Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitrocine 1 mg/ml solution for infusion, ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ampoules containing 10 mg glyceryl trinitrate in 10 ml (1 mg/ml).

For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear colourless and odourless isotonic sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Surgery
Nitrocine 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:
Nitrocine may be used to treat unresponsive congestive heart failure secondary to acute myocardial infarction.

Unstable angina:
Nitrocine may be used to treat unstable angina which is refractory to treatment with beta blockers and sublingual nitrates.

4.2 Posology and method of administration

Posology
Adults
The dose of Nitrocine 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.
Elderly
There is no evidence that a posology adjustment is required in the elderly.
Paediatric population
The safety and efficacy of Nitrocine has not yet been established in children.

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 stabilized. 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.
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.

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.

Method of Administration
Nitrocine solution may be used either diluted or undiluted, refer to section 6.6.
Nitrocine can be administered undiluted by slow intravenous infusion using a syringe pump incorporating a glass or rigid plastic syringe.

Alternatively, Nitrocine 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, Nitrocine 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 Nitrocine administration there should be close haemodynamic monitoring of the patient.
The posology of Nitrocine i.v. should be adjusted to achieve the desired clinical response.

Example of admixture preparation
To obtain an admixture of GTN at a concentration of 100 mcg/ml, add 50 ml Nitrocine 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. This is equivalent to a drip rate of 60 microdrops per minute or 20 standard drops per minute. At this drip rate the admixture provides enough solution for an infusion time of 8 hours 20 minutes.

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

DILUTED					**UNDILUTED**	
INFUSION RATE	**CONCENTRATION**				**INFUSION RATE**	**CONCENTRATION**
microdrops/min	**100 mcg/ml 5 x 10 ml amps Nitrocine in 500 ml Or 1 x 50 ml vial Nitrocine in 500 ml**	**200 mcg/ml 2 x 50 ml vials Nitrocine in 5**	**300 mcg/ml 3 x 50 ml vials Nitrocine in 5**	**400 mcg/ml 4 x 50 ml vials Nitrocine in 500 ml**	**ml/hr via Syringe pump**	**1000 mcg/ml Nitrocine via Syringe pump**

		00 ml	00 ml			
	Dosage (mcg/min)					Dosage (mcg/min)
6	10	20	30	40	0.6	10
12	20	40	60	80	0.9	15
18	30	60	90	120	1.2	20
24	40	80	1	160	1.5	25
30	50	1	20	200	1.8	30
36	60	00	1	240	2.4	40
42	70	1	50	280	3.0	50
48	80	20	1	320	4.5	75
54	90	1	80	360	6.0	100
60	100	40	2	400	9.0	150
66	110	1	10	440	12.0	200
72	120	60	2	480	15.0	250
78	130	1	40	520	18.0	300
84	140	80	2	560	21.0	350
90	150	2	70	600	24.0	400
		00	3			
		2	00			
		20	3			
		2	30			
		40	3			
		2	60			
		60	3			
		2	90			
		80	4			
		3	20			
		00	4			
			50			

1 ml = 60 microdrops = 20 standard drops

Bottles of Nitrocine are for single use only and should not be regarded as multi-dose containers.

4.3 Contraindications

Nitrocine should not be used in the following cases:

- Hypersensitivity to the active substance, other nitro compounds 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 hypotension (systolic blood pressure less than 90 mmHg)
- Severe hypovolemia
- Myocardial insufficiency due to obstruction, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy or constrictive pericarditis
- Cardiac tamponade

- 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 GTN resulting in severe hypotension* (see sections 4.4 and 4.5).

- Conditions associated with an increased intracranial pressure.

- During nitrate therapy, the soluble guanylate cyclase stimulator riociguat must not be used (see section 4.5).

4.4 Special warnings and precautions for use

Nitrocine 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

- Hypertrophic cardiomyopathy (nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy)

The development of tolerance and cross tolerance to other nitro compounds has been described.

Nitrocine must not be used in patients known to be taking phosphodiesterase inhibitor-containing products (e. g. sildenafil, vardenafil, tadalafil) in the intervening 24h (48h for tadalafil). Patients who receive GTN 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 polytetrafluorethylene (PTFE) have proven to be suitable for infusing GTN 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.

During treatment with GTN alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of GTN (see section 4.5)

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.

Methemoglobinemia
Following treatment with Nitrocine, methemoglobinemia has been reported. Treatment of methaemoglobinemia with methylene blue is contraindicated in patients with glucose-6-phosphate deficiency or methemoglobin-reductase deficiency (see also section 4.9).

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant treatment with other drugs with blood pressure lowering properties e.g. vasodilators (e.g. PDE5 inhibitors such as Sildenafil), calcium channel antagonists, ACE inhibitors, monoamine oxidase inhibitors, beta-blockers, diuretics, 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 Nitrocine 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 have recently taken phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil) therefore must not be treated with Nitrocine solution in the intervening 24h (48h for tadalafil). Patients who are on Nitrocine therapy therefore must not use phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil). To assure that the risk of adverse events with concomitant use is minimised, patients taken Nitrocine or PDE5 inhibitors must wait until either one is washed out.

