SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glyceryl Trinitrate 1mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 1 mg glycercy trinitrate.

Amount of active substance per pack size:

<table>
<thead>
<tr>
<th>Total Volume</th>
<th>Total GTN Content</th>
<th>Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ml</td>
<td>5mg</td>
<td>ampoule</td>
</tr>
<tr>
<td>10ml</td>
<td>10mg</td>
<td>ampoule</td>
</tr>
<tr>
<td>25ml</td>
<td>25mg</td>
<td>ampoule</td>
</tr>
<tr>
<td>50ml</td>
<td>50mg</td>
<td>vial</td>
</tr>
</tbody>
</table>

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

The product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.
4.2 **Posology and 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.

Recommendations on the dilution of the product are presented in this section. For further instructions on dilution of the product before administration, see section 6.6.

**Adults**
The dose of Glyceryl Trinitrate should be adjusted to meet the individual needs of the patient.

The recommended dosage range is 10 - 200 mcg/min but up to 400 mcg/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

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

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

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

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

**Method of administration**
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.

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

**Example of admixture preparation**

To obtain an admixture of Glyceryl Trinitrate at a concentration of 100 mcg/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 mcg/min. can be obtained by giving 60 ml of the admixture per hour.

Vials of Glyceryl Trinitrate are for single use only and should not be regarded as multi-dose containers.

### 4.3 Contraindications

Glyceryl Trinitrate should not be used in the following cases:

- Hypersensitivity to the active substance, other nitrates or any of the excipients listed in Section 6.1
- 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 (see sections 4.4 and 4.5).
- Conditions associated with an increased intracranial pressure.
- Myocardial insufficiency due to obstruction, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy or constrictive pericarditis.
4.4 Special warnings and precautions for use

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). Patients who receive Glyceryl Trinitrate solution therapy must be warned not to take phosphodiesterase inhibitor-containing products (e.g. sildenafil, vardenafil, tadalafil) (see sections 4.3 and 4.5).

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 (see also section 6.2).

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 (see also...
section 4.8). 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 (see also section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with other vasodilators, calcium antagonists, ACE 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 (see Section 4.3). This might lead to life threatening cardiovascular complications. Patients who are on nitrate therapy must not use phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil).

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).

4.6 Fertility, pregnancy and lactation

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.

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 methaemoglobinemia 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.

4.7 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.

4.8 Undesirable effects

Undesirable effects frequencies are defined as: very common ($\geq 1/10$), 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:

<table>
<thead>
<tr>
<th>Nervous system disorders:</th>
<th>Very Common: Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Dizziness (including dizziness postural),</td>
</tr>
<tr>
<td>Disorder</td>
<td>Common</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Cardiac disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Orthostatic Hypotension</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nausea, Vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Allergic skin reactions (e.g. rash,) Allergic contact dermatitis.</td>
</tr>
<tr>
<td>Not known</td>
<td>Rash</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions:</strong></td>
<td>Not known:Common:</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

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.

**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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 **Overdose**

**Symptoms of overdose**

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 can not 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 methaemoglobin reductase deficiency (see also section 4.4).
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vasodilators used in cardiac diseases
ATC-Code: C01DA02 Organic nitrates

Glyceryl trinitrate exerts a spasmolytic action on smooth muscle, particularly in the vascular system. This action is more marked on the venous capacitance vessels than the arterial vessels; the predominant increase in venous capacitance results in marked diminution of both the left ventricular filling pressure and volume (preload). The moderate dilation of the arteriolar resistance vessels results in a reduction in afterload. These haemodynamic changes (reductions) in preload and afterload lower the myocardial oxygen demand. In addition, by direct action and through the reduction of myocardial wall tension glyceryl trinitrate also lowers the resistance to flow in the coronary collateral channels and allows re-distribution of blood flow to ischaemic areas of the myocardium.

Administration of glyceryl trinitrate by intravenous infusion to patients with congestive heart failure results in a marked improvement in haemodynamics, reduction of elevated left ventricular filling pressure and systolic wall tension, and an increase in the depressed cardiac output. It reduces the imbalance that exists between myocardial oxygen demand and delivery, thereby diminishing myocardial ischaemia and controlling ischaemia-induced ventricular arrhythmias.

