NOVARTIS

Nitroderm® TTS

Composition

Active substance: Glyceryl trinitrate (= nitroglycerin)
Excipients: Patch excipients

Pharmaceutical form and quantity of active substance per unit

Transdermal therapeutic system (TTS) 5, containing 25 mg per 10 cm^2 and with mean active substance release rate of 5 mg/24 hours.
TTS 10, containing 50 mg per 20 cm^2 and with mean active substance release rate of 10 mg/24 hours.
TTS 15, containing 75 mg per 30 cm^2 and with mean active substance release rate of 15 mg/24 hours.
Nitroderm TTS is a flat, multilayer system designed to deliver nitroglycerin continuously through a release membrane following application to the skin.
The active substance penetrates the skin and thus becomes directly available to the systemic circulation at relatively constant concentrations throughout the recommended treatment period.
The number in the product name (TTS 5, TTS 10 and TTS 15) denotes the amount (in mg) of nitroglycerin delivered by the system over a 24 hour period.

Indications / Potential uses

Angina pectoris
Alone or in combination with other antianginal agents, e.g. beta-blockers and/or calcium channel blockers.

Heart failure
As supplementary medication in patients who do not respond adequately to conventional therapy with digitalis, other positively inotropic drugs or diuretics.
Prevention of phlebitis and extravasation in connection with infusion (Nitroderm TTS 5 only)
Prevention of phlebitis and extravasation secondary to fluid or drug administration via a peripheral vein in cases where infusion is expected to last for two days or longer and low-dose heparinization is not planned.

Dosage and Administration

The response to nitrate preparations varies from patient to patient. The lowest effective dose should be given. In order to avoid local skin reactions, the application site should be changed regularly (see **Warnings and Precautions).**

Angina pectoris
Treatment should be initiated with one Nitroderm TTS 5 patch daily. Depending on the patient's response, the daily dose may then be titrated upwards to:
One Nitroderm TTS 10 patch (usual maintenance dose); one Nitroderm TTS 15 patch or one Nitroderm TTS 10 patch plus one Nitroderm TTS 5 patch; one Nitroderm TTS 15 patch plus one Nitroderm TTS 5 patch or two Nitroderm TTS 10 patches.

Heart failure
It is recommended that treatment be started in hospital and the patient's haemodynamic status monitored; treatment should be continued in hospital until the required maintenance dose has been established.
The optimum dosage should be determined on the basis of clinical response and adverse effects; patients should be closely monitored for signs and symptoms of overdose (e.g. fall in blood pressure, tachycardia).
It must be kept in mind that bioavailability is, on average, 10–20% higher with a TTS 15 system than with three TTS 5 systems.

Prevention of phlebitis and extravasation (in connection with infusion)
Immediately after venepuncture, one Nitroderm TTS 5 patch should be applied close to the infusion site, on the distal side. It is advisable to change the patch daily. However, efficacy was found to be maintained in a study in which the patch was changed every 3–4 days. Treatment with Nitroderm TTS should be discontinued once intravenous therapy has stopped.

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

Use in children and adolescents
Owing to the lack of available data, the use of Nitroderm TTS in children cannot be recommended.

Contraindications

Concomitant administration of phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil or vardenafil with Nitroderm TTS is contraindicated (see **Warnings and Precautions** and **Interactions).**
Known hypersensitivity to nitroglycerin and related organic nitrates or to one of the excipients of Nitroderm TTS. Acute circulatory failure with severe hypotension (shock). Conditions associated with raised intracranial pressure. Myocardial failure due to obstruction (e.g. aortic or mitral stenosis, constrictive pericarditis).

Warnings and Precautions

Nitroderm TTS is not suitable for the immediate management of acute attacks of angina pectoris. Additional administration of fast-acting nitrate preparations is indicated in the event of such an attack.
Due to their pharmacological action (inhibition of cGMP degradation), PDE5 inhibitors potentiate the antihypertensive effect of nitrates and other nitric oxide (NO) donors, possibly resulting in severe treatment-resistant hypotension. Use of PDE5 inhibitors such as sildenafil, tadalafil or vardenafil during treatment with Nitroderm TTS is therefore contraindicated. Patients must be informed of this potentially life-threatening interaction.
As with other nitrate preparations, when switching a patient on long-term therapy to another form of medication, nitroglycerin should be gradually withdrawn and overlapping treatment started.
Nitroderm TTS contains an aluminium layer. The patch must therefore be removed before applying magnetic or electrical fields to the body (e.g. during procedures such as MRI, cardioversion, defibrillation or diathermy treatment).
In cases of recent myocardial infarction or acute heart failure, Nitroderm TTS should be used only in association with close medical surveillance and/or haemodynamic monitoring.

