NOVARTIS

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו במאי 2015.

NITRODERM® TTS (nitroglycerin)

25 mg or 50 mg transdermal patch

Prescribing Information

1 Trade name

NITRODERM® TTS 5

NITRODERM® TTS 10

2 Description and composition

Active substance

Nitroderm TTS contains Nitroglycerin (25mg or 50mg) in a transdermal therapeutic system (TTS).

List of excipients

Silica aerogel, silicone oil 360, ethylene-vinylacetate copolymer, medical adhesive CH 15 .

Pharmaceutical form

Transdermal Patch

Flat multilayer system designed to deliver nitroglycerin continuously through a release membrane following application to the skin. The release membrane limits delivery through hyperpermeable skin. The active substance penetrates the skin and thus becomes directly bioavailable to the systemic circulation at relatively constant concentrations during the recommended application period. The following two systems are available:

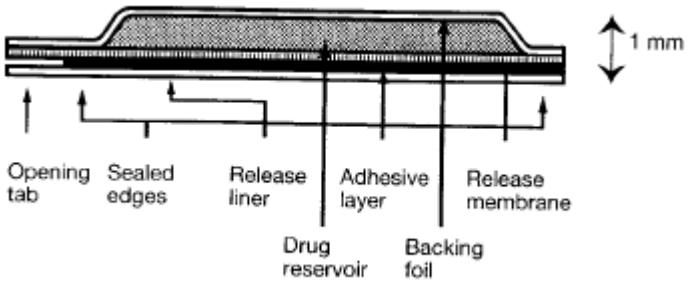
Table 2-1 Nitroderm TTS pharmaceutical forms

	Nitroderm TTS 5	Nitroderm TTS 10
Nitroglycerin content	25 mg	50 mg
Drug-releasing area	10 cm^2	20 cm^2
Imprint (backing side)	CG	CG
	DOD	DPD
Colour of the release liner	off-white to yellowish	

The numeric components of the product designations TTS 5 and TTS 10 denote the nominal amount of nitroglycerin in mg delivered by the system per 24 hours.

The remainder of the nitroglycerin in each system serves as a reserve and is not delivered during normal use. After 12 hours, for example, each system has delivered 10% of its original nitroglycerin content. Since nitroglycerin is released from Nitroderm TTS at a constant rate per cm^2, the dose administered is related to the size of the drug-releasing area. The nominal rate of nitroglycerin release in vivo is approximately 20-25 microgram/cm^2.h.

The following cross-sectional diagram shows the composition of Nitroderm TTS.



3 Indications

Prophylaxis of angina pectoris

4 Dosage and administration

General rules

Nitroderm TTS is not intended for the immediate relief of acute attacks of angina pectoris; if these occur, rapid-acting nitrate preparations should be used.

The response to nitrate preparations varies from patient to patient; the lowest effective dose should be prescribed. The application site should be changed regularly to prevent local irritation.

Development of tolerance or attenuation of therapeutic effect commonly occurs with prolonged or frequent administration of long-acting nitrates, including Nitroderm TTS or other transdermal systems. A patch-off period of 8-12 hours, usually at night, every 24 hours

is recommended to overcome tolerance. Clinical trials have shown that in most patients intermittent therapy is more effective than continuous administration. Continuous application of Nitroderm TTS may be appropriate for patients in whom long-term clinical responsiveness can be reliably assessed.

Prophylaxis of angina pectoris

Treatment should be initiated with one Nitroderm TTS 5 daily. According to the clinical response the daily dose can then be titrated upwards to:

- one Nitroderm TTS 10 (normal maintenance dose)
- one Nitroderm TTS 10 plus one Nitroderm TTS 5
- two Nitroderm TTS 10

Special populations

Geriatric patients (above 65 years age)

No specific information on use in the elderly is available; however, there is no evidence to suggest that the dosage needs to be adjusted in elderly patients.

Pediatric patients

Not enough is known about the effects of Nitroderm TTS in children, which means that it cannot be recommended for use in this age group.

5 Contraindications

Known hypersensitivity to nitroglycerin and related organic nitrates or any excipient of Nitroderm TTS.

Acute circulatory failure associated with marked hypotension (shock).

Conditions associated with elevated intracranial pressure.

Myocardial insufficiency due to obstruction, as in aortic or mitral stenosis or constrictive pericarditis.

Concomitant use of Nitroderm TTS and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil is contraindicated, because PDE5 inhibitors may amplify the vasodilatory effects of Nitroderm TTS resulting in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrite overdose, with elevation of the extremities and with central volume expansion.

Severe hypotension (systolic blood pressure less than 90 mmHg).

