

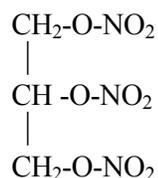
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NITROLINGUAL[®] Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of NITROLINGUAL[®] Spray is glyceryl trinitrate (nitroglycerin). It is an organic nitrate, an ester of nitric acid with the following structural formula:



Relative molecular weight: 227.1

One spray dose of 48 mg contains 0.40 mg of glyceryl trinitrate.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Sublingual spray

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Arrestation of angina pectoris attacks;
- As a prophylactic measure immediately prior to physical exertion or other situations known from experience to be capable of triggering episodic cardiac pain (prophylaxis of angina pectoris);
- Acute cardiac infarction;
- Acute left-heart failure (acute myocardial insufficiency, with acutely impaired left ventricular function);
- Catheter-induced coronary spasms during coronary angiography.

4.2. Posology and method of administration

Unless otherwise prescribed, at the onset of an angina pectoris attack or immediately preceding situations known from experience to provoke an angina pectoris attack depending on the severity of the attack administer 0.4 mg - 0.8 mg of glyceryl trinitrate, corresponding to 1 - 2 spray doses.

In acute left ventricular failure and acute myocardial infarction depending on the severity administer 0.4 mg - 1.2 mg of glyceryl trinitrate, corresponding to 1 - 3 spray doses while continually monitoring the circulatory conditions (systolic blood pressure above 100 mm Hg). If there is no response, the same dose can be administered again 10 minutes later.

As prophylaxis prior to coronary angiography, 0.4 - 0.8 mg of glyceryl trinitrate, corresponding to 1 - 2 spray doses are administered.

4.3. Contraindications

NITROLINGUAL[®] Spray may not be used in patients with:

- hypersensitivity to one of the components of the drug
- acute circulatory failure (shock, circulatory collapse)
- severe hypotension (systolic blood pressure below 90 mm Hg)
- cardiogenic shock, unless a sufficiently high left ventricular enddiastolic pressure is assured by intra-aortal counterpulsation or positive inotropic drugs
- hypertrophic obstructive cardiomyopathy
- constrictive pericarditis
- pericardial tamponade
- primary pulmonary hypertension, since hypoxaemia may occur due to a possible increase in blood flow to hypoventilated alveolar regions (pulmonary "shunt"-formation). This applies especially to patients with coronary artery disease.

Due to a considerable increase in the hypotensive effect and the resulting severe side effects (e.g. syncope, paradoxical myocardial ischaemia) certain drugs (phosphodiesterase inhibitors) for the treatment of erectile dysfunction may not be given additionally to an existing therapy with nitric oxide donors (e.g. NITROLINGUAL[®] Spray).

Especially careful monitoring by a doctor is necessary in:

- acute myocardial infarction with low filling pressure, a reduction of the systolic blood pressure below 90 mm Hg should be avoided.
- aortic and/or mitral stenosis
- tendency to orthostatic disturbances of circulatory regulation
- diseases accompanied by an elevated intracranial pressure (a further increase in pressure has only been reported with high IV doses of glyceryl trinitrate).

4.4. Special warnings and special precautions for use

None

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant intake of other vasodilators, antihypertensives, β -blockers, calcium antagonists, neuroleptics or tricyclic antidepressants and alcohol may potentiate the antihypertensive effect of NITROLINGUAL[®] Spray.

The hypotensive effects of nitrates are potentiated by concurrent administration of phosphodiesterase inhibitors used in the treatment of erectile dysfunction. A severe and possibly dangerous fall in blood pressure may occur. This can result in collapse, unconsciousness and paradoxical myocardial ischaemia. Such use is therefore contra-indicated

(see contraindications). If a patient treated with these drugs for erectile dysfunction needs a rapidly effective nitrate, he/she should be closely monitored.

In patients previously treated with organic nitrates (e.g. isosorbide dinitrate, isosorbide-5-mononitrate) it may be necessary to increase the glyceryl trinitrate dose to achieve the desired effect.

If used concomitantly with dihydroergotamine, NITROLINGUAL® Spray may increase the DHE level and consequently enhance its hypertensive effect.

