

DATA SHEET

NITRONAL AQUEOUS

Glyceryl trinitrate 1 mg/ml injection

Presentation

Glyceryl trinitrate 1 mg/ml in:

5 ml Ampoules: A clear aqueous solution in 5 ml amber glass appropriately labelled ampoules.

25 ml Ampoules: A clear aqueous solution in a colourless glass 25 ml appropriately labelled vial.

50 ml Ampoules: A clear aqueous solution in a colourless glass 50 ml appropriately labelled vial.

Uses

Actions

Glyceryl trinitrate relaxes smooth muscle, including vascular muscle and reduces blood pressure. Its anti-anginal effect is exerted by reducing myocardial oxygen demand through peripheral vasodilation. This causes decreased venous tone resulting in a reduction in preload and decreased arterial resistance resulting in a reduction in afterload.

Pharmacokinetics

Glyceryl trinitrate is rapidly metabolised after injection so that a constant infusion is required to maintain levels. Metabolism occurs by hydrolysis to dinitrates and the mononitrate. Extrahepatic clearance is high. A relationship between clinical effect and plasma concentration of glyceryl trinitrate has not been determined.

Indications

NITRONAL 1-mg/ml ampoules for intravenous infusion, after dilution if required, are indicated as follows:

1. Acute myocardial infarction with or without left ventricular failure.
2. Left heart failure associated with subacute and acute pulmonary oedema.
3. To reduce ventricular ectopic activity following myocardial infarction.
4. To reverse symptomatic coronary artery spasm following provocative testing in the diagnosis of variant angina.
5. Control of hypertension during surgical cardiovascular procedures and in the production of controlled hypotension during such procedures.

Dosage and Administration

Dosage is affected by the type of infusion set (*see below*) used. Dosage recommendations represented as μg glyceryl trinitrate per minute can only be offered as a starting infusion rate. The correct dose for individual patients will be determined by the response to therapy. All patients should be on continuous cardiovascular monitoring during infusion therapy.

The dosage for **NITRONAL** infusion solution should be initially $5 \mu\text{g}/\text{minute}$ delivered through an infusion pump capable of exact and constant medicine delivery. Increments should be cautious and adjusted to the clinical situation. Initially titration should be in $5 \mu\text{g}/\text{minute}$ increments with increases each 3-5 minutes until some response is noted.

If there is no response at $20 \mu\text{g}/\text{minute}$, larger increments may be used, but once a blood pressure response is observed the increment should be reduced in magnitude and with longer intervals.

There is no fixed dose of **NITRONAL**. Each patient must be titrated to his/her individual needs. Continuous monitoring of physiological parameters must be performed to achieve the correct dose. Maintenance of adequate systemic blood pressure and coronary perfusion is essential.

The maximum dose is 8 (-10) mg per hour of glyceryl trinitrate.

Administration/Dilution Table: Dilution is not necessary but if required for any reason **NITRONAL** injection is compatible with the following infusion solutions:

1. 0.9% NaCl solution
2. 5% Dextrose
3. 0.10% NaCl plus 4.3% Dextrose

Diluted solutions are isotonic.

Ampoules contain either 5 mg in 5 ml, 25 mg in 25 ml or 50 mg in 50 ml; however, the concentration of 5 mg/5 ml is the same.

| Mixing Schedule | Resulting Concentration |
|--|-----------------------------|
| 1 ampoule (5 ml) in 100 ml 25 ml in 500 ml 50 ml in 1000 ml | 50 $\mu\text{g}/\text{ml}$ |
| 1 ampoule (5 ml) in 50 ml 25 ml in 250 ml 50 ml in 500 ml 100 ml in 1000 ml | 100 $\mu\text{g}/\text{ml}$ |
| 1 ampoule (10 ml) in 50 ml 50 ml in 250 ml 100 ml in 500 ml 200 ml in 1000 ml | 200 $\mu\text{g}/\text{ml}$ |

Contraindications

Glyceryl trinitrate may not be used if there is:

- Acute circulatory failure (shock, circulatory collapse).
- Pronounced hypotension (systolic blood pressure < 90mmHg).
- Cardiogenic shock, in so far as sufficiently high left ventricular end-diastolic pressure is not ensured by intra-aortal counter pulsation or positive inotropic medicines.

For acute myocardial infarction with low filling pressures, glyceryl trinitrate should only be used with caution. Administration of glyceryl trinitrate for acute myocardial infarction should only be performed under a doctor's supervision. A drop in systolic pressure below 90 mmHg should be avoided.

Concomitant administration of certain medicines (phosphodiesterase inhibitors) for the treatment of erectile dysfunction and **NITRONAL** is contraindicated due to an increase in the hypotensive effect of **NITRONAL**. This may result in severe side effects such as syncope or myocardial infarction.

