PRODUCT INFORMATION

NITRO-DUR® TRANSDERMAL DELIVERY SYSTEM

NAME OF THE MEDICINE

Glyceryl trinitrate is 1,2,3-propanetriol trinitrate with a molecular weight of 227.09.

FIGURE 1: Chemical Structure of Nitroglycerin

\[
\begin{align*}
\text{H}_2\text{CONO}_2 \\
\text{HCONO}_2 \\
\text{H}_2\text{CONO}_2
\end{align*}
\]

CAS No. 55-63-0

DESCRIPTION

Composition
Glyceryl trinitrate.

NITRO-DUR Transdermal Delivery System supplies glyceryl trinitrate within the acrylic-based polymer adhesive of a patch. The rated release of the drug is dependent upon the area of the system; for every cm², approximately 0.02mg of glyceryl trinitrate is released per hour.

<table>
<thead>
<tr>
<th>Nitroglycerin</th>
<th>Glyceryl trinitrate transdermal release rate in vivo</th>
<th>Patch Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>NITRO-DUR 5</td>
<td>5mg/24hr (0.2mg/hr)</td>
<td>10cm²</td>
</tr>
<tr>
<td>NITRO-DUR 7.5</td>
<td>7.5mg/24hr (0.3mg/hr)</td>
<td>15cm²</td>
</tr>
<tr>
<td>NITRO-DUR 10</td>
<td>10mg/24hr (0.4mg/hr)</td>
<td>20cm²</td>
</tr>
<tr>
<td>NITRO-DUR 15</td>
<td>15mg/24hr (0.6mg/hr)</td>
<td>30cm²</td>
</tr>
</tbody>
</table>

List of excipients
GME-2397 (PI), GME-3011 (PI), polyoxymethylene melamine, sodium polyacrylate, purified water.
PHARMACOLOGY

Pharmacodynamic properties
Glyceryl trinitrate is a potent vasodilator, which relaxes both peripheral arteries and veins (with more prominent effects on the latter) and thereby, reduces cardiac work and myocardial oxygen consumption. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load). Dilation of the coronary arteries also occurs and could be an important mechanism of action for those anginal syndromes not clearly related to increases in myocardial oxygen demand.

Therapeutic doses of glyceryl trinitrate have been shown to reduce systolic and mean arterial blood pressures, especially when the patient assumes upright posture.

Pharmacokinetics

Absorption
In healthy volunteers, detectable plasma concentrations of glyceryl trinitrate are reached 30 minutes after application of a NITRO-DUR patch. Steady-state concentrations are reached on average 2 hours after application and are maintained for the duration of wearing the system. Upon removal of the patch, the skin serves as a reservoir, and the plasma concentration declines to approximately 50% of the steady-state concentration in approximately 30 minutes and to undetectable concentrations by two hours. Absorption is variable, with a large (5-10 fold) variability between individuals.

Metabolism
Glyceryl trinitrate is rapidly metabolized, principally by glucothio-nitrate reductase, to form glyceryl nitrate metabolites and inorganic nitrate. Two active major metabolites, the 1,2- and 1,3- dinitroglycerols, the products of hydrolysis, appear to be less potent than glyceryl trinitrate as vasodilators, but have longer plasma half-lives. The dinitrates are further metabolized to mononitrates (biologically inactive with respect to cardiovascular effects) and ultimately to glycerol and carbon dioxide. There is extensive first-pass deactivation by the liver following gastrointestinal absorption.

Although dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration, such a strategy is probably inappropriate for organic nitrates. Some well controlled clinical trials using exercise-induced angina testing have shown maintenance of effectiveness when transdermal infusion systems were worn continuously. The majority of such controlled trials, however, have shown the development of tolerance within the first day. Tolerance has occurred even when doses greater than 105mg/24hour (4mg/hour), a dose far in excess of the acutely effective dose, were delivered continuously. The development of tolerance to glyceryl trinitrate is not exclusive to transdermal delivery. It can also occur with oral organic nitrates when continuous blood levels are maintained. Tolerance to organic nitrates can be prevented or attenuated by allowing a nitrate-free period of approximately 12 hours during each 24-hour cycle.

