1. **NAME OF THE MEDICINAL PRODUCT**

   Nitronal®

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   The active ingredient of Nitronal® is glycercy trinitrate (nitroglycerin). It is an organic nitrate, an ester of nitric acid with the following formula:

   \[
   \begin{align*}
   &\text{CH}_2 - \text{O} - \text{NO}_2 \\
   &\text{CH} - \text{O} - \text{NO}_2 \\
   &\text{CH}_2 - \text{O} - \text{NO}_2
   \end{align*}
   \]

   Molecular weight: 227.1

   1 ml infusion solution contains 1.0 mg glycercy trinitrate.

3. **PHARMACEUTICAL FORM**

   Infusion solution

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

   - Severe angina pectoris: e.g. unstable and vasospastic
   - Acute myocardial infarction
   - Acute left ventricular failure
   - Hypertensive crisis with cardiac decompensation
   - Controlled hypotension
   - Catheter-induced coronary spasms
   - To increase ischaemia tolerance during PTCA
4.2. Posology and method of administration

Dosage guideline

Depending on the initial clinical and haemodynamic values, the dosage is determined by the patient's individual requirement and the response of the parameters to be controlled.

For clinical use, start with a dose of 0.5 - 1.0 mg glycercyl trinitrate per hour and adjust the dosage to meet individual requirements; the maximum dose is as a rule 8 mg glycercyl trinitrate per hour, rarely 10 mg per hour.

In acute myocardial infarction, continuous intravenous infusion should be started as soon as possible. If the systolic pressure exceeds 100 mm Hg, 2 - 8 mg may be infused per hour (33 - 133 µg per minute), in exceptional cases up to 10 mg per hour (166 µg per minute) until the symptoms of angina pectoris subside.

In acute left ventricular failure (pulmonary oedema): 2 - 8 mg per hour (33 – 133 µg per minute), for 1 - 2 days.

In severe angina pectoris, the patient should be placed in intensive care and treated with a dose of 2 to 8 mg per hour (33 - 133 µg per minute). The haemodynamic status must be checked continuously during the infusion. Constant monitoring of systolic and diastolic blood pressure, heart rate and haemodynamic parameters (right heart catheter) such as pulmonary arterial systolic pressure (PASP), pulmonary capillary pressure (PCP), pulmonary arterial diastolic pressure (PADP), cardiac output (CO) and ECG (measurement of the ST segment) is also necessary.

In hypertonic crisis with cardiac decompensation, infuse with continuous monitoring of blood pressure and heart rate at 2 - 8 mg per hour (average 5 mg per hour).

For controlled hypotension, depending on the anaesthetic procedure and the desired blood pressure reduction, 2 - 10 µg per kg body-weight per minute under ECG control and invasive blood pressure control.

In patients with impaired hepatic and renal function, the dose should be reduced according to the severity of the dysfunction.

In order to avoid reduction or loss of activity, select the lowest possible clinically effective dose; if appropriate, intermittent administration or alternating treatment with other vasodilators should be considered.
Method and duration of use:

The intravenous infusion of glyceryl trinitrate should take place in a hospital setting and under continuous cardiovascular control. Nitronal® can be infused either undiluted using appropriate devices or diluted (e.g. with physiological saline solution, glucose 5 %). When using the drug in combination with other infusion solutions the manufacturer's information on the solution concerned must be observed, including compatibility, contra-indications, adverse effects and drug interactions.