Severe hypovolemia.

The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

6 Warnings and precautions

Warnings

As with other nitrate preparations, when switching the patient on long-term therapy to another form of medication, nitroglycerin should be gradually withdrawn and overlapping treatment started.

The Nitroderm TTS patch contains an aluminium layer. Therefore, Nitroderm TTS must be removed before applying magnetic or electrical fields to the body during procedures such as MRI (Magnetic Resonance Imagining), cardioversion or DC defibrillation, or diathermy treatment.

In cases of recent myocardial infarction or acute heart failure, treatment with Nitroderm TTS should be carried out cautiously under strict medical surveillance and/or hemodynamic monitoring.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Nitroderm TTS patch. The arching that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

Precautions

Hypoxaemia

Caution should be exercised in patients with arterial hypoxemia (including G6PD deficiency induced forms) due to severe anemia, because in such patients the biotransformation of nitroglycerin is reduced. Similarly, caution is called for in patients with hypoxemia and ventilation/perfusion imbalance due to lung disease or ischemic heart failure. In patients with alveolar hypoventilation a vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung (Euler–Liljestrand mechanism). Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, nitroglycerin could reverse this protective vasoconstriction and thus result in increased perfusion of poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

Hypertrophic cardiomyopathy

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Increased angina

The possibility of increased frequency of angina during patch-off periods should be considered. In such cases the use of additional anti-anginal therapy is desirable.

Tolerance to sublingual nitroglycerin

As tolerance to nitroglycerin patches develops, the effect of sublingual nitroglycerin on exercise tolerance may be partially diminished.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Driving and using machines

Nitroderm TTS, especially at the start of treatment or dose adjustments, may impair the reactions or might rarely cause orthostatic hypotension and dizziness (as well as exceptionally syncope after overdosing). Patients experiencing these effects should refrain from driving or using machines.

Information for Patients

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

7 Adverse drug reactions

Adverse drug reactions from multiple sources (Table 7-1) are listed by MedDRA System-Organ Class (SOC). Within each System-Organ Class the adverse drug reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse drug reactions are ranked in order of decreasing seriousness. In addition, the corresponding frequency category, using the following convention (CIOMS III: *Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000), including isolated reports*

Table 7-1 Adverse drug reactions from multiple sources

Nervous system disorders	
Common:	Headache[1]
Very rare:	Dizziness
Cardiac disorders	
Rare:	Tachycardia[2]
Vascular disorders	
Rare:	Orthostatic hypotension, flushing[2]
Gastrointestinal disorders	
Very common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Uncommon:	Dermatitis contact
General disorders and administration site conditions	
Uncommon:	Application site erythema, pruritus, burning, irritation[3]
Investigations	
Rare:	Heart rate increased

[1]Like other nitrate preparations, Nitroderm TTS commonly causes dose-dependent headaches due to cerebral vasodilatation. These often regress after a few days despite the maintenance of therapy. If headaches persist during intermittent therapy, they should be treated with mild analgesics. Unresponsive headaches are an indication for reducing the dosage of nitroglycerin or discontinuing treatment.

[2]A slight reflex-induced increase in heart rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.

[3]Upon removal of the patch, any slight reddening of the skin will usually disappear within a few hours. The application site should be changed regularly to prevent local irritation.

There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinenia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see overdosage).

Adverse drug reactions from spontaneous reports and literature cases

The following adverse drug reactions have been derived from post-marketing experience with Nitroderm TTS via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of a certain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Within each System-Organ Class, adverse drug reactions are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Cardiac disorders:	Palpitation.
Skin and subcutaneous tissue disorders	Rash generalized.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic @moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

8 Interactions

Interactions resulting in concomitant use contraindicated

Concomitant administration of Nitroderm TTS and other vasodilators e.g PDE5 inhibitors such as sildenafil potentiates the blood-pressure-lowering effect of Nitroderm TTS.

Interactions to be considered

Concomitant treatment with calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquilizers may potentiate the blood pressure-lowering effect of Nitroderm TTS, as may alcohol.

Concurrent administration of Nitroderm TTS with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitroglycerin and may lead to coronary vasoconstriction.

The non-steroidal anti-inflammatory drugs except acetyl salicylic acid may diminish the therapeutic response of Nitroderm TTS.

Concurrent administration of Nitroderm TTS.with amifostine and acetyl salicylic acid may potentiate the blood pressure lowering effects of Nitroderm TTS.

9 Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

There is no data supporting any special recommendations in women of child-bearing potential.

Pregnancy

Like any drug, Nitroderm TTS should be employed with caution during pregnancy, especially in the first 3 months.