Since glyceryl trinitrate metabolism is extremely rapid and because delivery from transdermal patches can be abruptly stopped by simple removal, it is relatively easier to produce a nitrate-free period with transdermal than with oral therapy.
INDICATIONS

NITRO-DUR Transdermal Delivery System is indicated for the prevention of chronic stable angina pectoris due to coronary artery disease.
It is not intended for the treatment of acute attacks of angina pectoris. Sublingual glyceryl trinitrate should be used for this purpose.

CONTRAINDICATIONS

NITRO-DUR Transdermal Delivery System is contraindicated in patients with known hypersensitivity to organic nitrate drugs and in patients with marked anaemia. Allergy to the adhesive used in glyceryl trinitrate patches has been reported and constitutes a contraindication to the use of this product.

Do not use NITRO-DUR in patients who are taking phosphodiesterase inhibitors (such as sildenafil, tadalafil, or vardenafil) for erectile dysfunction or pulmonary arterial hypertension. Concomitant use can amplify the vasodilatory effects of NITRO-DUR and cause severe hypotension.

Do not use NITRO-DUR in patients who are taking the soluble guanylate cyclase stimulator riociguat for chronic thromboembolic pulmonary hypertension or pulmonary arterial hypertension. Concomitant use can cause hypotension.

PRECAUTIONS

The benefits and safety of transdermal glyceryl trinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use NITRO-DUR in these conditions, careful clinical or haemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

NITRO-DUR must be removed before cardioversion or DC defibrillation is attempted, as well as before applying diathermy treatment, since it may be associated with damage to the paddles and burns to the patients.

Headaches or symptoms of hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. A reduction in dose or discontinuation of treatment may be necessary.

Caution should be exercised when using glyceryl trinitrate in patients prone to or who might be affected by hypotension. The drug therefore should be used with caution in patients who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g. below 90mmHg). Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate-induced hypotension.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.
In industrial workers who have had long-term exposure to unknown (presumably high) doses of glyceryl trinitrate, tolerance clearly occurs. There is moreover, physical dependence since chest pain, acute myocardial infarction and even sudden death have occurred during temporary withdrawal of glyceryl trinitrate from these workers. In clinical trials of angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the haemodynamic effects soon after nitrate withdrawal. The importance of these observations to the routine clinical use of glyceryl trinitrate has not been fully elucidated but patients should be monitored closely for increased anginal symptoms during drug-free periods.
Caution should be exercised in patients with arterial hypoxaemia due to anaemia (see CONTRAINDICATIONS) because in such patients the biotransformation of glyceryl trinitrate is reduced. 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 (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, glyceryl trinitrate could reverse this protective vasoconstriction and thus result in increased perfusion to poorly ventilated areas, worsening of the ventilation/perfusion imbalance and a further decrease in the arterial partial pressure of oxygen.

Tolerance to glyceryl trinitrate with cross tolerance to other nitrates or nitrites may occur. If tolerance to glyceryl trinitrate patches develops, the effect of sublingual glyceryl trinitrate on exercise tolerance, although still observable, is somewhat blunted.

**Occupational Hazards**

As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment.

**Use in Pregnancy (Category B2)**

It is not known whether NITRO-DUR Transdermal Delivery System can affect reproductive capacity or cause foetal harm. Thus, it should be administered to pregnant women only if the potential benefits to the mother clearly outweigh the potential hazard to the foetus.

**Use in Lactation**

It is not known whether glyceryl trinitrate is excreted in human milk. As many drugs are excreted in human milk and because of the potential for adverse reactions from glyceryl trinitrate in nursing infants, caution should be exercised when NITRO-DUR Transdermal Delivery System is administered to a nursing woman.

**INTERACTIONS WITH OTHER MEDICINES**

Concomitant use of nitrates and alcohol, antihypertensive agents, beta adrenergic blockers, tricyclic antidepressents, phenothiazines or calcium channel blockers may cause additive hypotensive effects.

