Proteins, glycogen, lipids and ribonucleic acid) and is partly oxidised up to CO₂. This metabolic process occurs in the liver, but also in many other cells, e.g. the red blood cell. The degradation products have little or no vasodilator activity.

Mechanism of Action

Nitroglycerin acts as a donor of nitric oxide (NO). NO causes relaxation of vascular smooth muscle via the stimulation of guanylyl cyclase and the subsequent increase in intracellular cyclic guanosine monophosphate (cGMP) concentration. A cGMP-dependent protein kinase is thus stimulated, with resultant phosphorylation of various proteins in the smooth muscle cell. This eventually leads to the dephosphorylation of the light chain of myosin and the lowering of contractility.

Pharmacokinetics

Absorption

Nitroglycerin patch is a transdermal system which delivers its active ingredient nitroglycerin with a characteristic release profile. While the system is in place during its application period, the average dose of nitroglycerin released to the skin by Nitroglycerin transdermal patch is 5mg over 24 hours which corresponds to 0.2 mg / hour and by Nitroglycerin transdermal patch is 10mg over 24 hours which corresponds to 0.4 mg / hour.

Bioavailability

After peroral administration, nitroglycerin is subject to a pronounced first-pass effect, rendering a bioavailability of less than 1%. However, nitroglycerin is absorbed through the skin, bypassing the gastro-intestinal tract and hepatic first-pass effect. As a result, the bioavailability is higher (about 55%).

Distribution

Effective concentrations of nitroglycerin occur just one hour after applying Nitroglycerin transdermal patch, the maximum plasma concentration is seen after about 2 - 4 hours on average. The steady-state concentration in the plasma depends on the dose applied and the corresponding rate of absorption. At a rate of absorption of 0.4mg / h, the average steady-state concentration is reported to be about 0.2μg/ L.

The proposed site of application of the patch (upper arm, thorax, and hip) does not influence the plasma concentration. If the medication is stopped (this can be done at any time by removing the system) the nitroglycerin plasma concentration decreases rapidly.

Plasma protein binding is about 60%.

Metabolism

The metabolism of nitroglycerin, which occurs in the liver, but also in many other cells, e.g. the red blood cells, involves the cleaving of one or more nitrate groups. Nitroglycerin transdermal patch is very rapidly and almost completely metabolised in the organism. The degradation products have little or no vasodilator activity.

Nitroglycerin is enzymatically denitrated stepwise to glyceryl dinitrates, glyceryl mononitrates and finally to glycerol. The enzyme necessary for this process is glutathione-S transferase. This enzyme is present in many tissues. Glycerol is assimilated into intermediate metabolism (synthesis of proteins, glycogen, lipids and ribonucleic acid) and is partly oxidised up to CO₂ and expired.

Glyceryl dinitrates and glyceryl mononitrates are also glucuronidised and excreted in the urine and, to a small extent, in the bile ducts. Most of the metabolic data on nitroglycerin have been obtained from animal studies. It has been possible to detect mononitrates of nitroglycerin in the human urine.
There is no accumulation of nitroglycerin or its metabolites (1, 2-glycerol dinitrate and 1, 3-glycerol dinitrate).

**Elimination**
The nitroglycerin elimination half-life time is 2 - 4 min. Besides metabolism of nitroglycerin, there is a renal elimination of the metabolites.

**Special Patient Populations**
There is no evidence that a dosage adjustment is required in the elderly or in diseases like renal failure or hepatic insufficiency.

**Preclinical Safety Data**

**Acute toxicity:**

According to the RTECS®, the LD₅₀ values for nitroglycerin after a single dose are:

<table>
<thead>
<tr>
<th>Species</th>
<th>Route of administration</th>
<th>LD₅₀ (mg / kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>(intravenous)</td>
<td>10.6</td>
</tr>
<tr>
<td>Rat</td>
<td>(intravenous)</td>
<td>23.2</td>
</tr>
<tr>
<td>Mouse</td>
<td>(subcutaneous)</td>
<td>110.0</td>
</tr>
<tr>
<td>Rat</td>
<td>(subcutaneous)</td>
<td>94.0</td>
</tr>
</tbody>
</table>

*Registry of Toxic Effects of Chemical Substances*

**Chronic Toxicity:** A 26 week study with daily application of nitroglycerin to the skin of male rabbits revealed as NOEL (no observed effect level) 15mg / kg / day for the skin and 60mg / kg / day for the systemic system.

