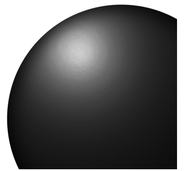
nitrocine® solution

GLYCERYL TRINITRATE



4005678 1105-1 9\20 631

PATIENT INFORMATION AND EXTENDED PRESCRIBING INFORMATION

nitrocine® solution

Drug substance: glyceryl trinitrate

COMPOSITION

Pharmaceutically active ingredients:
One ampoule with 10 ml of solution contains: glyceryl trinitrate 10 mg
One pierce-cap bottle with 50 ml of solution contains: glyceryl trinitrate 50 mg
Other ingredients: propylene glycol, glucose, water for injection

PRESENTATION AND SIZES

Ten ampoules, each containing glyceryl trinitrate 10 mg in 10 ml of solution
One pierce-cap bottle of glyceryl trinitrate 50 mg in 50 ml of solution

SUBSTANCE GROUP

Organic nitrates

NAME AND ADDRESS OF THE PHARMACEUTICAL MANUFACTURER

SCHWARZ PHARMA AG
Alfred-Nobel-Str. 10
D-40789 Monheim
Phone: 02173/48-0
Fax: 02173/48-1608

INDICATIONS

– severe angina pectoris: e.g. unstable and vasospastic forms
– acute myocardial infarction
– acute left ventricular failure
– hypertensive crisis with cardiac decompensation
– controlled hypotension

CONTRAINDICATIONS

In which cases must nitrocine® solution not be used?

nitrocine® solution must not be used in:
– allergy to nitrate-type drugs;
– acute circulatory failure (shock, circulatory collapse);
– cardiogenic shock, unless a sufficiently high left ventricular end-diastolic pressure is ensured by intra-aortic counter-pulsation or positive inotropic drugs;
– toxic pulmonary oedema;
– very low blood pressure (marked hypotension: systolic blood pressure less than 90 mm Hg);
– diseases associated with elevated intracranial pressure (further increases in pressure have so far been seen only after the i.v. administration of high doses of glyceryl trinitrate).

nitrocine® solution and phosphodiesterase type 5 inhibitors, e.g. Viagra®, must not be used concomitantly, as this may result in a serious blood pressure lowering effect.
Warning:
nitrocine® solution must never be used in patients who have recently taken Viagra® even if acute angina occurs.

In which cases may nitrocine® solution be used only with particular caution and on certain conditions?
The following section describes the cases in which nitrocine® solution may be used only on certain conditions and observing particular caution. Please ask your doctor in such cases. This section is also relevant when the factors mentioned below applied to you in the past. Particularly careful monitoring is necessary in:
– myocardial disease with reduction of the ventricular cavities (hypertrophic obstructive cardiomyopathy), constrictive pericarditis, and cardiac tamponade;
– low filling pressures e.g. in acute myocardial infarction; impaired left ventricular function (left ventricular failure). Decreasing the systolic blood pressure below 90 mm Hg should be avoided;
– narrowing of the aortic and/or mitral valve (aortic and/or mitral stenosis);
– tendency toward circulatory dysregulation in the presence of low blood pressure (orthostatic dysfunction);
– patients with severe liver or kidney dysfunction.

In cases of hypovolemia, adequate volume expansion is necessary at the beginning of therapy.
What do you have to observe during pregnancy and lactation?
Because there is no sufficient experience with using glyceryl trinitrate in pregnant or nursing women, it is recommended for reasons of particular caution to use the drug during pregnancy and lactation only at a physician's special order and following a careful benefit-risk evaluation. Animal experiments have not yielded any indication of fetal damage.

WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Which precautions have to be observed for the use of the drug?
The concomitant use of heparin and nitrocine® solution is associated with a decrease in the effect of heparin. The heparin dose has to be adjusted accordingly, the blood clotting parameters closely monitored. When glyceryl trinitrate is discontinued, a marked reduction of blood clotting may occur (sudden increase in PTT) so that a reduction of the heparin dose may be necessary.
When treating insulin-dependent patients with nitrocine® solution, bear in mind that the solution contains about 5 % of glucose.
The solution is sterile, but has not been manufactured using preservative substances. The pierce-cap bottle is not intended for multiple withdrawals. nitrocine® solution should be used aseptically immediately after the container has been opened.
Materials made of polyethylene (PE), polypropylene (PP) or polytetrafluoroethylene (PTFE) have proved suitable for being used for the infusion of nitrocine® solution. Infusion materials of polyvinylchloride (PVC) or polyurethane (PU) result in substantial loss of drug substance because of adsorption.