Dilution table

<table>
<thead>
<tr>
<th>Amount of active ingredient (glyceryl trinitrate)</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
<th>40 mg</th>
<th>50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitronal® solution</td>
<td>5 ml</td>
<td>10 ml</td>
<td>20 ml</td>
<td>30 ml</td>
<td>40 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>Infusion solution on dilution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+10</td>
<td>50 ml</td>
<td>100 ml</td>
<td>200 ml</td>
<td>300 ml</td>
<td>400 ml</td>
<td>500 ml</td>
</tr>
<tr>
<td>1+20</td>
<td>100 ml</td>
<td>200 ml</td>
<td>400 ml</td>
<td>600 ml</td>
<td>800 ml</td>
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<tr>
<td>1+40</td>
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<tr>
<td>Finished solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1+10</td>
<td>55 ml</td>
<td>110 ml</td>
<td>220 ml</td>
<td>330 ml</td>
<td>440 ml</td>
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</tr>
<tr>
<td>1+20</td>
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<td>210 ml</td>
<td>420 ml</td>
<td>630 ml</td>
<td>840 ml</td>
<td>1050 ml</td>
</tr>
<tr>
<td>1+40</td>
<td>205 ml</td>
<td>410 ml</td>
<td>820 ml</td>
<td>1230 ml</td>
<td>1640 ml</td>
<td>2050 ml</td>
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</table>
## Infusion table

<table>
<thead>
<tr>
<th>Desired glyceryl trinitrate amount / h</th>
<th>Infusion 1 + 10</th>
<th>Infusion 1 + 20</th>
<th>Infusion 1 + 40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/h</td>
<td>drops/min</td>
<td>ml/h</td>
</tr>
<tr>
<td>0.50 mg</td>
<td>5.5</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>0.75 mg</td>
<td>8.25</td>
<td>3</td>
<td>15.75</td>
</tr>
<tr>
<td>1.0 mg</td>
<td>11.0</td>
<td>3 - 4</td>
<td>21.0</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>13.75</td>
<td>4 - 5</td>
<td>26.25</td>
</tr>
<tr>
<td>1.5 mg</td>
<td>16.5</td>
<td>5 - 6</td>
<td>31.5</td>
</tr>
<tr>
<td>2.0 mg</td>
<td>22.0</td>
<td>6 - 7</td>
<td>42.0</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>27.5</td>
<td>9</td>
<td>52.5</td>
</tr>
<tr>
<td>3.0 mg</td>
<td>33.0</td>
<td>11</td>
<td>63.0</td>
</tr>
<tr>
<td>3.5 mg</td>
<td>38.5</td>
<td>12 - 13</td>
<td>73.5</td>
</tr>
<tr>
<td>4.0 mg</td>
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<td>13</td>
<td>84.0</td>
</tr>
<tr>
<td>4.5 mg</td>
<td>49.5</td>
<td>14 - 15</td>
<td>94.5</td>
</tr>
<tr>
<td>5.0 mg</td>
<td>55.0</td>
<td>18</td>
<td>105.0</td>
</tr>
<tr>
<td>5.5 mg</td>
<td>60.5</td>
<td>20</td>
<td>115.5</td>
</tr>
<tr>
<td>6.0 mg</td>
<td>66.0</td>
<td>22</td>
<td>126.0</td>
</tr>
<tr>
<td>7.0 mg</td>
<td>77.0</td>
<td>25 - 26</td>
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<td>8.0 mg</td>
<td>88.0</td>
<td>28 - 29</td>
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</tr>
<tr>
<td>9.0 mg</td>
<td>99.0</td>
<td>31 - 32</td>
<td>189.0</td>
</tr>
<tr>
<td>10.0 mg</td>
<td>110.0</td>
<td>36</td>
<td>210.0</td>
</tr>
</tbody>
</table>

Depending on clinical status, haemodynamics and ECG, treatment may be continued for up to three days or longer.
The medical practitioner decides on the duration of use.

Note:
For the infusion of Nitronal® polyethylene or polytetrafluorethylene tubings proved worthwhile.
Polyvinylchloride tubings lead to a considerable loss of active substance due to adsorption.
4.3. Contraindications

Glyceryl trinitrate must not be used in patients with:
- Hypersensivity to nitro compounds
- Acute circulatory failure (shock, circulatory collapse)
- Cardiogenic shock, unless intra-aortic counterpulsation or positively inotropic drugs ensure an adequately high left-ventricular end-diastolic pressure
- Toxic pulmonary oedema
- Severe hypotension (systolic blood pressure below 90 mm Hg)
- Diseases associated with increased intracranial pressure (further elevation of the blood pressure has so far been observed only in association with high-dose IV administration of glyceryl trinitrate)

Due to a considerable increase in the hypotensive effect and the resulting severe side effects (e.g. synapses, paradoxic myocardial ischemia), certain drugs (phosphodiesterase inhibitors) for the treatment of erectile dysfunction or pulmonary arterial hypertension may not be given additionally to an existing therapy with nitric oxide donors (e.g. Nitronal).

