may be observed.

Nervous system disorde□s	
Very common	Headache
Common	Dizziness (including dizziness postural), somnolence
Cardiac disorders	
Common	Tachycardia
Uncommon	Enhanced angina pectoris symptoms
Not known	Palpitations
Vascular disorders	
Common	Orthostatic hypotension
Uncommon	Circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope)
Not known	Flushing, hypotension
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 generalized
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, 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.

Like other nitrate preparations, glyceryl trinitrate commonly causes dose-dependent headaches due to

cerebral vasodilation. These often regress after a few days despite the maintenance of therapy. If headaches persist during intermittent therapy, they should be treated with mild analgesics. Unresponsive headaches are an indication for reducing the dosage of glyceryl trinitrate or discontinuing treatment.

A slight reflex-induced increase in heart in heart rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

Overdose and Treatment:
Signs and symptoms
Symptoms could include the following:
- Fall in blood pressure ≤90 mmHg.
- Pallor.
- Sweating.
- Weak pulse.
- Reflex tachycardia.
- Collapse.
- Syncope.
- Dizziness postural.
- Headache.
- Asthenia.
- Dizziness.
- Nausea.
- Vomiting.
- Diarrhea.
- Methemoglobinemia has been reported in patients receiving other organic nitrates. During glyceryl trinitrate biotransformation nitrite ions are released, which may induce methemoglobinemia and cyanosis with subsequent tachypnea, anxiety, loss of consciousness, and cardiac arrest. It cannot be excluded that an overdose of glyceryl trinitrate may cause this adverse reaction.
- In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

Treatment
General procedure:
- Stop delivery of the drug.
- General procedures in the event of nitrate-related hypotension:
  The patient should be kept horizontal with the head lowered and legs raised or, if necessary, compression bandaging of the patient's legs.
  Supply oxygen.
  Expand plasma volume.
  For specific shock treatment admit patient to intensive care unit.

Special procedure:
- Raising the blood pressure if the blood pressure is very low.
- Treatment of methemoglobinemia.
  Treatment with intravenous methylene blue
  - Initially 1 to 2 mg/kg, not exceeding 4 mg/kg of a 1% solution over 5 minutes.
  - Repeat dose in 60 minutes if there is no response.
  - Administer oxygen (if necessary).
  - Initiate artificial ventilation.

  Treatment of methemoglobinemia with methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or methemoglobin reductase deficiency.
  Where treatment with methylene blue is contraindicated or is not effective, exchange transfusion and/or transfusion of packed red blood cells is recommended.
- Resuscitation measures
  In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

Pharmaceutical Precautions:
Instruction for use and handling
Glyceryl trinitrate solution for injection for infusion need not be diluted before use but can be diluted by 1:10 up to 1:40 with 5% glucose solution, 5% glucose solution and 0.9% sodium chloride solution, or with 0.9% sodium chloride solution.
The solution, whether or not diluted, should be infused slowly and not given by bolus injection. To ensure a constant infusion rate of glyceryl trinitrate it is recommended that glyceryl trinitrate be administered by means of a syringe pump or polyethylene infusion bag with a counter, or with a glass or rigid polyethylene syringe and polyethylene tubing.

Incompatibilities
Glyceryl trinitrate is incompatible with polyvinylchloride (PVC) and severe losses of glyceryl trinitrate (up to 50%) may occur if this material is used, resulting in a reduction of delivered dose and efficacy. Contact with polyvinylchloride bags should be avoided. Polyurethane (PU) also induces a loss of the active ingredient.
Glyceryl trinitrate is compatible with glass infusion set and with rigid infusion packs made of polyethylene. Glyceryl trinitrate may also be infused slowly using a syringe pump with a glass or plastic syringe.

Shelf-life:
2 years.

Storage condition:
After dilution
In-use stability shows that GLICE solution for injection for infusion diluted with 0.9% sodium chloride and 5% dextrose solution are stable for up to 5 days when stored at 30°C.

STORE AT TEMPERATURES BELOW 30°C.

KEEP OUT OF REACH OF CHILDREN.

ON MEDICAL PRESCRIPTION ONLY.

Presentation and Registration Number:
10 ml solution in 10 ml Type I clear glass ampoules packed in PVC blister. Each box contains 10 ampoules; MALXXXXXXXACZ

Manufactured by:
PT Ferron Par Pharmaceuticals
Kawasan Industri Jababeka I
Jl. Jababeka VI, Blok J3, Cikarang
Kabupaten Bekasi-Indonesia.

