Package Leaflet: Information for the patient
Nitrocine® 1 mg/ml Solution for Infusion
Glyceryl trinitrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or nurse
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Nitrocine is and what it is used for

Nitrocine belongs to a group of medicines called 'nitrates'. These are used to widen your blood vessels and reduce the workload of your heart.

Nitrocine is usually used in emergency situations to:

- Rapidly control high blood pressure during surgery, especially heart surgery
- Treat unstable angina. (Angina attacks feel like a tight pain in your chest, neck or arm and are a sign that your heart is not getting enough oxygen for the amount of work it is doing)
- Treat heart failure following a heart attack. It is very important that your doctor treats these conditions as quickly and effectively as possible, as left untreated the consequences could be fatal.

2. What you need to know before you are given Nitrocine

Do not use Nitrocine:

- If you are allergic to glyceryl trinitrate or any of the other ingredients of this medicine (listed in section 6)
- If you are allergic to any other nitrates
- If you are taking medicines for failure to achieve an erection such as Viagra. Using Nitrocine with these medicines could cause a severe drop in blood pressure and could lead to collapse and unconsciousness, and may be fatal
- If you suffer from low blood pressure
- If you suffer from low blood volume
- If you suffer from severe anaemia (low iron levels in your blood)
- If you have ever had a serious head injury, cerebral haemorrhage (bleeding in the brain) or a disease which is accompanied by increased pressure on the brain
- If you have or had heart conditions
- If you are using riociguat, a medicine used in treating pulmonary hypertension

Warnings and precautions
Talk to your doctor or nurse before using Nitrocine:

- If you have an underactive thyroid gland
- If you have any diseases of the liver or kidneys
- If you have hypothermia (very low body temperature)
- If you are malnourished (severe lack of food)
- If you are pregnant or breastfeeding.

Other medicines and Nitrocine

- **Do not take Nitrocine with medicines for failure to achieve an erection such as Viagra. Using Nitrocine with these medicines could cause a severe drop in blood pressure and could lead to collapse and unconsciousness, and may be fatal.**

Tell your doctor or nurse if you are taking, have recently taken or might take any of the following medicines:

- Medicines which reduce blood pressure (e.g. beta-blockers, calcium channel blockers, vasodilators) ACE-inhibitors, monoamine oxidase inhibitors)
- Tricyclic anti-depressants (used to treat depression)
- Neuroleptics (used to treat anxiety)
- Any other medicine, including medicines obtained without a prescription.
- Non-steroidal anti-inflammatory drugs except acetyl salicylic acid.
- Sapropterine containing medicines.

Nitrocine with alcohol
Do not drink alcohol whilst using Nitrocine as it can cause your blood pressure to drop. This may make you feel dizzy or faint.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before you are given Nitrocine.

Driving and using machines
Nitrocine may give you a headache, or make you feel dizzy or tired. If this happens to you, do not drive or operate machinery.

3. How you will be given Nitrocine

Important: Your doctor will choose the dose that is right for you. Your medicine will be administered by a doctor in hospital. It will be given via a drip into your bloodstream and may be diluted or undiluted.

Use in children
Nitrocine is not suitable for children.

Adults and Elderly

- The usual dose is between 10 micrograms and 200 micrograms per minute, but sometimes as much as 400 micrograms per minute may be needed

- The exact dose that the doctor will give you depends on the condition you are being treated for. As a guide:

To control high blood pressure during surgery:
- 25 micrograms per minute will be given as a starting dose
- This may be increased by 25 micrograms per minute at 5 minute intervals until your blood pressure is stabilised
- Doses up to 400 micrograms per minute may occasionally be needed.

To control myocardial ischaemia during and after cardiovascular surgery:
- 15-20 micrograms per minute will be given as a starting dose.
- Depending on your response, the dose may be increased by increments of 10-15 micrograms per minute until the desired effect is obtained.

To treat unstable angina:
- 10 micrograms per minute will be given as a starting dose
- Depending on your response, the dose may be increased or decreased by 10 micrograms every 30 minutes until the desired effect is achieved.

Treat heart failure following a heart attack:
- 20-25 micrograms per minute will be given as a starting dose
- Depending on your needs, the doctor may decrease the dose by 10 micrograms per minute or give you a further 20-25 micrograms per minute until the required effect is obtained.

While you are being given Nitrocine, the doctor may monitor your heart rate and breathing to make sure that the medicine is working properly.

If you are given more Nitrocine than you should
This is unlikely as Nitrocine will be injected slowly by a doctor who will monitor your heart continuously during treatment. If any problem occurs, Nitrocine can be stopped and any symptoms of over dosage treated urgently.