Breast-feeding

It is not known whether the active substance passes into the breast milk. The benefits for the mother must be weighed against the risks for the child.

Fertility

There is no data available on the effect of Nitroderm TTS on fertility in humans.

In rats, there were no effects on fertility, viability, growth or development of offspring at doses up to approximately 38mg/kg/day (see section 13 Non-clinical safety data).

10 Overdosage

Hemodynamic effects

The ill effects of nitroglycerin overdose are generally the results of nitroglycerin's capacity to induce vasodilation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death. Methaemoglobinaemia has also been reported following accidental overdosage.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g. maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which – if any – of these substances can usefully be removed from the body by hemodyalysis.
No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial

hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.
Hypotension or collapse can be treated by elevation or, if necessary, compression bandaging of the patient's legs.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia:

Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome B_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq$ 10%) methemogolobinemia. In patients with normal reductase function, significant production of methemoglobin should required even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial PO_2. Classically, methemoglonibemic blood is described as chocolate brown, without color change n exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

11 Clinical pharmacology

Pharmacodynamic properties (PD)

Pharmacotherapeutic group: Vasodilators used in cardiac diseases, ATC code: C01DA02

Nitroglycerin relaxes smooth muscle throughout the body. In the vascular system it mainly acts on the systemic veins and accessorily on the large coronary arteries. At low dose nitroglycerin is bioactivated by mitochondrial aldehyde dehydrogenase activity, and is converted to nitrites and denitrated metabolites (1,2-glyceryl dinitrate, 1-3-glyceryl dinitrate) by glutathione-dependent organic nitrate reductase. Nitrite is further activated by cytochrome oxidase or acidic disproportionation in the intermembrane space (H^+), finally yielding nitric oxide (NO) or a related species, which activate soluble guanylyl cyclase and trigger cyclic

guanosine monophospate (cGMP) signaling via cGMP dependent protein kinase, which causes relaxation. At high doses glyceryl dinitrate, mononitrate and nitroglycerin are bioactivated by P450 enzyme(s) in the smooth endoplamic reticulum directly yielding NO which causes relaxation.

In angina pectoris, a fundamental mechanism of action of nitroglycerin is an increase in venous capacitance (venous pooling) leading to a decreased return of blood to the heart. This lowers left ventricular end-diastolic pressure (preload) and hence filling volume, which in turn lowers the myocardial oxygen requirement at rest and especially during exercise, hence enhancing the exercise capacity.

In the coronary arterial circulation, nitroglycerin dilates both extramural conductance and small resistance vessels. The drug appears to redistribute coronary blood flow to ischaemic subendocardium by selectively dilating large epicardial vessels. It can also dilate stenoses caused by eccentric atheroma. In addition, nitroglycerin relaxes vasospasm, whether spontaneous or induced by ergonovine.

Nitroglycerin dose-dependently dilates the arteriolar vascular bed, thereby lowering systemic vascular resistance (afterload) and left ventricular systolic wall tension, and further reducing myocardial oxygen consumption.

Dosing regimens for most chronically used drugs aim for plasma concentrations that continuously exceed the minimally effective concentration, but this strategy is probably inappropriate for organic nitrates. Although some well-controlled clinical trials using exercise tolerance testing showed that efficacy is maintained when patches are worn continuously, most of them reported the development of tolerance (i.e. attenuation of effect as measured by exercise testing) within the first day. As might be expected on pharmacological grounds, tolerance is also observed with high transdermal doses exceeding 4 mg/h.

Efficacy of organic nitrates is restored after a nitrate-free interval. The shortest drug-free interval sufficient to restore response has not been defined. Intervals of 8 to 12 hours are known to be sufficient, shorter intervals have not been fully studied. When administered according to an intermittent regimen, doses of Nitroderm TTS delivering 0.4-0.8 mg/h (20-40 cm^2) have shown increased exercise capacity for 8 to 12 hours.

Controlled clinical trial data suggest that intermittent use of nitrates may be associated with a decrease in exercise tolerance compared with placebo during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown (see section “Warnings and precautions”).

In chronic heart failure the venodilator action of nitroglycerin lowers the elevated left ventricular filling pressure, while maintaining or slightly increasing cardiac output. In this indication, the beneficial effects of nitroglycerin are restricted to severe heart failure with predominant symptoms of pulmonary venous congestion due to a pronounced increase in left ventricular filling pressure. Where improve-stroke volume is desired, combined treatment with an arterial vasodilator such as hydralazine is recommended.