Glyceryl trinitrate may only be administered carefully with
- Hypertrophic obstructive cardiomyopathy, constrictive pericarditis and pericardial tamponade
- Low filling pressures, e.g. with acute myocardial infarction, impaired function of the left ventricle (left ventricular failure). A reduction of the systolic blood pressure below 90 mm Hg must be avoided.
- Aortic and/or mitral stenosis
- Tendency to orthostatic disturbances of circulatory regulation
- Patients with severe hepatic or renal dysfunction

In volume depleted patients, adequate volume replacement is required at the start of treatment.

4.4. Special warnings and special precautions for use

For the infusion of Nitronal® polyethylene or polytetrafluorethylene tubings proved worthwhile. Polyvinylchloride tubings lead to a considerable loss of active substance due to adsorption.
4.5. Interaction with other medicinal products and other forms of interaction

The concomitant intake of other vasodilators, antihypertensives, β-blockers, calcium antagonists, neuroleptics or tricyclic antidepressants, and alcohol may potentiate the antihypertensive action of Nitronal®.

Concomitant intake of nitric oxide donors (e.g. Nitronal) and certain drugs (phosphodiesterase inhibitors) for the treatment of erectile dysfunction or pulmonary arterial hypertension enhances the hypotensive effect. Therefore the concomitant administration of nitric oxide donors, e.g. the active ingredient of Nitronal, and these drugs is contraindicated (see contraindications). If a patient treated with these drugs for erectile dysfunction or pulmonary arterial hypertension needs a rapidly effective nitrate (e.g. in case of an acute angina pectoris attack), he/she must be closely monitored.

Consistent with their known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil and other phosphodiesterase inhibitors for the treatment of erectile dysfunction were shown to potentiate the hypotensive effects of nitrates, and their conadministration with nitric oxide donors or nitrates in any form is therefore contraindicated.

If used concomitantly with dihydroergotamine, Nitronal® may lead to an increase in the DHE level and thus potentiate its hypertensive action.

When heparin and glyceryl trinitrate are used simultaneously, the effects of heparin are reduced. The heparin dosage must be adjusted accordingly while closely monitoring blood coagulation parameters. After discontinuation of glyceryl trinitrate, blood coagulation may be considerably reduced (sharp increase in the PTT), which may necessitate a reduction of the heparin dose.
In patients previously treated with organic nitrates, e.g. isosorbide dinitrate, isosorbide-5-mononitrate, a higher dose of glyceryl trinitrate may be necessary to achieve the desired haemodynamic effect.

4.6. Pregnancy and lactation

As an extra precaution, glyceryl trinitrate may only be taken during pregnancy and lactation, if specifically directed by a doctor, since there is not enough experience with pregnant and nursing women.
Animal studies have provided no evidence of damage to the foetus.
4.7. Effects on ability to drive and use machines

Even when used as directed, this drug may effect the ability to drive or operate machinery. This can occur in particular at the beginning of the treatment, with an increase of the dosage, when changing the medicinal product or when used in combination with alcohol.

4.8. Undesirable effects

At the start of therapy, a nitrate-induced headache can frequently occur, but usually subsides with continued use.

A dose-dependent drop in blood pressure and heart rate increase may occur. In case of a more severe drop in blood pressure, the infusion must be discontinued. If no spontaneous recovery follows, possibly cardiovascular measures have to be taken, e.g. elevation of the legs or volume replacement.

Rarely nausea, vomiting, transient redness of the skin (flush) and allergic skin reactions, may occur.

In rare cases, with a large drop in blood pressure angina pectoris symptoms may be intensified (paradoxical nitrate reaction).

Rarely collapse states, occasionally with cardiac dysrhythmia with a slower pulse rate (bradicardial arrhythmia) and syncope (sudden loss of consciousness) are observed.