Warnings and Precautions

Warning: Intravenous Giving Sets

- Glyceryl trinitrate is readily absorbed onto certain plastics. The dilution and storage of glyceryl trinitrate for i.v. infusion should only be in glass. Plastic parenteral solution containers should not be used.
- Some filters absorb glyceryl trinitrate. Filters in the i.v. giving set should be avoided.

Adsorption is substantially less (5 % or less) where polyethylene or polypropylene sets are utilised. Highest adsorption rates occur when the flow rates are low, glyceryl trinitrate concentrations are high, and the tubing is long.

However, because the amount of vascular binding varies inter-individually there is no correlation between plasma level and the effect. Higher plasma levels can be measured in arterial than in venous blood. In patients showing a greater response to nitrates, lower plasma levels indicate a high vascular binding. Therefore, the dose is always chosen individually according to the prevailing haemodynamic parameters.

It should be noted that published dose rates may have utilised general use PVC tubing and recommended doses may be excessive. We recommend:

- That low adsorptive giving sets are utilised where possible.
- That dosage is individually titrated to patient needs by careful attention to dosage rates and response as documented by physiological monitoring.

In summary, the ideal giving set should be as short as possible, not include a blood filter or burette chamber and, if possible, be of different material than PVC.

Pregnancy and Lactation [(Category B2) 3rd edition "Medicines in Pregnancy" {Australia}]
Animal experiments have provided no evidence of damage to the foetus by glyceryl trinitrate.

However, glyceryl trinitrate should only be administered under a doctor's supervision during pregnancy and lactation.

Diabetes Special care is required when treating diabetic patients since the medicine contains 5% w/v glucose.

Adverse Effects

Headaches caused by vasodilation occur frequently, especially at the onset of therapy. Flushing, drowsiness, orthostatic hypotension and reflex tachycardia are reported occasionally. Less often states of collapse occur, sometimes accompanied by bradyarrhythmias. In rare cases where there is a large drop in blood pressure, symptoms of angina pectoris may be enhanced.

Interactions

Concurrent administration of other vasodilators, antihypertensive agents, calcium antagonists, tricyclic antidepressives and alcohol may enhance the antihypertensive effect of glyceryl trinitrate. When used concurrently with dihydroergotamine, glyceryl trinitrate may cause an increase in the DHE level and thus enhance its effect. Simultaneous administration of heparin and glyceryl trinitrate diminishes the effect of heparin.

Concomitant use of **NITRONAL** and certain medicines (phosphodiesterase inhibitors) for the treatment of erectile dysfunction enhances the hypotensive effect. Therefore, the concomitant administration of **NITRONAL** and these medicines is contraindicated. If a patient treated with these medicines for erectile dysfunction needs a rapidly effective nitrate (eg in the case of an acute angina pectoris attack) the patient must be hospitalised immediately.

Overdosage

Glyceryl trinitrate is well tolerated and has a very wide safety margin. In the event of overdose a higher incidence of the known undesirable effects may occur, such as headaches, drop in blood pressure with orthostatic regulatory disorders and reflex tachycardia. At higher doses (> 20 µg/kg body weight) anticipate formation of methaemoglobin, cyanosis and tachypnoea resulting from nitrate ions formed during metabolism (degradation).

Emergency Procedure: Direct all therapeutic counter-measures towards raising the blood pressure. In less serious cases placing the patient in the supine position with the legs higher than the head will cause the symptoms to disappear.

In cases of severe overdose apply general guidelines for treating overdose and/or shock therapy. For pronounced hypotension, volume substitution can be performed.

In exceptional cases use sympathomimetic agents.

Depending on the degree of severity, the following antidotes may be used:

1. Vitamin C: 1 g p.o. or as sodium salt i.v.
2. Methylene blue: up to 5 ml of a 1% methylene blue solution i.v.
3. Toluidine blue: initially 2-4 mL/kg body weight strictly intravenously.
4. Oxygen therapy, haemodialysis, exchange transfusion.

Pharmaceutical Precautions

NITRONAL ampoules 1 mg/ml are stable for 3 years. **NITRONAL** should not be used after the expiry date.

Medicine Classification

Prescription Medicine.

Package Quantities

NITRONAL 5 ml ampoules are supplied in boxes each containing 10 x 5 ml ampoules.

NITRONAL 25 ml ampoules are supplied in boxes each containing 10 x 25 ml ampoules.

NITRONAL 50 ml vials are supplied in boxes each containing a 50 ml vial.

Further Information

Glyceryl trinitrate is propane-1,2,3-triol trinitrate. It has a molecular formula and weight of $C_3H_5H_3O_9$ and 227.1 respectively.

Name and Address

Manufactured by:
G. Pohl-Boskamp GmbH & Co.
Kieler Strabe 11
D-2214 Hohenlockstedt
Federal Republic of Germany

Distributed by:
Douglas Pharmaceuticals Ltd
PO Box 45-027
AUCKLAND 0651

Ph: (09) 835-0660

Fax: (09) 835-0665

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