Hypoxaemia
Caution is required in patients with arterial hypoxaemia due to severe anaemia as the biotransformation of nitroglycerin is reduced in such cases.
Similarly, caution is called for in patients with hypoxaemia and a ventilation/perfusion imbalance due to lung disease or ischaemic heart failure. Patients with angina pectoris, myocardial infarction or cerebral ischaemia frequently suffer from abnormalities of the small airways (in particular 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. This would result in worsening of the ventilation/perfusion imbalance, causing a further reduction in the arterial particle 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 the periods when the patch is left off should be taken into account. In such cases the use of concomitant antianginal therapy is desirable.

Development of tolerance or attenuation of therapeutic effects frequently occurs with prolonged or frequent administration of long-acting nitrates, including Nitroderm TTS and other transdermal systems. To avoid tolerance, it is recommended that the patch be left off for a period of 8–12 hours (usually at night) every 24 hours. In the majority of patients intermittent therapy has been found to be more effective than continuous administration. Continuous use may be appropriate for patients in whom long-term clinical responsiveness can be reliably judged.

Tolerance to sublingual nitroglycerin
As tolerance to the nitroglycerin patch develops, the effect of sublingual nitroglycerin will also be reduced.

Use of Nitroderm TTS 5 in the prevention of phlebitis
The infusion site should be examined regularly. If phlebitis develops, it should be treated accordingly.

Interactions

The antihypertensive effect of acutely and chronically administered nitrates and other NO donors is potentiated by PDE5 inhibitors such as sildenafil (Viagra®), tadalafil (Cialis®) or vardenafil (Levitra®). Use of these substances during Nitroderm TTS therapy is therefore contraindicated. In the event that a patient does take one of these substances, use of Nitroderm TTS is contraindicated for the following 24 hours.
Concomitant treatment with other vasodilators (e.g. PDE5 inhibitors such as sildenafil [Viagra®], calcium channel blockers, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants or neuroleptics, or consumption of alcohol, may potentiate the hypotensive effects of Nitroderm TTS.
Concomitant use of Nitroderm TTS and dihydroergotamine may increase the bioavailability of dihydroergotamine. Special caution is required in patients with coronary heart disease as dihydroergotamine may antagonize the effects of nitroglycerin, resulting in coronary vasoconstriction.
The possibility that acetylsalicylic acid and non-steroidal anti-inflammatory drugs may reduce the therapeutic response to Nitroderm TTS cannot be excluded.

Pregnancy and Lactation

There have been no controlled studies in animals or in pregnant women. The drug should therefore only be given during pregnancy if the potential benefit to the patient outweighs the risk to the fetus.
It is not known whether the active substance is excreted in breast milk. The benefits for the mother must be weighed against the risks for the infant.

Effects on ability to drive and use machines

Nitroderm TTS may impair the patient's reactions, especially at the beginning of treatment, e.g. when driving or using machines.

Adverse effects

Frequency
Very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10 000 to < 1/1000), very rare (< 1/10 000).

Nervous system disorders
Very common: Headache.
Rare: Dizziness.
Very rare: Light-headedness.

Cardiac disorders
Rare: Reflex tachycardia

Vascular disorders
Rare: Orthostatic hypotension, flush

Gastrointestinal disorders
Very common: Nausea, vomiting.

Skin
Uncommon: Contact dermatitis, transient reddening of the skin (flush) and allergic reactions.

General disorders and administration site conditions
Uncommon: Erythema, pruritus, burning sensation, irritation.

- Local: Mild reddening of the skin usually disappears within a few hours of patch removal. In order to avoid local reactions, the application site should be changed regularly.
- A slight reflex-induced increase in heart rate may be avoided, if necessary, by introducing a beta-blocker.

Overdose

Signs and symptoms
High doses of nitroglycerin may lead to a marked fall in blood pressure and reflex tachycardia or collapse and syncope. There have also been reports of methaemoglobinaemia (cyanosis, dyspnoea, tachypnoea) following accidental overdosage. However, with Nitroderm TTS the release membrane reduces the risk of overdosage.

Management
Reduced blood pressure and signs of collapse may be managed by raising the patient's legs and, if necessary, bandaging them. In addition to these general measures, the patient must be placed under intensive care, with monitoring and, if necessary, correction of vital parameters. Volume substitution is indicated in the event of hypotension and/or shock; exceptionally, infusion of noradrenaline and/or dopamine to treat circulatory disturbances.
Administration of adrenaline and related substances is contraindicated.
Methaemoglobinaemia may require treatment, depending on severity.