If you have any further questions about this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people)
- Headaches

Common side effects (may affect up to 1 in 10 people)
- Low blood pressure (hypotension) and light-headedness upon standing which you may notice as dizziness, drowsiness, rapid heartbeat (reflex tachycardia) and a feeling of weakness at the start of treatment or when the dosage is increased.

Uncommon side effects (may affect up to 1 in 100 people)
- Collapse sometimes with a slow heartbeat and fainting

- Very low blood pressure (severe hypotension) where you are being sick, feeling sick, are restless, have pale skin and sweat a great deal. This may lead to a worsening of the chest pain you often get with angina
- Temporary low oxygen level in the blood (temporary hypoxaemia). For people with heart disease this may lead to low oxygen level in the tissue surrounding the heart (myocardial hypoxia)
- Allergic skin rash, which may be severe
- Feeling sick
- Being sick

Very rare side effects (may affect up to 1 in 10,000 people)
- Heartburn

Not known (frequency cannot be estimated from the available data)
- Palpitations
- Flushing of the face
- Low blood pressure
- Very red skin with scaling and thickened itchy skin (exfoliative dermatitis)
- Rash
- Heart rate increase

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

UK
The Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

By reporting side effects, you can help provide more information on the safety of the medicine.

5. How to store Nitrocine

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Nitrocine is for single use only. Unopened, this medicinal product does not require any special storage conditions. When opened, Nitrocine must be used immediately. If it has to be diluted, the mixed product should also be used immediately.

Your doctor or nurse will make sure your medicine is correctly stored and disposed of.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nitrocine contains

- The active substance is glyceryl trinitrate. Each 1 ml of solution contains 1 mg glyceryl trinitrate.
- The other ingredients are glucose, propylene glycol, water for injection and hydrochloric acid for pH adjustment.

What Nitrocine looks like and contents of the pack
Nitrocine 1mg/ml solution for infusion is an isotonic sterile solution. It is supplied in packs of 10 ampoules, each containing 10 mg glyceryl trinitrate in 10 ml solution, or in a single glass vial containing 50 mg glyceryl trinitrate in 50 ml solution.

Marketing Authorisation Holder
In UK
Merus Labs Luxco II S.à r.l.
26-28, rue Edward Steichen
L-2540 Luxembourg

In Ireland
Merus Labs Luxco II S.à r.l.,26-28, rue Edward Steichen
L-2540 Luxembourg

Manufacturer
Aesica Pharmaceuticals GmbH, Alfred-Nobel-Strasse 10, D-40789 Monheim, Germany.

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If this leaflet is difficult to read and you would like it in a different format, please contact

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

The following information is intended for healthcare professionals only:

Nitrocine® 1 mg/ml Solution for Infusion
GLYCERYL TRINITRATE
User information leaflet

Nitrocine® 1mg/ml solution for infusion
glyceryl trinitrate

PRESENTATION
Nitrocine® is a solution for infusion and is available in 10 ml ampoules containing 10 mg glyceryl trinitrate or 50 ml vials containing 50 mg glyceryl trinitrate.
In both cases, each ml of solution contains 1 mg glyceryl trinitrate.
Nitrocine® also contains glucose anhydrous, propylene glycol, water for injection and hydrochloric acid for pH adjustment.
Nitrocine® is an isotonic sterile solution.

USES
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.

PHARMACOLOGICAL ACTIONS
Glyceryl trinitrate reduces the tone of vascular smooth muscle, with a more marked effect on the venous capacitance vessel than on the arterial vessels. This reduces venous return to the heart and lowers elevated filling pressure. The 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 and arterial pressure are also reduced by glyceryl trinitrate and there is a net reduction in afterload. Glyceryl trinitrate improves the myocardial oxygen supply by redistributing blood flow along collateral channels from epicardial to endocardial regions.

DOSAGE
Use as directed by your physician.

Adults:
The dose of Nitrocine® should be adjusted to meet the individual needs of the patient.

The recommended dosage range is 10-200mcg/min but up to 400mcg/min may be necessary during some surgical procedures.

Children:
The safety and efficacy of Nitrocine® has not yet been established in children.

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

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

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

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

ADMINISTRATION
Refer to compatibilities at the end of this leaflet.
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.

Admixture preparation:
Admixtures are prepared by replacing a given volume of infusion vehicle with an equal volume of Nitrocine® to produce the final infusion solution. For example to obtain an admixture of glyceryl trinitrate at a concentration of 100mcg/ml, add 50 ml Nitrocine® solution (containing 50 mg glyceryl trinitrate) to 450ml of infusion vehicle to give a final volume of 500ml. For different concentrations, refer to summary of product characteristics.