NOTES ON REACTIVITY

Even when used in accordance with the instructions, this drug can alter the patient's reaction rate to an extent such as to impair his/her ability to drive a motor-vehicle or to operate machinery or to work in unsafe places. This is particularly true when the therapy is started, the dose is raised or the preparation is changed, or when the preparation interacts with alcohol.

INTERACTIONS WITH OTHER DRUGS

Which other drugs affect the effect of nitrocine® solution, and what influence does nitrocine® solution have on the effects of other drugs?
The concomitant use of other vasodilators, antihypertensives, beta blockers, calcium antagonists, neuroleptics or tricyclic antidepressants, and alcohol can enhance the hypotensive effect of nitrocine®solution. This is particularly true for the concomitant use of phosphodiesterase type 5 inhibitors, e.g. Viagra® (see „Contraindications").
When used together with dihydroergotamine (DHE), nitrocine® solution may lead to an increase in the DHE level and thus enhance the hypotensive effect of the latter.
The concomitant use of heparin and nitrocine® solution is associated with a decrease in the effect of heparin. The heparin dose has to be adjusted accordingly, the blood clotting parameters being closely monitored. When glyceryl trinitrate is discontinued, a marked reduction of blood clotting may occur (sudden increase in PTT) so that a reduction of the heparin dose may be necessary.
The concomitant use of glyceryl trinitrate solution and tissue plasminogen activator (tPA) has been described to be associated with a decrease in the tPA plasma concentration and thus with a reduced efficacy of the tPA dose given to the patient.
In patients who have received a prior therapy with organic nitrates, e.g. isosorbide dinitrate or isosorbide-5-mononitrate, a higher dosage of glyceryl trinitrate may be necessary to achieve the desired haemodynamic effect.
Please note that this information may also apply to drugs you took a short time ago.

DOSAGE, MODE AND DURATION OF ADMINISTRATION

At what dosages should nitrocine® solution be used?
Depending on the initial clinical and haemodynamic values, the dosage is determined according to the patient's demand and the response by the parameters monitored. In clinical use, the starting dose is 0.5 to 1.0 mg/h of glyceryl trinitrate; the dose is then adapted to the individual demand. The maximum doses are usually 8 mg of glyceryl trinitrate an hour, rarely 10 mg an hour.
Cases of severe angina pectoris are treated with a dose of 2 to 8 mg an hour (33 to 133 µg a minute) in a hospital (intensive-care unit). The patient's haemodynamics have to be continuously monitored during infusion. The systolic and diastolic blood pressures, heart rate, and hemodynamic parameteters (right-heart catheter) such as systolic and diastolic pulmonary artery pressure (PASP, PADP), pulmonary capillary wedge pressure (PCP), cardiac output (CO) and ECG (measurement of the ST segment) have to be recorded continuously.

Dilution table

Quantity of drug substance (glyceryl trinitrate)		10 mg	20 mg	30 mg	40 mg	50 mg
nitrocine® solution		10 ml	20 ml	30 ml	40 ml	50 ml
Quantity of infusion solution for rate of dilution	1 + 10	100	200	300	400	500
	1 + 20	200	400	600	800	1000
	1 + 40	400	800	1200	1600	2000
Quantity of ready-made infusion solution	1 + 10	110	220	330	440	550
	1 + 20	210	420	630	840	1050
	1 + 40	410	820	1230	1640	2050