**Teratology:** Animal teratology studies have not been conducted with nitroglycerin patches. Teratology studies in rats and rabbits however were conducted with topical applied nitroglycerin ointment at doses up to 80mg / kg / day and 240mg / kg / day respectively. No toxic effects on dams and foetuses were seen in any dose tested.

**Mutagenecity:** Nitroglycerin has not been extensively examined for mutagenic effects. A gene mutation test in *S. typhimurium* (Ames test) revealed a negative result.

**Carcinogenecity:** No state-of-the-art carcinogenic toxicity studies have been performed to determine the carcinogenic potential of nitroglycerin.

**INDICATIONS**
- Long-term treatment of coronary artery disease.
- Long-term treatment and prevention of angina pectoris (even after sufficiently treated myocardial infarction).
- Long-term treatment of severe chronic myocardial insufficiency in combination with cardiac glycosides, diuretics, ACE Inhibitors or arterial vasodilators.
- Pulmonary hypertension

**DOSAGE AND ADMINISTRATION**
The medication is usually started with one Nitroglycerin (Deponit® NT) transdermal patch daily. If necessary, the dose may be increased for the doses 5mg and 10mg (2 patches simultaneously). There is no evidence to suggest an adjustment of the dosage in elderly patients. The safety and efficacy of Nitroglycerin (Deponit® NT) transdermal patch has yet to be established in children.

**Administration**
The patch should be applied to healthy, undamaged and relatively crease-free and hairless skin. Skin-care products should not be used before applying Nitroglycerin (Deponit® NT) transdermal patch. The same site should not be used again before some days have passed. To avoid development of tolerance, the patch should remain on the skin only for about 12 to 16 hours, to ensure a nitrate free interval of 8 to 12 hours. An additional anti-angina therapy with drugs not containing nitro compounds should be considered for the nitrate-free period.

For the purpose of individual dosing for each patient, the nitroglycerin patch can be cut into smaller pieces. The pieces adhere just as well as full-size systems. The dose is determined by the surface area of the piece relative to that of the original system.

**CONTRAINdications**
Nitroglycerin (Deponit® NT) transdermal patch must not be used in patients with:
- Hypersensitivity to nitroglycerin, other nitrate compounds or to any of the excipients
- Acute circulatory failure (shock, collapse)
- Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures)
- Hypertrophic obstructive cardiomyopathy
- Constrictive pericarditis
- Cardiac tamponade
- Severe hypotension (systolic blood pressure less than 90 mmHg)
- During nitrate therapy, phosphodiesterase inhibitors (e.g. sildenafil) must not be used (see Drug Interactions)

**WARNINGS AND PRECAUTIONS**
Nitroglycerin (Deponit® NT) transdermal patch should be used only with particular caution and under medical supervision in:
- Low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure)
• Tachycardia
• Weak pulse
• Sweating
• Paleness

Symptoms:
In view of the transdermal mode of delivery, an overdose of nitroglycerin i.v. in high dosages has only been observed following the administration of nitroglycerin in high dosages.

Orthostatic dysfunction

Nitroglycerin (Deponit® NT) transdermal patch is not suitable for treatment of acute angina attacks. The development of tolerance and cross tolerance to other nitro compounds has been described. Patients who undergo a maintenance treatment with nitroglycerin should be informed that they must not use phosphodiesterase inhibitor-containing products (e.g. sildenafil). Nitroglycerin (Deponit® NT) transdermal patch therapy should not be interrupted to take phosphodiesterase inhibitor-containing products (e.g. sildenafil), because the risk of inducing an attack of angina pectoris could increase by doing so (see Drug Interactions).

Effects on ability to drive and use machines
Nitroglycerin (Deponit® NT) transdermal patch may affect the patient’s reactivity to an extent that her/his ability to drive or to operate machinery is impaired. This effect is increased in combination with alcohol.

