

Drug Regulatory Affairs

**NITRODERM<sup>®</sup> TTS**  
**(nitroglycerin)**

25, 50 or 75 mg transdermal patch

**Basic Prescribing Information**

**NOTICE**

The **Basic Prescribing Information (BPI)** is the **Novartis Core Data Sheet**. It displays the company's current position on important characteristics of the product, including the **Core Safety Information** according to ICH E2C.

**National Prescribing Information** is based on the **BPI**. However, because regulatory requirements and medical practices vary between countries, **National Prescribing Information** (incl. **US Package Insert** or **European SPCs**) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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## 1 Name of the medicinal product

NITRODERM<sup>®</sup> TTS 25, 50 or 75 mg transdermal patch

## 2 Qualitative and quantitative composition

1,2,3-Propanetriol trinitrate (= nitroglycerin), 25 mg, 50 mg, or 75 mg in a transdermal therapeutic system (TTS). Nitroglycerin is an organic nitrate derivative.

For excipients, see section 6.1 List of excipients

## 3 Pharmaceutical form

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 three systems are available:

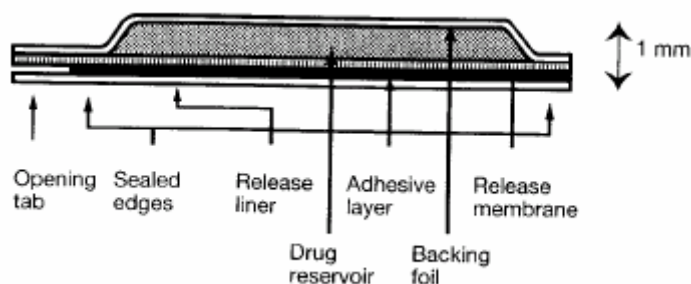
**Table 3-1 Nitroderm pharmaceutical forms**

	Nitroderm TTS 5	Nitroderm TTS 10	Nitroderm TTS 15
Nitroglycerin content	25 mg	50 mg	75 mg
Drug-releasing area	10 cm <sup>2</sup>	20 cm <sup>2</sup>	30 cm <sup>2</sup>
Imprint (backing side)	CG DOD	CG DPD	CG EJE
Colour of the release liner		off-white to yellowish	

The numeric components of the product designations TTS 5, TTS 10, and TTS 15 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 in normal use. After 12 hours, for example, each system has delivered 10% of its original content of nitroglycerin. Since nitroglycerin is released from Nitroderm TTS at a constant rate per cm<sup>2</sup>, 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<sup>2</sup>.h.

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



## **4 Clinical particulars**

### **4.1 Therapeutic indications**

#### **Angina pectoris**

As monotherapy or in combination with other anti-anginal drugs such as beta-blockers and/or calcium antagonists.

#### **Congestive heart failure**

As supplementary medication in patients not responding adequately to conventional therapy with digitalis or other positive inotropic agents and diuretics.

#### **Prevention of phlebitis and extravasation (only for Nitroderm TTS 5)**

Prophylactic treatment of phlebitis and extravasation secondary to venous cannulation for intravenous fluid and drug administration when treatment is expected to last for two days or longer.

### **4.2 Posology and method of 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.

#### **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 15
- one Nitroderm TTS 15 plus Nitroderm TTS 5 or two Nitroderm TTS 10

### **Congestive heart failure**

It is recommended that treatment be started in hospital and the patient's haemodynamic status monitored; treatment should also be continued in hospital until the requisite maintenance dosage has been established.

The optimal dosage should be determined in the light of the clinical response, the side effects encountered, and careful monitoring for signs of overdose such as a fall in blood pressure and tachycardia.

### **Prevention of phlebitis and extravasation**

One Nitroderm TTS 5 patch should be applied close to the site of intravenous cannulation, on the distal side, when the vein is punctured. It is advisable for the patch to be replaced daily. However, in one study the patch was replaced every 3-4 days and efficacy was maintained. 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; however, there is no evidence to suggest that the dosage needs to be adjusted in elderly patients.

### **Use in children**

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.

## **4.3 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 (Viagra<sup>®</sup>) is contraindicated, because PDE5 inhibitors may amplify the vasodilatory effects of Nitroderm TTS resulting in severe hypotension.