In acute left ventricular failure (pulmonary oedema): 2 to 8 mg/hour (33 to 133 µg/minute), for 1 to 2 days.
In hypertensive crisis with cardiac decompensation, infuse 2 to 8 mg an hour (5 mg an hour on the average) with continuous monitoring of blood pressure and heart rate.
For controlled hypotension: depending on the anaesthetic method and the target blood pressure, 2 to 10 µg per kg body weight per minute with ECG monitoring and invasive blood pressure measurements.
In patients with reduced liver or kidney function, the dose should be lowered depending on the seriousness of the dysfunction.
To avoid a decrease in, or loss of, action, the lowest possible clinically efficacious dosage should be chosen, and an intermittent administration or an alternating administration with other vasodilators should be considered if necessary.
How should nitrocine® solution be used?
The intravenous infusion of glyceryl trinitrate should be performed with continuous cardiac and circulatory monitoring in a hospital.
nitrocine® solution can be infused intravenously undiluted with appropriate equipment or diluted (dilution e.g. with physiological saline, 5 % glucose, 10 % glucose). When combining nitrocine® solution with infusion solutions, observe the manufacturers' information on their infusion solutions, specifically the information concerning the compatibility, contraindications, side effects and interactions.

Infusion table

Dilution	1 + 10	1 + 20	1 + 40
	Infusion		
Desired dose of glyceryl trinitrate/hour	ml/hour	ml/hour	ml/hour
0.50 mg	5.5	10.5	20.5
0.75 mg	8.25	15.75	30.75
1.0 mg	11.0	21.0	41.0
1.25 mg	13.75	26.25	51.25
1.5 mg	16.5	31.5	61.5
2.0 mg	22.0	42.0	82.0
2.5 mg	27.5	52.5	102.5
3.0 mg	33.0	63.0	123.0
3.5 mg	38.5	73.5	143.5
4.0 mg	44.0	84.0	164.0
4.5 mg	49.5	94.5	184.5
5.0 mg	55.0	105.0	205.0
5.5 mg	60.5	115.5	225.5
6.0 mg	66.0	126.0	246.0
7.0 mg	77.0	147.0	287.0
8.0 mg	88.0	168.0	328.0
9.0 mg	99.0	189.0	369.0
10.0 mg	110.0	210.0	410.0

Depending on the kind and severity of the clinical picture, invasive haemodynamic measurements are indicated to supplement the usual measurements (symptoms, blood pressure, heart rate, urine output) during the therapy.
Depending on the clinical picture, haemodynamics and ECG, the treatment may be continued for up to 3 days or longer.
Note
Materials made of polyethylene (PE), polypropylene (PP) or polytetrafluoroethylene (PTFE) have proved suitable for being used for the infusion of nitrocine® solution. Infusion materials of polyvinylchloride (PVC) or polyurethane (PU) result in substantial loss of drug substance because of adsorption.

Product Name	nitrocine LSG
Identification No.	4005678 1105-1
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Operators Name	Tim Neumann
Creation Date	16.04.2003
Amended by	Hartl
Modification Date	25.01.06
Edition No. Print	1
APPROVAL Customer/INFB	**Date Signa**
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Resubmission after correction	
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Shipment Date	26.01.06
Contract Manuf.	
ID.-No. Contr. Manuf	
PDF Print	
Remarks	

Digital transmitted PDF reference files are valid without signature. Originals are deposited in packaging technology department.

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ATTENTION! NEW SETTING!
Please read text carefully and complete!

OVERDOSAGE AND OTHER CASES OF FAULTY USE (EMERGENCY MEASURES, SYMPTOMS AND ANTIDOTES)

What has to be done, if too much nitrocine® solution has been taken (intentional or accidental overdosage)?
If overdosage with major quantities of nitrocine® solution is suspected, a doctor has to be called immediately.

SYMPTOMS OF OVERDOSAGE

Depending on the extent of overdosage, a marked reduction of blood pressure (hypotension) with orthostatic dysregulation, a reflex increase in heart rate, a feeling of weakness, vertigo and dizziness, and headache, skin reddening, nausea, vomiting and diarrhoea can occur.
After high doses (more than 20 mg/kg body weight), nitrite ions as are formed during the decomposition of glyceryl trinitrate are not unlikely to induce methaemoglobinaemia, cyanosis, dyspnoea and tachypnoea.
Very high doses can lead to an increase in intracranial pressure and cerebral symptoms.
Elevated methaemoglobin concentrations were measured in cases of chronic overdosage, but are debated as to their clinical relevance.