Example:
If a dosage of 100mcg/min is required, this can be obtained using an admixture of glyceryl trinitrate containing 100mcg/ml by giving 60 ml of the admixture per hour. This is equivalent to a drip rate of 60 paediatric microdrops/minute, or 20 standard drops/minute. At this drip rate, the infusion will last for 8 hours and 20 minutes.
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.

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

CHILDREN:
The safety and efficacy of Nitrocine has not yet been established in children.

CONTRAINDICATIONS, WARNINGS, ETC.
Contraindications:
Nitrocine should not be used in the following cases: known hypersensitivity to the active substance, other nitro compounds or to any the excipients, acute circulatory failure, cardiogenic shock, severe anaemia, closed angle glaucoma, severe hypotension, severe hypovolemia, hypertrophic obstructive cardiomyopathy, aortic and mitral stenosis, constrictive pericarditis, cardiac tamponade, conditions with increased intracranial pressure.
Nitrocine® must not be given to patients taking phosphodiesterase 5 inhibitors, e.g. sildenafil due to potentially life threatening potentiation of hypotension by sildenafil.
Beta blockers, calcium antagonists, vasodilators, ACE inhibitors, monoamine oxidase inhibitors, diuretics, antihypertensives and alcohol may also exacerbate the hypotensive effects of Nitrocine®. This might also occur with neuroleptics and tricyclic antidepressants.
Simultaneous intravenous infusions of tissue plasminogen activator (tPA) may accelerate plasma clearance of tPA.
Nitrocine may increase the blood level of dihydroergotamine and its affects. Nitrocine administered with heparin may lead to partial loss of action of heparin. Concurrent administration of nitrocine with salicylic acid may potentiate the blood pressure lowering effects of Nitrocine.
Nitrocine must not be given to patient using riociguat.

Precautions:
Nitrocine must be used only with particular caution and under medical supervision low filling pressures, aortic/mistral stenosis, orthostatic dysfunction. Tolerance and cross tolerance to other nitro compounds has been described. The material of PVC/PU may induce a loss of the active due to adsorption.
The solution contains glucose, this should be considered for diabetes mellitus patients.
Nitrocine should be used in caution in patients with hypoxaemia and methemoglobinemia.

Pregnancy and lactation:
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.

Adverse effects:
Severe hypotension responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration. Other possible adverse reactions include headache, dizziness, tachycardia, enhanced angina pectoris symptoms, orthostatic hypotension, circulatory collapse, nausea, vomiting, heartburn, allergic skin reactions and skin dermatitis, dermatitis exfoliative, asthenia, pruritus, burning, erythema and irritation.

Reporting of side effects

If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

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The Yellow Card Scheme
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Overdose:
Mild overdose usually results in hypotension and tachycardia. If arterial systolic blood pressure drops below 90 mmHg and if heart rate increases 10 % above its initial value, the infusion should be discontinued to allow a return to pretreatment levels.
If hypotension persists, or in more severe cases, this may be reversed by elevating the legs, supply oxygen, expand plasma volume and/or treatment with hypertensive agents.

PHARMACEUTICAL PRECAUTIONS
Chemical and physical in-use stability of the admixture has been demonstrated for 24hrs at 25°C in suitable containers.
From a microbiological point of view, the admixture should be used immediately. If not used immediately, in-use storage conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
Open ampoules or vials should be used immediately and any unused drug discarded.

Compatibility:
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. 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.
This product does not require any special storage conditions.
Keep out of the reach and sight of children.

LEGAL CATEGORY
POM

PACKAGE QUANTITIES
Ampoules: each pack contains 10 x 10 ml ampoules of Nitrocine®
Bottles: each pack contains 1 x 50 ml vial of Nitrocine®

PRODUCT LICENCE NUMBER

PL 44374/0019

PRODUCT AUTHORISATION NUMBERS
Nitrocine® 1mg/ml solution for infusion, 10 ml ampoule PA2118/001/001
Nitrocine® 1mg/ml solution for infusion, 50 ml vial PA2118/001/002

NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

In UK
Merus Labs Luxco II S.à r.l.
26-28, rue Edward Steichen
L-2540 Luxembourg

In Ireland
Merus Labs Luxco II S.à r.l.
26-28, rue Edward Steichen
L-2540 Luxembourg

NAME AND ADDRESS OF MANUFACTURER
Aesica Pharmaceuticals GmbH Alfred-Nobel-Strasse 10, Monheim D 40789, Germany

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