In individual cases exfoliative dermatitis (inflammatory skin disease) may occur.

Tolerance development and the occurrence of cross tolerance to other nitro compounds have been described.
In order to avoid an attenuation or loss of effect, high continuous dosage should be avoided.

Note:
During the infusion of Nitronal®, a transient hypoxaemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar regions, and in patients with coronary heart disease it may lead to ischaemia.
4.9. Overdose

a) Symptoms of overdose

Drop in blood pressure with orthostatic regulatory disturbances, reflex tachycardia and headaches, weakness, dizziness, somnolence, flush, nausea, vomiting and diarrhoea may occur.

At high doses (more than 20 mg/kg body-weight) methaemoglobinemia, cyanosis, dyspnoea and tachypnoea must be anticipated owing to nitrite ions formed during the metabolism of glyceryl trinitrate.

At very high doses an increase in intracranial pressure with cerebral symptoms may occur.

At chronic overdosage increased methaemoglobin levels were measured of which the clinical relevance is controversial.

b) Treatment in the event of overdose

In addition to general emergency procedures such as gastric lavage and placing the patient in the recumbent position with the legs raised, the vital parameters must be monitored under intensive-care conditions and corrected if required.

If there is pronounced hypotension and/or shock a volume replacement should be performed; in exceptional cases, norepinephrine and/or dopamine can be infused as a cardiovascular therapy. Administration of epinephrine and related substances is contraindicated.

If methaemoglobinemia occurs, the following antidotes can be used depending on the degree of severity:

1. Vitamin C: 1 g PO or as the sodium salt IV

2. Methylene blue: up to 50 ml of a 1% methylene blue solution IV

3. Toluidine blue: initial dose 2 - 4 mg/kg body-weight, IV only; if necessary, repeated dose of 2 mg/kg body-weight in intervals of 1 h

4. Oxygen therapy, haemodialysis, exchange transfusion.
5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC: C01 DA 02

Glyceryl trinitrate has a direct relaxing effect on smooth vascular muscles and causes a vasodilatation.

The postcapillary capacitance vessels and the large arteries, in particular the parts of coronary arteries still able to respond, are more strongly affected than the resistance vessels. Vasodilatation in the systemic vascular system increases the venous capacity (pooling), reducing venous return to the heart. The ventricular volumes and filling pressures decrease (preload reduction). The smaller ventricular radius and reduced systolic wall tension lower the myocardial energy and O₂ requirements, respectively.

The reduction in cardiac filling pressures promotes perfusion of subendocardial wall layers threatened by ischaemia. Regional wall motion and stroke volume can be improved.

Dilatation of the large pericardial arteries leads to a reduction not only of the systemic (afterload reduction) but also the pulmonary ejection resistance.

Glyceryl trinitrate relaxes the bronchial muscles, the efferent urinary passages, the muscles of the gallbladder, the bile duct as well as the oesophagus, and large and small intestines, including the sphincters.

On a molecular level, nitrates most likely act via formation of nitric oxide (NO) and cyclic guanosyl monophosphate (cGMP), which is thought to mediate relaxation.
5.2. **Pharmacokinetic properties**

Glyceryl trinitrate is completely absorbed by the intestines, however it is subject to an extensive hepatic first-pass metabolism as well as spontaneous hydrolysis in the blood. In addition there is a high erythrocyte binding and accumulation in the vascular wall.

Despite constant dosage and constant nitrate levels the efficacy decreases. An existing tolerance subsides within 24 hours after discontinuation of the therapy. No tolerance has been observed at intermittent administration.

After sublingual application glyceryl trinitrate is rapidly absorbed from the mouth cavity.

The first-pass effect varies after sublingual and topical administration. Thus the absolute bioavailability after sublingual administration is approximately 39% and after topical administration as patch approximately 55%.

The plasma protein binding is approximately 60%.

The elimination half-life of glyceryl trinitrate is short. Following sublingual administration values of 2.5 - 4.4 minutes, following IV administration values of 2 - 2.5 minutes are reported.