Pharmacokinetic properties (PK)

Nitroderm TTS

Absorbtion

Following single application of Nitroderm TTS, the plasma concentrations of nitroglycerin reach a plateau within 2 hours, which is maintained over the recommended application period. The height of this plateau is directly proportional to the size of the system's drug-releasing area. The same plasma levels are attained regardless of whether the system is applied to the skin of the upper arm, pelvis, or chest. Levels fall rapidly after patch removal. Accumulation does not occur on repeated application of Nitroderm TTS.

Nitroglycerin

Distribution

The plasma protein binding is 61-64%, for nitroglycerin, 23% and 11% for 1, 2-glyceryl dinitrate and 1, 3-glyceryl dinitrate, respectively.

Metabolism

The active substance is rapidly biotransformed to glyceryl dinitrates and mononitrates by glutathione-dependent organic nitrate reductase in the liver. In addition, and probably more importantly, *in vitro* studies have shown that the human erythrocyte is also a site of biotransformation via a sulfhydryl-dependent enzymatic process and interaction with reduced hemoglobin. In human erythrocytes, the reduced haemoglobin level seems to play a major role in metabolic activity, and caution should therefore be exercised in patients with anemia. In animal studies it has been found that extrahepatic vascular tissues (femoral vein, inferior vena cava, aorta) also play an important role in nitroglycerin metabolism, a finding which is consistent with the large systemic clearance seen with nitrates. It has also been shown in vitro that the biotransformation of nitroglycerin occurs concurrently with vascular smooth muscle relaxation; this observation is consistent with the hypothesis that nitroglycerin biotransformation is involved in the mechanism of nitroglycerin-induced vasodilatation.

Excretion

Nitroglycerin is excreted renally as dinitrate and mononitrate metabolites, glucuronide conjugates and glycerol. The elimination half-lives of nitroglycerin, 1,2-glyceryl dinitrate and glyceryl mononitrates are 10, 30-60, 5-6 minutes respectively.

12 Clinical studies

Nitroderm TTS is an established product.

13 Non-clinical safety data

Mutagenicity

Standard mutagenicity tests provided contradictory results in vitro. Cell culture and in vivo studies revealed no evidence of mutagenic activity of nitroglycerin, and therefore its use is considered devoid of genotoxic potential at exposures relevant to men. .

Carcinogenicity

Dietary studies in rodents led to the conclusion that nitroglycerin has no carcinogenic effects relevant for the therapeutic dose range in man. .

Reproduction toxicity

Animal teratology studies have not been conducted with nitroglycerin transdermal systems. Conventional reproduction studies involving the oral, intravenous, intraperitoneal and dermal (as ointment) administration routes of nitroglycerin have been performed in rats and rabbits. Nitroglycerin showed no teratogenic potential in these animals.

Fertility

A three-generation reproduction study was performed in CD rats. In this study, the rats received dietary nitroglycerin at doses of up to 363 mg/kg/day in males and of up to 434 mg/kg/day in females (i.e. 0.01, 0.1 or 1% of nitroglycerin) for six months prior to mating of the F_0 generation, with treatment continuing through successive F_1 and F_2 generations. Control groups received diets free of nitroglycerin. Matings consisted of 10 males and 20 females from each group for the F_0 generation. Twenty to 24 pups from the second litters were randomly chosen in equal numbers from each treatment group and maintained in each respective treatment. At 3 months of age, each male was mated with a female from each group and again, only the second-generation offspring were selected for continued treatment. This was repeated until the animals from the 3rd generation were weaned.

No specific effect on the fertility of the F_0 generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. There were no effects on fertility, viability, growth or development of offspring at doses of up to approximately 38 mg/kg/day. The latter was confirmed in an intraperitoneal fertility study in rats receiving nitroglycerin doses of up to 20 mg/kg/day for 63 days (Oketani et al., 1981b, English summary) (see section 9 Women of child-bearing potential, pregnancy, breast-feeding and fertility).

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Store below 25°C.

Nitroderm TTS should be kept out of the sight and reach of children both before and after use.

Nature and contents of container

Nitroderm TTS 5, Nitroderm TTS 10: individually packaged in sealed sachets: paper/PE/Al/Surlyn Worldwide.

Instructions for use and handling

Each Nitroderm TTS patch is sealed in a separate sachet with a tear-off edge to facilitate removal. After removing the white protective backing, apply the Nitroderm TTS patch to a clean, non-hairy, dry area of intact skin on the trunk or upper arm. Hold the patch in position for 10-20 seconds with the palm of the hand. Switch application sites daily, wait several days before using the same area again.

Each transdermal patch must be removed from the individual package immediately prior to use.

Manufacturer:

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