Glyceryl trinitrate relaxes smooth muscles cells in other organs to some extent. The cellular molecular mechanism of action is a synthesis of nitric oxide and cyclic guanosyl monophosphate which acts as a mediator for muscle relaxation.

5.2 Pharmacokinetic properties

After intravenous administration, glyceryl trinitrate is widely distributed in the body with an estimated apparent volume of distribution of approximately 200 litres. It is strongly bound to erythrocytes and vessel walls; the plasma protein binding is approx. 60%. The therapeutic plasma concentration range is 0.1 to 3
ng/ml (up to 5 ng/ml). Glyceryl trinitrate is rapidly metabolised to dinitrate and mononitrate and further metabolised by glucuronidation in the liver, showing a marked first-pass effect.

Spontaneous hydrolysis occurs in plasma. The estimated plasma half-life of glyceryl trinitrate is 1 to 4 minutes. The rapid disappearance from plasma is consistent with the high systemic clearance values (up to 3270 litres per hour). The less active metabolites resulting from biotransformation can be recovered from the urine within 24 hours.

5.3 Preclinical safety data

The acute toxicity has been reported for rats after intravenous (LD₅₀ 17-41 mg/kg body weight), as well as in dogs after intravenous administration (LD₅₀ 19-24 mg/kg body weight). Autopsy did not reveal any pathological findings.

Subacute studies in rats at doses of 2.5, 5.0 and 10.0 mg/kg per day, and in dogs at doses of 1.0 and 3.0 mg/kg per day elicited only minimal reactions. In rats, suppression of body weight gain and food consumption occurred among treated and vehicle-control animals. Mild tissue irritation at injection sites was noted in treated and vehicle-control groups. There were no clearly drug-related clinical or pathological findings in dogs. Further results of studies on repeated-dose toxicity in different species revealed no indication of drug-specific clinically relevant toxicity.

Glyceryl trinitrate is insufficiently tested for a potential mutagenic action. There are no adequate state-of-the-art long-term studies on a possible tumourigenic action of glyceryl trinitrate.

There is inadequate experience with glyceryl trinitrate during human pregnancy, particularly during the first trimester. Sufficient evidence is available from animal studies with intravenous, intraperitoneal and topical administration. Studies on fertility and embryotoxicity did not result in any toxic effect on the embryo or on reproductive performance. Any indication of a teratogenic potential of glyceryl trinitrate was not found. Doses in excess of 1 mg/kg/day (i.p.) or 28 mg/kg/day (topical) reduced the birth weight in rats. There are no investigations on the passage of glyceryl trinitrate into breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injections
Glucose monohydrate
Hydrochloric acid

6.2 **Incompatibilities**

Glyceryl Trinitrate is not compatible with polyvinylchloride (PVC) and severe losses of glyceryl trinitrate (up to 50%) may occur if polyvinylchloride is used, resulting in a reduction of delivered dose and efficacy. Contact of the solution with polyvinylchloride bags should be avoided.

The product is compatible with glass infusion sets and with rigid infusion packs made of polyethylene; it may also be infused slowly using a syringe pump with a glass or plastic syringe.

6.3 **Shelf-life**

Unopened ampoules: 3 years
Unopened vials: 2 years

Opened ampoules or 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.

6.4 **Special precautions for storage**

Keep container in the outer carton.
Do not store above 25°C.

6.5 **Nature and contents of container**

5 ml, 10 ml or 25 ml ampoules, made of colourless glass, type I (Ph. Eur.).
50 ml vial, made of colourless glass, type I (Ph. Eur.), bromobutyl rubber stopper.

Box of 10 ampoules with 5 ml
Box of 10 ampoules with 10 ml
Box of 10 ampoules with 25 ml
Box of 1 vial with 50 ml
Box of 10 vials with 50 ml
Box of 25 vials with 50 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Glyceryl Trinitrate 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. Systems made of polyvinyl chloride (PVC) may absorb up to 50% of the glyceryl trinitrate from the solution.

Vials of 50 ml Glyceryl Trinitrate are for single use only and should not be regarded as multi-dose containers.

7 MARKETING AUTHORITY/PRODUCT HOLDER

hameln pharma plus gmbh
Langes Feld 13
31789 Hameln
Germany

8 MARKETING AUTHORITY NUMBER(S)

PL 25215/0011

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

04/09/2008
10 DATE OF REVISION OF THE TEXT

22/09/2016