Concomitant administration of heparin and glyceryl trinitrate weakens the effect of heparin.

4.6. Pregnancy and lactation

As a special precaution during pregnancy and lactation, glyceryl trinitrate should not be taken unless specifically prescribed by a doctor. 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 NITROLINGUAL® Spray may affect the reactions to such an extent that the ability to drive or use machines is impaired. This is especially true in combination with alcohol.

4.8. Undesirable effects

At the start of therapy headaches (nitrate-induced headaches) occur frequently, but usually subside with continued use.

Occasionally a drop in blood pressure and/or orthostatic hypotension have been observed when glyceryl trinitrate was used for the first time or the dose was increased. This may be accompanied by a reflex increase in heart rate, somnolence, dizziness and weakness.

Rarely nausea, vomiting, transient flushing 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).

Rare cases of states of collapse, occasionally with bradyarrhythmias and syncope have been observed.

Rarely an exfoliative dermatitis may occur.

A tolerance development and occurrence of a cross-tolerance to other nitro compounds have been reported.

With continued use the haemodynamic effects abate within 24 hours.

4.9. Overdose

The clinical picture depends on the extent of overdosage and is characterised mainly by the following symptoms:

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

At high doses 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 an increase of the methaemoglobin level has been measured, of which the clinical relevance is controversial.

Treatment in the event of overdosage

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 contra-indicated.

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 hour.
4. Oxygen therapy, haemodialysis, exchange transfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glyceryl trinitrate has a directly 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 esophagus, 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 a spontaneous hydrolysis in the blood. In addition, there is a high erythrocyte binding and accumulation in the vascular wall.

After sublingual administration, glyceryl trinitrate is rapidly absorbed from the mouth cavity. The systemic availability is subject to strong individual variations and is on average approx. 39%.

The plasma protein binding is approx. 60%.

Glyceryl trinitrate has a short elimination half-life. After sublingual administration, values of 2.5 - 4.4 min are reported.

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

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

Therapeutic blood level: 0.1 ng/ml to 3(-5) ng/ml.

Plasma concentration:

After sublingual administration, a wide range of intra-individual and interindividual variations is observed for the plasma concentration. For a sublingual dose of 0.4 mg, C_{max} is 1.9 ± 1.6 ng/ml (coefficient of variation: 87%) and t_{max} 5 ± 2 min (range: 2 to 10 min).

Bioavailability

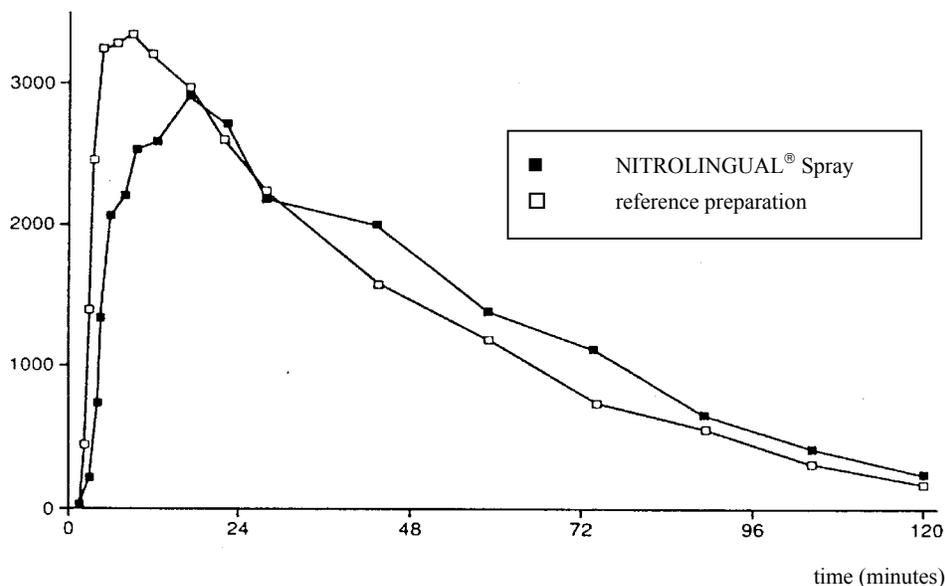
In a bioavailability study, conducted in 1992 in 24 subjects, after administration of 2 doses (corresponding to 0.8 mg GTN) the following results were obtained for 1,2-dinitrate metabolites compared with the reference preparation.