For:
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia.

Product Registration Holder:
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Date of Revision: 21 September 2023

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Specification Packaging Material

E-60930-00, LEAFLET GLICE INJECTION MALAYSIA

Author(s):

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Reviewed by:

26.09.2023, Riski Amanda Tambunan, Supervisor Packaging Design,

Approved by:

26.09.2023, RA Officer 03, Regulatory Affairs Officer,

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335 mm

Glice
Glyceryl Trinitrate 1 mg/ml
Solution for Injection for Infusion

Dexa Medica

Composition:
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50 mg diluted glyceryl trinitrate equivalent to Glyceryl trinitrate 1 mg

Product Description:
Clear and colorless solution, odorless.
After dilution: Clear, colorless solution, free from foreign particles

Pharmacodynamics:
Glyceryl trinitrate reduces the tone of vascular smooth muscle. This action is more marked on the venous capacitance vessels than the arterial vessels. There is a reduction in venous return to the heart and a lowering of elevated filling pressure. This lowering of filling pressure reduces the left ventricular end diastolic volume and preload. The net effect is a lowering of myocardial oxygen consumption. Systemic vascular resistance, pulmonary vascular pressure, and arterial pressure are also reduced by glyceryl trinitrate and there is a net reduction in the afterload. By reducing the preload and afterload, glyceryl trinitrate reduces the workload on the heart. Glyceryl trinitrate affects oxygen supply by redistributing blood flow along collateral channels from the epicardial to endocardial regions.

Pharmacokinetics:
Biotransformation
As with all commonly used organic nitrates the metabolic degradation of glyceryl trinitrate occurs via denitration and glucuronidation. The less active metabolites resulting from this biotransformation can be recovered from the urine within 24 hours.

Elimination
Glyceryl trinitrate is eliminated from plasma with a short half-life of about 2–3 minutes. This rapid disappearance from plasma is consistent with the high systemic clearance values for this drug (up to 3,270 l/hour).

Indications:
- Unresponsive congestive heart failure, including that secondary to acute myocardial infarction; acute left-sided heart failure and acute myocardial infarction.
- Refractory unstable angina pectoris and coronary insufficiency, including Prinzmetal's angina.
- Control of hypertensive episodes and/or myocardial ischemia during and after cardiac surgery.
- Induction of controlled hypotension for surgery.

Recommended Dose:
Adults
The dose of glyceryl trinitrate should be adjusted to meet the individual needs of the patient.
The recommended dosage range is 10–200 micrograms/minute but up to 400 micrograms/minute may be necessary during some surgical procedures.

Pediatric population
The safety and efficacy of glyceryl trinitrate has not yet been established in children.

Elderly population
There is no evidence that a dosage adjustment is required in the elderly.

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

Use in surgery
A starting dose of 25 micrograms/minute is recommended for the control of hypertension, or to produce hypotension during surgery. This may be increased by increments of 25 micrograms/minute at 5-minute intervals until the blood pressure is stabilized. Doses between 10–200 micrograms/minute are usually sufficient during surgery, although doses of up to 400 micrograms/minute have been required in some cases.

Myocardial ischemia
The treatment of perioperative myocardial ischemia may be started with a dose of 15–20 micrograms/minute, with subsequent increments of 10–15 micrograms/minute until the required effect is obtained.

Unresponsive congestive heart failure
The recommended starting dose is 20–25 micrograms/minute. This may be decreased to 10 micrograms/minute or increased in steps of 20–25 micrograms/minute every 15–30 minutes until the desired effect is obtained.

Unstable angina
An initial dose of 10 micrograms/minute is recommended with increments of 10 micrograms/minute being made at approximately 30-minute intervals according to the needs of the patient.

Method of administration
For intravenous use. Glyceryl trinitrate should be administered by means of a microdrip set infusion pump or similar device which permits maintenance of constant infusion rate.
Glyceryl trinitrate can be administered undiluted by slow intravenous infusion using a syringe pump incorporating a glass or rigid plastic syringe. Alternatively, glyceryl trinitrate may be administered intravenously as an admixture using a suitable vehicle such as sodium chloride injection BP or dextrose injection BP. In case of dilution, glyceryl trinitrate must be mixed under aseptic conditions immediately after opening. For further instructions on dilution of the product before administration, see Instruction for use and handling. Prepared admixtures should be given by intravenous infusion or with the aid of a syringe pump to ensure a constant rate of infusion.
During glyceryl trinitrate administration, there should be close hemodynamic monitoring of the patient. The posology of glyceryl trinitrate IV should be adjusted to achieve the desired clinical response.

