Summary of product characteristics

hameln

Glyceryl trinitrate-hameln 1 mg/ml Injection

DESCRIPTION

The product is a clear and colourless solution.

CONTENTS

1 ml solution contains 1 mg glyceryl trinitrate.

PROPERTIES

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.

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.

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 3270 L/hour)

INDICATIONS

The following indications exist for glyceryl trinitrate:

- 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 ischaemia during and after cardiac surgery,
- Induction of controlled hypotension for surgery.

RECOMMENDED DOSAGE

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/min but up to 400 micrograms/min may be necessary during some surgical procedures.

Paediatric population

The safety and efficacy of Glyceryl Trinitrate has not yet been established in children.

Elderly population

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

Patients with renal and hepatic impairment

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

Myocardial ischaemia

The treatment of perioperative myocardial ischaemia may be started with a dose of 15-20 micrograms/min, with subsequent increments of 10-15 micrograms/min until the required effect is obtained.

Unresponsive congestive heart failure:

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

Unstable angina:

An initial dose of 10 micrograms/min is recommended with increments of 10 micrograms/min 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 micro-drip 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 B.P. or Dextrose Injection B.P. 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 section 6.6.

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 haemodynamic monitoring of the patient.

The posology of Glyceryl Trinitrate i.v. 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/min. 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
- Acute circulatory failure (shock, collapse)
- Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures)
- Severe anaemia,
- Severe cerebral haemorrhage
- Head trauma
- Uncorrected hypovolaemia and hypotensive shock
- Arterial hypoxaemia and angina caused by hypertrophic obstructive cardiomyopathy
- Constrictive pericarditis
- Pericardial tamponade
- Toxic pulmonary oedema.
- 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 & 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 (e.g. sildenafil, vardenafil, tadalafil).

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 polytetrafluorethylene (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.

Hypoxaemia

Caution should be exercised in patients with arterial hypoxaemia due to severe anaemia (including G6PD deficiency induced forms), because in such patients the biotransformation of nitroglycerin is reduced.

Similarly, caution is called for in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure.

Patients with angina pectoris, myocardial infarction, or cerebral ischaemia 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 regions of the lung. As a potent vasodilator, nitroglycerin 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.

Methaemoglobinaemia

Following treatment with Glyceryl Trinitrate, methaemoglobinaemia has been reported. Treatment of methaemoglobinaemia with methylene blue is contraindicated in patients with glucose-6-phosphate deficiency or methaemoglobin-reductase deficiency.

Instruction for use and handling

Glyceryl Trinitrate need not be diluted before use but can be diluted by 1:10 upto 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 en- sure 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 polyethyl- ene syringe and polyethylene tubing.

Systems made of polyvinyl chloride (PVC) may absorb up to 50% of the glyceryl trinitrate from the solution.

INTERACTION 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 (e.g. sildenafil, vardenafil, tadalafil) therefore must not be treated with Glyceryl Trinitrate in the intervening 24h (48h for tadalafil). Patients who are on nitrate therapy must not use phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil).

The use of Glyceryl Trinitrate with riociguat, a soluble guanylate cyclase stimulator, is contraindicated since concomitant use can cause hypotension.

Simultaneous intravenous infusions 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 antagonises 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 non-steroidal 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).

FERTILITY, PREGNANCY & 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.

Breast-feeding

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 methaemoglobinaemia 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 breast-feeding or to discontinue/abstain from Glyceryl Trinitrate therapy taking into account the benefit of breast feeding 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.

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.

ADVERSE REACTIONS

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 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 rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.

SYMPTOMS & TREATMENTS OF OVERDOSAGE

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
- Diarrhoea
- Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During glyceryl trinitrate biotransformation nitrite ions are released, which may induce methaemoglobinaemia and cyanosis with subsequent tachypnoea, 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 of overdose:

General procedure:

- Stop delivery of the drug.
- General procedures in the event of nitrate-related hypotension:
- 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 methaemoglobinaemia:

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 methaemoglobinaemia with methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or methaemaglobin 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.

STORAGE CONDITIONS & PHARMACEUTICALS PRECAUTIONS

Do not store above 30°C. Do not freeze.

Keep the container in the outer carton in order to protect from light.

Keep out of the reach and sight of children!

Jauhi daripada kanak-kanak!

SHELF LIFE

For shelf life, please refer to the outer carton.

Opened ampoules and vials:

The product should be used immediately after opening the container.

Any unused solution from opened containers should be discarded.

Prepared infusion solutions:

Chemical and physical in-use stability has been demonstrated in glucose solution 5% and sodium chloride solution 0.9% for 24 hours at room temperature.

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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

PACKING/PACK SIZE:

Box of 10 ml glass ampoule: [5x10 ml] & [10x10 ml]

Box of 1 glass vial with 50 ml

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