Glyceryl trinitrate is metabolised in the liver as well as in many other cells, e.g. in the erythrocytes, with cleavage of one or more nitrate groups.

In addition to glyceryl trinitrate metabolism there is a renal elimination of the metabolites.

Range of therapeutic blood level:
0.1 ng/ml to 3 (-5) ng/ml.

**Plasma concentrations**

After sublingual administration large intra-individual and interindividual variations were observed for the plasma concentrations.

For a sublingual dose of 0.4 mg $C_{\text{max}}$ is $1.9 \pm 1.6$ ng/ml (coefficient of variation 87%) and $t_{\text{max}}$ 5 ± 2 min (range: 2 to 10 min).
5.3. Preclinical safety data

a. Acute toxicity
LD₅₀:
Rats:  (IV)  40.83 mg/kg body-weight
       (oral)  525.00 mg/kg body-weight
Dogs:  (IV)  19.00 mg/kg body-weight

Autopsy of the animals treated revealed no pathological findings.

b. Subchronic toxicity

In a 13-week study glyceryl trinitrate was administered orally to:
dogs:  up to 5 mg/kg/day
rats:  up to 234 mg/kg/day
mice  up to 608 mg/kg/day

with no signs of toxic effects. Only the rats showed a retarded weight gain at high doses.

c. Chronic toxicity

Dogs were administered oral doses of up to 25 mg/kg/day for 12 months. Only a slight
dose-dependent formation of methaemoglobin was observed. Otherwise there were no
toxic effects.

After administration of up to 38.1 mg/kg/day for two years in rats, there were no
statistically significant toxic effects compared with the control group. At higher doses the
weight gain was very retarded and there was methaemoglobin formation and
hepatocellular changes.

Mice were given up to 114 mg/kg/day for two years. These amounts were tolerated with
no signs of a toxic effect. At higher doses there was a reduced weight gain and
methaemoglobin formation. There were no other toxic effects.
d. Mutagenic and tumorigenic potential

Glyceryl trinitrate has not been fully tested for its mutagenic effects. A gene mutation test in bacteria (AMES test) was negative.

Long-term animal studies corresponding to the current state-of-the-art are not available for determining the tumorigenic potential of glyceryl trinitrate.

e. Reproduction toxicity

There are no adequate studies especially for the first trimester of pregnancy for humans.

Sufficient studies on the reproduction of animals after intravenous, intraperitoneal and dermal administration are available.

In studies on the embryotoxicity and fertility there were no signs of an effect on the embryo or impairment of fertility, even at doses toxic to the parent animals. In particular the studies revealed no evidence of teratogenic properties. Doses above 1 mg/kg/day (IP) and 28 mg/kg/day (dermal) showed a foetotoxic effect (reduced initial weight) after administration during foetation of gravid rats.

Studies to determine the effective concentration in breast milk are not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose monohydrate</td>
<td>49.0 mg</td>
</tr>
<tr>
<td>Dilute hydrochloric acid (for pH adjustment)</td>
<td>ad pH 3.9</td>
</tr>
<tr>
<td>Water for injections</td>
<td>ad 1.0 ml</td>
</tr>
</tbody>
</table>

6.2. Incompatibilities

See 4.4. "Special warnings and special precautions for use".
6.3. Shelf life

Nitronal® has a shelf-life of 4 years (closed container).
The dilution of Nitronal® with physiological saline solution or glucose solution 5 % has a
durability of 48 hours.
The drug should not be used after the expiry date.

6.4. Special precautions for storage

Store below 25 °C.

6.5. Nature and contents of container

10 ampoules of 5 ml

6.6. Instructions for use and handling

None

7. MARKETING AUTHORISATION HOLDER

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Tel.: (0216) 474 04 14
Fax: (0216) 474 10 70
E-mail: info@farma-tek.com
Website: www.farma-tek.com

8. MARKETING AUTHORISATION NUMBER

119-32
9. DATE OF AUTHORISATION

24 February 2006

10. DATE OF (PARTIAL) REVISION OF THE TEXT

November 2006

11. PRESCRIPTION ONLY MEDICINE