	NITROLINGUAL[®] Spray	Reference preparation
Maximum plasma concentration (C_{max}):	3.8 ng/ml (± 1.9 ng/ml)	4.3 ng/ml (± 2.1 ng/ml)
Time to reach maximum plasma conc. (t_{max}):	20.5 min (± 12.4 min)	15.6 min (± 7.0 min)
Area under the conc.-time curve (AUC):	158.7 ng/ml x min (± 77.0 ng/ml x min)	155.2 ng/ml x min (± 57.5 ng/ml x min)

The data are reported as mean value and standard deviations.

The changes in mean plasma concentration relative to the reference preparation are depicted in a concentration-time diagram:

Concentration of 1,2 – GDN
(pg/ml)



No differences in the pharmacodynamic effects can be determined for NITROLINGUAL® Spray and the reference preparation.

5.3. Preclinical safety data

- a) Acute toxicity
LD₅₀:

Rat:	(IV)	40.83	mg/kg body-weight
	(oral)	525.00	mg/kg body-weight
Dog:	(IV)	19.00	mg/kg body-weight

Autopsy of the treated animals revealed no pathological findings.

- b) Chronic toxicity

In a 13 week study glyceryl trinitrate was administered orally

to dogs:	up to	5 mg/kg/day
to rats:	up to	234 mg/kg/day
and to mice:	up to	608 mg/kg/day

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

- c) Mutagenic and tumorigenic potential

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

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

Mice were administered up to 114 mg/kg/day for two years. These amounts were tolerated without any signs of toxicity. At higher dosages there can be a reduction in weight gain and methaemoglobin formation. No other toxic effects were observed.

Assuming a possible maximum daily dose of 25 spray doses of 0.4 mg of glyceryl trinitrate each, the maximum total intake in humans would be 10 mg. This corresponds to approximately 0.14 mg/kg body-weight in a person weighing 70 kg. This dose is considerably lower than the one safely tolerated in long-term studies.

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

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

d) **Reproduction toxicity**

Clinical data in humans are inadequate, especially for the first trimester of pregnancy.

Reproduction studies in animals for oral administration have not been performed. However, studies have been performed in rats and rabbits after intraperitoneal or intravenous administration. These include studies on fertility and reproductive capacity, embryo toxicity and perinatal and postnatal development. They did not reveal any effects on the embryo, foetus or young animal even at doses of up to 5-20 mg/kg body-weight, which were toxic to the parent animals. Specifically, no teratogenic properties of glyceryl trinitrate were revealed.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Medium-chain triglycerides, ethanol, medium-chain partial glycerides, peppermint oil.

6.2. Incompatibilities

None known

6.3. Shelf life

The shelf life is three years.

This drug should not be used after the date of expiry.

6.4. Special precautions for storage

None

6.5. Nature and contents of container

Glass bottles with metering pump.

1 bottle containing 11.2 g (12.2 ml) of solution.

6.6. Instructions for use and handling

Before each use, the protective cap is removed by pulling off in a vertically upwards direction. To familiarise oneself with the use of NITROLINGUAL[®] Spray and to fill the dose-metering chamber completely when first using, the valve is first of all operated and the contents sprayed into the air until liquid comes out (press the spray nozzle down firmly as far as it will go, and then release).

This may also be necessary if the spray has not been used for a long time. The spray is now ready to use, and needs not be shaken first.

When spraying, the bottle has to be held vertically with the spray nozzle uppermost. The orifice in the spray nozzle should be positioned as close as possible to the mouth. This orifice is easily felt, and can therefore also be used as a reliable indicator of the bottle orientation when using the spray at night. The spray is puffed into the mouth, preferably under the tongue, at intervals of about 30 sec while holding the breath. Do not inhale.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

MA097/00101

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10th October 2006

10. DATE OF REVISION OF THE TEXT