Example of admixture preparation:
To obtain an admixture of glyceryl trinitrate at a concentration of 100 micrograms/ml, add 50 ml glyceryl trinitrate solution (containing 50 mg glyceryl trinitrate) to 450 ml of infusion vehicle to give a final volume of 500 ml.
A dosage of 100 micrograms/minute can be obtained by giving 60 ml of the admixture per hour.

Contraindications:
Glyceryl trinitrate should not be used in the following cases:
- Hypersensitivity to the active substance, other nitrates, or any of the excipients.
- Severe anemia.
- Severe cerebral hemorrhage.
- Head trauma.
- Uncorrected hypovolemia and hypotensive shock.
- Arterial hypoxemia and angina caused by hypertrophic obstructive cardiomyopathy.
- Constrictive pericarditis.
- Pericardial tamponade.
- Toxic pulmonary edema.
- Acute circulatory failure (shock, collapse).
- Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures).
- During nitrate therapy, phosphodiesterase inhibitors type 5 (PDE5) (e.g. sildenafil, vardenafil, tadalafil) must not be used because PDE5 inhibitors may amplify the vasodilatory effects of glyceryl trinitrate resulting in severe hypotension.
- Conditions associated with an increased intracranial pressure.
- Myocardial insufficiency due to obstruction, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, or constrictive pericarditis.
- During nitrate therapy, the soluble guanylate cyclase stimulator riociguat must not be used.

Warnings and Precautions:
- Caution should be exercised in patients with severe liver or renal disease, hypothermia, hypothyroidism.
- Glyceryl trinitrate should not be given by bolus injection.
- Glyceryl trinitrate must be used only with particular caution and under medical supervision in:
  - low filling pressures e.g., in acute myocardial infarction, impaired left ventricular function (left ventricular failure). Reducing systolic blood pressure below 90 mmHg must be avoided.
  - orthostatic dysfunction.
- The development of tolerance and cross tolerance to other nitro compounds has been described.
- Glyceryl trinitrate must not be used in patients known to be taking phosphodiesterase inhibitor-containing products (e.g., sildenafil, vardenafil, tadalafil) in the intervening 24 hours (48 hours for tadalafil). Patients who receive glyceryl trinitrate solution therapy must be warned not to take phosphodiesterase inhibitor-containing products.
- During treatment with glyceryl trinitrate, alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of glyceryl trinitrate.
- Materials made of polyethylene (PE), polypropylene (PP), or polytetrafluoroethylene (PTFE) have proven to be suitable for infusing glyceryl trinitrate solution. However, infusion material made of polyvinyl chloride (PVC) or polyurethane (PU) has been shown to induce a loss of the active substance due to adsorption. If these materials are used the dose must be adjusted to suit patient's needs.
- The solution contains glucose, this should be taken into account in patients with diabetes mellitus.
- Hypoxemia:
  Caution should be exercised in patients with arterial hypoxemia due to severe anemia (including G6PD deficiency induced forms), because in such patients, the biotransformation of glyceryl trinitrate is reduced.
  Similarly, caution is called for in patients with hypoxemia and ventilation/perfusion imbalance due to lung disease or ischemic heart failure. Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia).
  Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated region of the lung. As a potent vasodilator, glyceryl trinitrate could reverse this protective vasoconstriction and thus result in increased perfusion of poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.
- Methemoglobinemia
  Following treatment with glyceryl trinitrate, methemoglobinemia has been reported. Treatment of methemoglobinemia with methylene blue is contraindicated in patients with glucose-6-phosphate deficiency or methemoglobin-reductase deficiency.

Effects on ability to drive and use machines
Glyceryl trinitrate may affect the patient's reactivity to an extent that her/his ability to drive or to operate machinery is impaired. This effect is increased in combination with alcohol.