The use of Nitrocine with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (see section 4.3) 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, nitrocine 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 Nitrocnine and may lead to coronary vasoconstriction.

The use of heparin and nitrocine solution can lead to a partial loss of action of heparin when both drugs are given simultaneously by intravenous route.

Concurrent administration of Nitrocine with acetyl salicylic acid may potentiate the blood pressure lowering effects of Nitrocine.

The non-steroidal anti-inflammatory drugs except acetyl salicylic acid may diminish the therapeutic response of Nitrocine.

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 Nitrocine 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.
There is no, or inadequate, evidence of safety of the drug in human pregnancy or lactation, but it has been in widespread use for many years without apparent ill consequence, animal studies having shown no hazard. If drug therapy is needed in pregnancy, this product can be used if there is no safer alternative.

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 breast-feeding or to discontinue/abstain from Nitrocine 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

Nitrocine 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

During administration of **NITROCINE** the following undesirable effects may be observed:

SOC:	**very common (≥1/10)**	**common (≥1/100 <1/10),**	**uncommon (≥1/1,000 <1/100)**	**rare (≥1/10,000 <1/1,000),**	**very rare (<1 /10,000),**	**not known (cannot be estimated from the available data).**
Nervous system disorders	Headache	Dizziness (including dizziness postural), somnolence				
Cardiac disorders		Tachycardia	Enhanced angina pectoris symptoms			Palpitations
Vascular disorders		Orthostatic hypotension	Circulatory collapse (sometimes accompanied by bradyarrythmia and syncope)			Flushing, hypotension
Gastrointestinal disorders			Nausea, vomiting		Heartburn	
Skin and subcutaneous tissue disorders			Allergic skin reactions (e.g. rash), Allergic contact dermatitis			Dermatitis exfoliative, rash generalized
General disorders and administration site conditions		Asthenia	Pruritus, pruritus at patch application site, burning, erythema, irritation			
Investigations						Heart rate increase

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

During treatment with Nitrocine, 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, Nitrocine 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 Nitrocine 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Animal experience:
In rats and mice, significant lethality (LD_{50}) at single intravenous doses of 23.2 mg/kg and 10.6 mg/kg, respectively, was observed.
In rats and mice, significant lethality (LD_{50}) at single subcutaneous doses of 94 mg/kg and 110 mg/kg, respectively, was observed

Human experience:
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

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 methaemoglobinemia with methylene blue is contraindicated in patients with glucose-6-phosphate deficiency or methemoglobin-reductase deficiency (see also section 4.4). Where this treatment is contraindicated or 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
Pharmacotherapeutic group: vasodilators used in cardiac diseases
ATC Code: C01DA 02 – Organic Nitrates

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.

5.2 Pharmacokinetic properties

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)

5.3 Preclinical safety data

Conventional studies of acute and repeated dose toxicity reveal no special hazard to humans.

Reproductive and Developmental Toxicity:
Reproductive toxicity studies, in rats and rabbits using various routes of administration did not show any adverse effects on fertility or embryo fetal development at dosages which did not induce parental toxicity.

Mutagenicity:
Standard mutagenicity tests provided contradictory results in vitro, however in vivo studies provided no evidence of genotoxicity.

Carcinogenicity:
Long term dietary studies in rodents led to the conclusion that Glyceryl trinitrate has no carcinogenicity effect relevant for the therapeutic dose range in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose
Propylene glycol
Water for injections
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Nitrocine 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 (see also section 4.4).
This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

As packaged for sale:
Nitrocine may be stored unopened for 5 years.
The product should be used immediately after opening.
Admixture: Chemical and physical in-use stability of the admixture when prepared as in section 6.6 has been demonstrated for 24 hours at 25 °C in suitable containers. From a microbiological point of view, the admixture should be used immediately. If not used immediately, the in-use storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hrs at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale:
This medicinal product does not require any special storage conditions.
For storage of open or admixed product, see Section 6.3

6.5 Nature and contents of container

Colourless glass (Type I) ampoules containing 10 ml.
Ampoules are packed in tens in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Ampoules of Nitrocine are for single use only and should not be regarded as multi-dose containers.

Nitrocine contains glyceryl trinitrate in isotonic sterile solution and is compatible with commonly employed infusion solutions, Sodium Chloride Injection BP and Dextrose Injection BP. No incompatibilities have so far been demonstrated.

Nitrocine is compatible with glass infusion bottles and with rigid infusion packs made of polyethylene. Nitrocine may also be infused slowly using a syringe pump with a glass or plastic syringe.

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 precautions, refer to Section 6.3. For further information on the preparation of different concentrations, refer to the User Information Leaflet.

7 MARKETING AUTHORISATION HOLDER

Merus Labs Luxco II S.à.R.L.
26-28 rue Edward Steichen
L-2540
Luxembourg

8 MARKETING AUTHORISATION NUMBER

PA2118/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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