THERAPY OF OVERDOSAGE

Besides general measures such as horizontal position of the patient with elevation of the legs, monitoring and – if necessary – adjustment of the vital parameters under intensive care is required.
In cases of marked hypotension and/or shock, volume expansion should be performed; norepinephrine and/or dopamine may be infused in exceptional cases to support the circulation. The administration of epinephrine or of related substances is contraindicated.
According to severity, the following antidotes can be used to treat methaemoglobinaemia:

1. vitamin C: 1 g orally or i.v. as sodium salt
2. methylene blue up to 50 ml i.v. of a 1 % solution of methylene blue
3. toluidine blue: initially 2 - 4 ml/kg BW, strictly i.v.; several subsequent administrations of 2 ml/kg BW at one-hour intervals are possible, if necessary
4. administration of oxygen, haemodialysis, exchange transfusion.

SIDE EFFECTS

What side effects can appear during the use of nitrocine® solution?
Headache ("nitrate headache") commonly occurs when the treatment begins; experience has shown it to subside in most cases after few days of regular use.
A dose-dependent decrease in blood pressure and/or orthostatic hypotension (circulatory disturbance on changes of position) may be observed; these symptoms can be accompanied by a reflex increase in heart rate, dizziness, and feelings of vertigo and weakness. The infusion has to be stopped, when there is a major fall in blood pressure. If the patient does not show spontaneous recovery, actions to support the heart and circulation such as elevation of the legs and volume expansion may be necessary.
Nausea, vomiting, temporary skin reddening (flushing), and allergic skin reactions are rare.
Infrequently a marked decrease in blood pressure may lead to an exacerbation of the anginal symptoms.
States of collapse, sometimes associated with cardiac arrhythmias with a reduction of heart rate (bradycardic arrhythmias) and syncopes (sudden loss of consciousness), are seldom seen.
Exfoliative dermatitis (inflammatory skin disease) may occur in isolated cases.
The development of tolerance (decrease in effect) as well as cross-tolerance towards other nitro substances (decrease in effect as a result of a prior therapy with other nitrate drugs) have been described. For a decrease in, or loss of, effect to be prevented, continuously high dosages should be avoided.

Note
Due to a relative redistribution of blood flow into hypoventilated alveolar areas of the lungs, the use of nitrocine® solution can result in temporary reductions of the content of oxygen in the arterial blood (hypoxaemia) and may induce an undersupply with oxygen (hypoxia) of the myocardium in patients suffering from disturbed blood flow in the coronary vessels (coronary heart disease).
Please inform your doctor or pharmacist of any side-effects not listed in this package insert.
Which countermeasures have to be taken in case of side effects?
If you observe any of the above mentioned side effects, inform your doctor so he can evaluate their seriousness and decide on any additional measures that may be necessary.
nitrocine® solution must not be taken again once first indications of hypersensitivity have been observed.

NOTES AND SHELF-LIFE INFORMATION

Unopened original package
nitrocine® solution in ampoules: The shelf-life is 5 years.
nitrocine® solution in pierce-cap bottles: The shelf-life is 5 years.
The expiry date of this drug is printed on the container and the folding box. Do not use the drug after this date.
The solution is sterile, but has not been manufactured using preservative substances. The piece-cap bottle is not intended for multiple withdrawals. nitrocine® solution should be used aseptically immediately after the container has been opened.

Store drugs out of the reach of children!

DATE OF THIS VERSION OF THE PACKAGE INSERT

February 1999

ADDITIONAL INFORMATION FOR SPECIALISTS:

Prescription status

PRESCRIPTION DRUG

Pharmacological and toxicological properties, pharmacokinetics, bioavailability, as far as the data are necessary for the therapeutic use
Pharmacological properties
Glyceryl trinitrate has a direct relaxant effect on the smooth vascular muscles and induces vasodilation.
The postcapillary capacitance vessels and the large arteries – in particular those parts of the coronary arteries that are still able to react – are more affected than the resistance vessels. Vasodilation in the systemic vasculature results in an increase in venous capacitance („pooling"), a decrease in venous return, and a reduction of the ventricular volumes and filling pressures (decrease in preload).
The shortening of the ventricular radius and the lower systolic wall tension reduce the myocardial demand for energy and oxygen.
The decrease in cardiac filling pressures is beneficial for the perfusion of subendocardial wall layers at a risk of becoming ischaemic, and the regional wall motion and the stroke volume can be improved.
The dilatation of the large arteries near the heart leads to a decrease in both systemic resistance (decrease in afterload) and pulmonary impedance to ejection.
Glyceryl trinitrate effects a relaxation of the bronchial muscles, the efferent urinary tract, the muscles of the gall bladder, the bile duct and the oesophagus, the small and large intestines as well as of the sphincters.
At the molecular level, the action of nitrates is very likely to result from the formation of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP), which is considered the mediator of relaxation.

TOXICOLOGICAL PROPERTIES

Acute toxicity: see "Emergency measures, symptoms and antidotes"
Chronic toxicity:
Rats showed no significant toxic effects after two years of receiving up to 38.1 mg/kg BW/day in their feed. Higher dosages were associated with a decrease in feed intake, reduced weight gain, methaemoglobinaemia, and hepatocellular alterations.
Mice showed no toxic effects after two years of receiving up to 115 mg/kg BW/day in their feed. Higher dosages were associated with a decrease in feed intake, reduced weight gain, and methaemoglobinaemia.
Dogs were treated with oral administrations of 25 mg/kg BW/day for 12 months and likewise showed slight dose-dependent elevations of methaemoglobin formation.

MUTAGENIC AND CARCINOGENIC POTENTIAL

The examination of glyceryl trinitrate in cell cultures and animal experiments produced no mutagenic or carcinogenic effects of relevance for the therapeutic dose range.

REPRODUCTIVE TOXICITY

There is no sufficient experience in humans, especially for the first trimester of pregnancy.
Sufficient reproductivity studies in animals have been performed with intravenous, intraperitoneal and dermal administrations. Embryotoxicity and fertility studies were not indicative of influences on the embryo or fertility disorders even at dosages toxic for the parent animals.
There were in particular no indications of teratogenic properties. Doses above 1 mg/kg/day (i.p.) and 28 mg/kg/day (dermal) produced fetotoxic effects (reduced birth weights) when given to pregnant rats during fetus development. Examinations to determine the concentration of the drug substance in breast milk are not known.

PHARMACOKINETICS

The elimination half-life of glyceryl trinitrate is short. Values of 2 to 2.5 minutes are reported for intravenous administrations.
The substance is about 60 % bound to plasma protein. There is further a high degree of red blood cell binding and enrichment in the vascular wall.
The decomposition of glyceryl trinitrate that takes place in the liver, but also in many other cells, e.g. in the red blood cells, means the separation of one or several nitrate groups. Besides being metabolized, glyceryl trinitrate, in the form of its metabolites, is excreted by the kidneys.
Great intraindividual and interindividual variations of the plasma levels were observed after intravenous administrations.
The efficacy was found to decrease despite constant dosage and constant nitrate concentrations. Tolerance disappears within 24 hours of discontinuation of the therapy. No tolerance was observed under therapies with appropriate intermittent administrations.

BIOAVAILABILITY

The bioavailability of nitrocine® solution is 100 % by definition, as is the case for all drugs given i.v.

OTHER NOTES

Besides the drug substance, glyceryl trinitrate (1 mg/ml), nitrocine® solution contains an isotonic aqueous solution of glucose (49.44 mg/ml) and propylene glycol (1.03 mg/ml).
The solution is free from ethanol and does not contain potassium ions.
No physical or chemical incompatibilities with admixed substances or solutions are known.
Note on the OPC ampoule:
The ampoule has been presawn below the blue spot.
It is therefore not necessary to saw the ampoule.
Break off the ampoule as usual.

THIS IS A MEDICAMENT

– A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed.
– Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Ara Pharmacists

SCHWARZ PHARMA

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Shipment Date	26.01.06
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Remarks	

Digital transmitted PDF reference files are valid without signature. Originals are deposited in packaging technology department.

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