Interactions with Other Medicaments:
- Concomitant treatment with other vasodilators, calcium channel antagonists, ACE inhibitors, monoamine oxidase inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and neuroleptics, as well as the consumption of alcohol, may potentiate the hypotensive effect of the preparation.
- The blood pressure lowering effect of glyceryl trinitrate will be increased if used together with phosphodiesterase inhibitors (e.g., sildenafil, vardenafil, tadalafil) which are used for erectile dysfunction. This might lead to life threatening cardiovascular complications. Patients who have recently taken phosphodiesterase inhibitors therefore must not be treated with glyceryl trinitrate in the intervening 24 hours (48 hours for tadalafil). Patients who are on nitrate therapy must not use phosphodiesterase inhibitors.
- The use of glyceryl trinitrate with riociguat, a soluble guanylate cyclase stimulator, is contraindicated since concomitant use can cause hypotension.
- Simultaneous intravenous infusion of tissue plasminogen activator (tPA) and glyceryl trinitrate may accelerate plasma clearance of tPA by increasing hepatic blood flow.
- 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

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Last revised: dd/mm/yyyy

Fiber direction

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***Double side leaflet**	***Page 1***

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dihydroergotamine antagonizes the effect of glyceryl trinitrate and may lead to coronary vasoconstriction.
- The use of heparin and glyceryl trinitrate solution can lead to a partial loss of action of heparin when both drugs are given simultaneously by intravenous route.
- Concurrent administration of glyceryl trinitrate with acetyl salicylic acid may potentiate the blood pressure lowering effects of glyceryl trinitrate.
- The nonsteroidal anti-inflammatory drugs except acetyl salicylic acid may diminish the therapeutic response of glyceryl trinitrate.
- Sapropterine (tetrahydrobiopterine, BH4) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterine-containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g., glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), isosorbide 5-mononitrate (5-ISMN), and others).

Pregnancy and Lactation:
Pregnancy
Developmental toxicity studies performed in rats and rabbits using various routes of administration did not reveal any effect on the embryos, fetuses, or the young animals even at toxic doses for the dam.

Lactation
Available evidence is inconclusive or inadequate for determining infant risk when used during breastfeeding. There is data that nitrates are excreted in breast milk and may cause methemoglobinemia in infants. The extent of excretion of nitroglycerin in human breast milk has not been determined. A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from glyceryl trinitrate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Reproduction toxicity studies performed in rats and rabbits using various routes of administration did not reveal any effect on mating, fertility, and general reproductive parameters. There is no data available on the effect of glyceryl trinitrate on fertility in humans.

Adverse 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).
During administration of glyceryl trinitrate, 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	Palpitations
Vascular disorders	
Common	Orthostatic hypotension
Uncommon	Circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope)
Not known	Flushing, hypotension
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 generalized
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, 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.

Like other nitrate preparations, glyceryl trinitrate commonly causes dose-dependent headaches due to cerebral vasodilation. These often regress after a few days despite the maintenance of therapy. If headaches persist during intermittent therapy, they should be treated with mild analgesics. Unresponsive headaches are an indication for reducing the dosage of glyceryl trinitrate or discontinuing treatment.

A slight reflex-induced increase in heart in heart rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

Overdose and Treatment:
Signs and symptoms
Symptoms could include the following:
- Fall in blood pressure ≤90 mmHg.
- Pallor.
- Sweating.
- Weak pulse.
- Reflex tachycardia.
- Collapse.
- Syncope.
- Dizziness postural.
- Headache.
- Asthenia.
- Dizziness.
- Nausea.
- Vomiting.
- Diarrhea.
- Methemoglobinemia has been reported in patients receiving other organic nitrates. During glyceryl trinitrate biotransformation nitrite ions are released, which may induce methemoglobinemia and cyanosis with subsequent tachypnea, anxiety, loss of consciousness, and cardiac arrest. It cannot be excluded that an overdose of glyceryl trinitrate may cause this adverse reaction.
- In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

Treatment
General procedure:
- Stop delivery of the drug.
- General procedures in the event of nitrate-related hypotension:
  The patient should be kept horizontal with the head lowered and legs raised or, if necessary, compression bandaging of the patient's legs.
  Supply oxygen.
  Expand plasma volume.
  For specific shock treatment admit patient to intensive care unit.

Special procedure:
- Raising the blood pressure if the blood pressure is very low.
- Treatment of methemoglobinemia.
  Treatment with intravenous methylene blue
  - Initially 1 to 2 mg/kg, not exceeding 4 mg/kg of a 1% solution over 5 minutes.
  - Repeat dose in 60 minutes if there is no response.
  - Administer oxygen (if necessary).
  - Initiate artificial ventilation.