## **4.4 Special warnings and special precautions for use**

### **Warnings**

As with other nitrate preparations, when transferring 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 Imaging), 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 haemodynamic monitoring.

## **Precautions**

### **Hypoxaemia**

Caution should be exercised in patients with arterial hypoxaemia due to severe anaemia, because in such patients the biotransformation of nitroglycerin is reduced. Similarly, caution is called for in patients with hypoxaemia and 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 (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 concomitant 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.

### **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.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant treatment with other vasodilators (e.g PDE5 inhibitors such as sildenafil [Viagra<sup>®</sup>]), calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquillisers 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 antagonises the effect of nitroglycerin and may lead to coronary vasoconstriction.

The possibility that the ingestion of acetylsalicylic acid and non-steroidal anti-inflammatory drugs might diminish the therapeutic response to Nitroderm TTS cannot be excluded.

## 4.6 Pregnancy and lactation

### Pregnancy

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

### Lactation

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.

## 4.7 Effects on ability to drive and use machines

Nitroderm TTS, especially at the start of treatment, may impair the reactions, e.g. when driving or using machines.

## 4.8 Undesirable effects

*Adverse reactions are ranked in descending order of frequency, as follows: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1000$ ); very rare ( $< 1/10,000$ ), including isolated reports*

**Table 1**

<b>Nervous system disorders</b>	
Common:	Headache
Very rare:	Dizziness
<b>Cardiac disorders</b>	
Rare:	Tachycardia
<b>Vascular disorders</b>	
Rare:	Postural hypotension, flushing
<b>Gastrointestinal disorders</b>	
Very common:	Nausea, vomiting
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon:	Dermatitis contact
<b>General disorders and administration site conditions</b>	
Uncommon:	Erythema, pruritus, burning, irritation
<b>Investigations</b>	

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

## 4.9 Overdose

### Signs

High doses of nitroglycerin may lead to severe hypotension and reflex tachycardia or to collapse and syncope. Methaemoglobinaemia has also been reported following accidental overdosage. However, with Nitroderm TTS, the release membrane will reduce the likelihood of overdosage.

### Management

The nitrate effect of Nitroderm TTS can be rapidly terminated simply by removing the system(s).

Hypotension or collapse can be treated by elevation or, if necessary, compression bandaging of the patient's legs.

## 5 Pharmacological properties

### 5.1 Pharmacodynamic properties

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

Nitroglycerin relaxes smooth muscle throughout the body. In the vascular system it acts chiefly on the systemic veins and accessorially on the large coronary arteries.

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 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<sup>2</sup>) 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 4.4 Special warnings and special precautions for use).

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 improved stroke volume is desired, combined treatment with an arterial vasodilator such as hydralazine is recommended.

## 5.2 Pharmacokinetic properties

### Nitroderm TTS

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

The active substance is rapidly metabolised 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 sulphhydryl-dependent enzymatic process and interaction with reduced haemoglobin. 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 anaemia. In animal studies it has been found that extrahepatic vascular tissues (femoral vein, inferior vena cava, aorta) likewise 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.

### **5.3 Preclinical safety data**

#### **Mutagenicity**

Studies performed with trinitroglycerin (TNG) have provided no evidence of mutagenic potential.

#### **Carcinogenicity**

Rats receiving very high doses of TNG (363 mg/kg/day in males and 434 mg/kg/day in females) for two years had hepatocellular carcinomas and testicular interstitial cell tumours. Mice receiving 1,022 (males) or 1,058 mg/kg/day (females) and rats receiving 31.5 (males) or 38.1 mg/kg/day (females) for the same period showed no treatment-related tumours.

#### **Reproduction toxicity**

TNG exhibited no teratogenic potential in rats.

## **6 Pharmaceutical particulars**

### **6.1 List of excipients**

Silica aerogel, silicone oil 360 medical adhesive.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Do not store above 25°C.

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

## **6.5 Nature and contents of container**

Nitroderm TTS 5, Nitroderm TTS 10, Nitroderm TTS 15: individually packaged in sealed sachets: paper/PE/Al/Surllyn Worldwide.

## **6.6 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.