DRUG INTERACTIONS
Concurrent intake of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel antagonists, vasodilators etc, and/or alcohol may potentiate the hypotensive effect of Nitroglycerin (Deponit® NT) transdermal patch. This might also occur with neuroleptics and tricyclic antidepressants.

A blood pressure lowering effect of nitroglycerin patch will be increased, if used together with phosphodiesterase inhibitors (e.g. sildenafil) which are used for erectile dysfunction (see Warnings and Precautions). This might lead to life-threatening cardiovascular complications. Patients who are on Nitroglycerin (Deponit® NT) transdermal patch therapy therefore must not use phosphodiesterase inhibitors (e.g. sildenafil).

Reports suggest that, when administered concomitantly, nitroglycerin may increase the blood level of dihydroergotamine and its hypertension effect.

PREGNANCY AND LACTATION
Pregnancy Category: C

Reproduction studies performed in rats and rabbits with topically applied nitroglycerin ointment at doses up to 80mg / kg / day and 240mg / kg / day respectively have revealed no evidence of harm to the foetus due to nitroglycerin. There are, however, no adequate and well-controlled studies in pregnant women. Since animal studies are not always predictive of human response, it is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nitroglycerin (Deponit® NT) transdermal patch is administered to a nursing woman.

ADVERSE EFFECTS
Adverse effects frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) or very rare (<1/10,000).

During administration of Nitroglycerin (Deponit® NT) transdermal patch the following undesirable effects may be observed:

Cardiac disorders:
common: reflex tachycardia, uncommon: enhanced angina pectoris symptoms.

Gastrointestinal disorders:
uncommon: nausea, vomiting, very rare: heartburn.

General disorders and administration site conditions:
common: feeling of weakness.

Nervous system disorders:
very common: headache, common: light headedness, dizziness, drowsiness.

Skin and subcutaneous tissue disorders:
uncommon: allergic skin reactions (e.g. rush, itching or burning at application site, reddening), allergic contact dermatitis. In single cases exfoliative dermatitis may occur.

Vascular disorders:
common: hypotension on standing, uncommon: collapse (sometimes accompanied by bradyarrhythmia and syncope). Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration.

Advice:
During treatment with Nitroglycerin (Deponit® NT) transdermal patch, a temporary hypoxemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas. Particularly in patients with coronary artery disease this may lead to a myocardial hypoxia.

OVERDOSEAGE AND TREATMENT

Animal experience:
In rats and mice, significant lethality (LD₅₀) at single subcutaneous doses of 94mg / kg and 110mg / kg, respectively, was observed.

Human experience:
In view of the transdermal mode of delivery, an overdose of nitroglycerin is unlikely to occur.

Symptoms:
• Fall of blood pressure ≤ 90 mmHg
• Paleness
• Sweating
• Weak pulse
• Tachycardia
• Light-headedness on standing
• Headache
• Weakness
• Dizziness
• Nausea
• Vomiting
• Diarrhoea

• Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During nitroglycerin biotransformation nitrite ions are released, which may induce methaemoglobinaemia and cyanosis with subsequent tachypnoea, anxiety, loss of consciousness and cardiac arrest. It cannot be excluded that an overdose of nitroglycerin may cause this adverse reaction.
• In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

Treatment
General procedure:
• Stop delivery of the drug
  Since Nitroglycerin (Deponit® NT) transdermal patch is applied to the skin, removing the patch immediately stops delivery of the drug.
• General procedures in the event of nitrate-related hypotension
  − Patients should be kept horizontal with the head lowered and legs raised
  − Supply oxygen
  − Expand plasma volume
  − Specific shock treatment (admit patient to intensive care unit!)

Special procedure:
• Raising the blood pressure if the blood pressure is very low
• Additional administration of a vasoconstrictor, e.g. norepinephrine HCl
  − Treatment of methaemoglobininaemia
    − Reduction therapy of choice with vitamin C, methylene blue, or toluidine blue
    − Administer oxygen (if necessary)
    − Initiate artificial ventilation
    − Haemodialysis (if necessary)
• Resuscitation measures
  In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

STORAGE CONDITIONS
Store at temperatures not exceeding 25°C.
Store in the original package.