  Treatment of methemoglobinemia with methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or methemoglobin reductase deficiency.
  Where treatment with methylene blue is contraindicated or is not effective, exchange transfusion and/or transfusion of packed red blood cells is recommended.
- Resuscitation measures
  In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

Pharmaceutical Precautions:
Instruction for use and handling
Glyceryl trinitrate solution for injection for infusion need not be diluted before use but can be diluted by 1:10 up to 1:40 with 5% glucose solution, 5% glucose solution and 0.9% sodium chloride solution, or with 0.9% sodium chloride solution.
The solution, whether or not diluted, should be infused slowly and not given by bolus injection. To ensure a constant infusion rate of glyceryl trinitrate it is recommended that glyceryl trinitrate be administered by means of a syringe pump or polyethylene infusion bag with a counter, or with a glass or rigid polyethylene syringe and polyethylene tubing.

Incompatibilities
Glyceryl trinitrate is incompatible with polyvinylchloride (PVC) and severe losses of glyceryl trinitrate (up to 50%) may occur if this material is used, resulting in a reduction of delivered dose and efficacy. Contact with polyvinylchloride bags should be avoided. Polyurethane (PU) also induces a loss of the active ingredient.
Glyceryl trinitrate is compatible with glass infusion set and with rigid infusion packs made of polyethylene. Glyceryl trinitrate may also be infused slowly using a syringe pump with a glass or plastic syringe.

Shelf-life:
2 years.

Presentation and Registration Number:
10 ml solution in 10 ml Type I clear glass ampoules packed in PVC blister. Each box contains 10 ampoules; MALXXXXXXXACZ

ON MEDICAL PRESCRIPTION ONLY.

Storage Condition:
After dilution
In-use stability shows that GLICE solution for injection for infusion diluted with 0.9% sodium chloride and 5% dextrose solution are stable for up to 5 days when stored at 30°C.

STORE AT TEMPERATURES BELOW 30°C.

KEEP OUT OF REACH OF CHILDREN.

Manufactured by
PT Ferron Par Pharmaceuticals
Kawasan Industri Jababeka I
Jl. Jababeka VI, Blok J3, Cikarang
Kabupaten Bekasi-Indonesia

For
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

Product Registration Holder
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Date of revision: 21 September 2023

Fiber direction

Color :	**Font type (Product name) :** Aller
	(Redactional) : Arial
Black	**Font size (Product name) :** 18 pt
	(Redactional) : 8 pt
	Double side leaflet** ***Page 2

No.	Parameters	Specification
1.	Material	HVS (Lihat CoA / *See CoA*)
2.	Gramatur / *Gramature* (gsm)	54 – 66 gsm
3.	Dimensi panjang / *Length dimension* (mm)	334 – 336 mm
4.	Dimensi lebar / *Width dimension* (mm)	214 – 216 mm
5.	Arah serat / *Fiber direction*	Vertikal / *Vertical*
6.	Warna / *Colour*	Lihat proof print / *See proof print*
7.	Redaksional / *Redactional*	Lihat proof print / *See proof print*

HISTORY

Revision No.	Revision Date	Details	Reason
00	-	Dokumen baru	ProdCom001147/1
01	04 Jan 2021	Update konten menyesuaikan PI acuan	CMCOthRec069033/1
		Perubahan dimensi menjadi 250x150 mm	Menyesuaikan PI acuan
02	22 Juli 2022	- Perubahan nama brand menjadi Glice Glyceryl Trinitrate 1mg/ml for Injection or Infusion - Perubahan komposisi	CMCOthRec089480/1 CMCOthRec089481/1
03	10 Okt 2022	- Perubahan dimensi menjadi 335x215 mm mengikuti acuan drawing cartoning - Perubahan penulisan komposisi - Perubahan storage condition after reconstitution - Penambahan redaksional	CC006418/1 CMCOthRec092608/1 CMCOthRec092649/1
04	04 Juli 2023	- Perubahan bentuk sediaan menjadi "Solution for Injection for Infusion" - Perubahan komposisi - Perubahan in use storage condition "after reconstitution" menjadi "after dilution" - Perubahan alamat manufactur - Penambahan redaksional	CMCOthRec105614/1
05	25 Sep 2023	- Perubahan in use storage condition	CMCOthRec109710/1