Properties and Actions

ATC code: C01DA02

Mechanism of action / Pharmacodynamics
Nitroglycerin relaxes smooth muscle throughout the body. In the vascular system it acts primarily on the systemic veins and also on the large coronary arteries.
The fundamental mechanism of action in angina pectoris is primarily based on an increase in venous capacitance (venous pooling), leading to a reduction in venous return to the heart. This lowers left-ventricular end-diastolic pressure (preload) and hence also filling volume, which in turn lowers myocardial oxygen requirement at rest and, especially, during exercise, thus enhancing exercise capacity.
In the coronary arteries, nitroglycerin dilates both extramural vessels and small resistance vessels.
There is some evidence that the drug causes redistribution of coronary blood flow to the ischaemic subendocardium by selectively dilating large epicardial vessels. It is even capable of dilating atherosclerotic stenoses where the atheroma is eccentrically located.
Nitroglycerin also produces relaxation of vasospasm, whether spontaneous or induced by ergometrine.
In addition, nitroglycerin exerts a dose-dependent dilating effect on the arterioles, as a result of which systemic vascular resistance (afterload) and left-ventricular systolic wall tension decrease. This leads to a reduction in myocardial oxygen consumption.
Dosing regimens for most drugs used in the long-term treatment of angina pectoris are aimed at achieving plasma concentrations that are consistently higher than the minimally effective concentration. This strategy is probably inappropriate for organic nitrates, however. Some controlled clinical studies including exercise tolerance testing have shown maintenance of efficacy with continuous patch use. However, the majority of such studies have shown 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 (including those greater than 4 mg/hour).
The efficacy of organic nitrates is restored after a drug-free interval. The shortest such interval sufficient to restore response has not yet been determined. It is known that intervals of 8–12 hours are sufficient. Shorter intervals have not yet been fully studied. Intermittent use of Nitroderm TTS at a dosage of 0.4–0.8 mg/hour (20–40 cm^2) resulted in increased exercise capacity over 8–12 hours.
The results of controlled clinical studies lead to the conclusion that, compared to placebo, intermittent use of nitrates may be associated with a decrease in exercise tolerance during the last part of the nitrate-free interval. The clinical significance of this observation is not known (see **Warnings and Precautions).**
In chronic heart failure, the dilating action exerted by nitroglycerin on the veins lowers raised left-ventricular filling pressure, while at the same time cardiac output remains unchanged or increases slightly.
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. In cases where an increase in stroke volume is desired, combined treatment with an arterial vasodilator (such as hydralazine) is recommended.

Pharmacokinetics

The rate of nitroglycerin release *in vivo* is approximately 20–25 µg/cm^2/hour.

Absorption
Following single application of Nitroderm TTS, plasma concentrations of nitroglycerin reach a plateau within 2 hours.
This plateau is maintained throughout the 24 hour application period and is directly proportional to the contact surface area of the patch.

Distribution
The same plasma level is attained regardless of the site of application (upper arm, chest or pelvis). Repeated application of Nitroderm TTS does not result in accumulation.

Metabolism
The active substance is rapidly metabolized in the liver by a glutathione-dependent organic nitrate reductase. In addition, and probably more importantly, studies with human erythrocytes *in vitro* have shown that the erythrocyte is a site of biotransformation of nitroglycerin by a sulphydryl-dependent enzymatic process and by an interaction with reduced haemoglobin. The amount of reduced haemoglobin in erythrocytes appears to play an important role in their metabolic activity. Caution is therefore required in patients with anaemia.
Animal studies have shown that extrahepatic vascular tissues (femoral vein, inferior vena cava, aorta) also play an important role in nitroglycerin metabolism. This finding is consistent with the pronounced systemic clearance normally seen with nitrates. *In vitro* studies also showed that 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 vasodilation.

Elimination
Owing to its short elimination half-life, plasma concentrations of nitroglycerin fall below the detection limit within one hour of system removal.

Preclinical data

Cell culture and animal studies performed with glyceryl trinitrate revealed no mutagenic or carcinogenic effects relevant for the therapeutic dose range. Animal reproduction toxicity studies involving intravenous, intraperitoneal and dermal administration have been carried out.
In embryotoxicity and fertility studies, there was no evidence either of an effect on embryos or of fertility disorders at doses in the parent animals extending into the toxic range. There was, in particular, no evidence of teratogenic properties. Doses higher than 1 mg/kg/day (i.p.) or 28 mg/kg/day (dermal) showed fetotoxic effects (reduced birthweight) following use in pregnant rats during the fetal development period. No studies are known in which the concentrations of active substance in the milk have been determined.

Other information

Each Nitroderm TTS patch is sealed in a separate sachet. The sachet has a marked edge to facilitate removal of the patch. Following removal of the white protective backing, the patch should be applied to a clean, dry, non-hairy area of intact skin on the trunk or upper arm and held in position for 10–20 seconds with the palm of the hand. A different site of application should be chosen each day and several days allowed to elapse before the same site is used again.

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage:
See folding box.

Pack sizes

Country specific pack sizes

Manufacturer
See folding box

Information last revised

June 2005

Approval date (text)

18 April 2006

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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