INSTRUCTIONS FOR USE/ HANDLING
Dosage according to indications:
The treatment should be adjusted as closely as possible to the patient's needs, in the light of the severity of his/her illness and response to the treatment. General dosage recommendations (to be followed unless a different dosage is specified by the prescriber):

For the long-term treatment of coronary artery disease and prevention of angina pectoris medication is usually started with one Nitroglycerin (Deponit® NT) transdermal patch daily in the morning. If necessary, the dose may be increased (2 patches simultaneously).

As with all nitrates, the effect of nitroglycerin patches may decline in some patients receiving long-term treatment. These patients should remove the patch before they go to sleep at night. Patients who experience angina mainly during the night should only wear a patch at night.

To protect the patient from angina attacks the treatment must not be stopped abruptly. If the patient is being switched to another type of treatment the two treatments should overlap.

Where on the body should Deponit NT be applied?
As long as it is not applied to an area of the skin which is very thick (e.g. foot) and has poor circulation, Nitroglycerin (Deponit® NT) transdermal patch is effective wherever it is applied. To avoid skin irritation, Nitroglycerin (Deponit® NT) transdermal patch should be applied to a different area of skin each day. An application site should not be re-used for at least 2 to 3 days. The best places to apply nitroglycerin patches are the easily reached, fairly static areas at the front or side of the chest. However, Nitroglycerin (Deponit® NT) transdermal patch may be also applied to the upper arm, thigh, abdomen or shoulder (Figure 1).
The skin at the application site:
The skin at the application site should be healthy, undamaged and relatively crease-free and hairless.

- Nitroglycerin (Deponit® NT) transdermal patch should not be applied to damaged or diseased skin.
- Nitroglycerin (Deponit® NT) transdermal patch will adhere better if it is applied to a region of skin which is not subject to significant shearing movements as the patient moves.
- Nitroglycerin (Deponit® NT) transdermal patch must not be applied to very hairy skin. Shaving the area or trimming hairs with scissors is inadvisable, because hairs may lift the patch off the skin as they regrow.

The application site should be cleaned and dried before Nitroglycerin (Deponit® NT) transdermal patch is applied.
- Before applying, Nitroglycerin (Deponit® NT) transdermal patch, the skin should be washed with soap in the normal manner. It is not necessary to wash the skin with strong cleansing agents such as alcohol.
- After showering or bathing, Nitroglycerin (Deponit® NT) transdermal patch should not be applied until the body has cooled down to normal temperature and the skin is dry. If Nitroglycerin (Deponit® NT) transdermal patch is already in place before the patient takes a shower or bath or goes swimming, generally it adheres firmly to the skin and goes on working. However, to be on the safe side the patient should not stay in the water too long.

Skin-care products should not be used before applying Nitroglycerin (Deponit® NT) transdermal patch.
- Toiletries which contain oils and creams, lotions, etc. must not be used on the application site of the skin before applying Nitroglycerin (Deponit® NT) transdermal patch, because the patches do not adhere well to greasy skin.

Applying Nitroglycerin (Deponit® NT) transdermal patch

Each patch is packed in a unit dose pouch and should be left in it until needed. The sealed pouch is easy to tear open from one of the slits in the edge (Figure 2).

The patch is removed from the pouch and held in both hands with the release liner (protective foil) uppermost. One half of the patch is then turned down so that the S-shaped break in the middle opens (Figure 3).

One half of the release liner can then be peeled off. The adhesive surface should not be touched. The patch is then applied to the prepared area of skin and the other half of the release liner removed (Figure 4).

The patch is then pressed down hard with the flat of the hand to ensure that the whole of the adhesive surface of the patch is adhering firmly to the skin (Figure 5).
AVAILABILITY
Nitroglycerin (Deponit® NT 5) 5mg / 24 hours TDDS: transdermal patch: (box of 10’s)
Nitroglycerin (Deponit® NT 10) 10mg / 24 hours TDDS: transdermal patch: (box of 10’s)

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.
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