Glyceryl trinitrate acts directly on vascular muscle. Therefore, any other agent that directly or indirectly acts on vascular smooth muscle may have decreased or increased effect depending upon the agent.

The risk of postural hypotension is increased with the combination of glyceryl trinitrate and antihypertensive agents, especially in the elderly.

Concurrent administration of glyceryl trinitrate with dihydroergotamine may increase the bioavailability of dihydroergotamine. Special attention should be paid to this point in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of glyceryl trinitrate and may lead to coronary vasoconstriction.
Concomitant use of NITRO-DUR with phosphodiesterase inhibitors in any form is contraindicated (see CONTRAINDICATIONS). Amplification of the vasodilatory effects of NITRO-DUR by phosphodiesterase inhibitors, e.g., sildenafil, tadalafil, or vardenafil can result in severe hypotension. The course and dose dependence of this interaction has not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

Concomitant use of NITRO-DUR with soluble guanylate cyclase stimulators (riociguat) is contraindicated (see CONTRAINDICATIONS).

ADVERSE EFFECTS

Adverse reactions to glyceryl trinitrate are generally dose related, and almost all of these reactions are the result of glyceryl trinitrate’s activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at high doses. Headache may be treated with mild analgesics while NITRO-DUR therapy is continued; if headaches fail to respond to treatment, NITRO-DUR dosage should be reduced or the product discontinued. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy.

Application-site irritation may occur but is rarely severe. Local irritation may be prevented by regularly changing the site of application.

Less frequently reported adverse reactions include dizziness, faintness, facial flushing, and postural hypotension which may be associated with reflex tachycardia. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon. Nausea and vomiting have been reported rarely.

DOSAGE AND ADMINISTRATION

Adults: The recommended initial dose is usually one NITRO-DUR 10 (20cm²) Transdermal Delivery System applied for a period of approximately 12 hours. Following a 12-hour nitrate-free interval, a fresh NITRO-DUR Transdermal Delivery System is applied for another period of approximately 12 hours. To ensure maintenance of response, NITRO-DUR Transdermal Delivery System should be worn for approximately 12 hours daily, providing a nitrate-free interval of approximately 12 hours in any 24-hour cycle. In some patients, it may be necessary to titrate to a higher dose to achieve optimum therapeutic effect. Dosage should be titrated while monitoring clinical response.

The NITRO-DUR 5 (10cm²) patch is intended for use when a low starting dose is required. Most patients will require a maintenance dose higher than this.

Patients currently maintained on continuous therapy without clinical evidence of nitrate tolerance may continue the regimen as long as they show clinical benefit. Newly treated patients should be started on intermittent therapy.

NITRO-DUR Transdermal Delivery System may be applied to any convenient skin area; a recommended site of application is the upper arm or chest. Application sites should be rotated. Suitable areas should be shaved if necessary. Do not apply NITRO-DUR Transdermal Delivery System to the distal part of the extremities.
To apply the NITRO-DUR Transdermal Delivery System, tear open the printed pouch and remove the unit. With the brown lines facing you, bend the unit away from and then towards you to break open the plastic cover along the brown line. Peel away both halves of the plastic cover starting at the brown line. Apply NITRO-DUR Transdermal Delivery System firmly to the skin surface. Hands should be washed thoroughly after application.

A discarded patch should be disposed of appropriately to avoid accidental application or use.

**Children:** Safety and effectiveness in children have not been established.

**OVERDOSAGE**

Nitrate overdosage may result in severe hypotension, persistent throbbing headache, vertigo, palpitations, visual disturbances, flushing and perspiring skin (later becoming cold and cyanotic), nausea and vomiting (possibly with colic and even bloody diarrhoea), syncope (especially in the upright posture), methaemoglobinemia and cyanosis and anorexia, initial hyperpnoea, dyspnoea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intracranial pressure with cerebral symptoms of confusion and moderate fever, paralysis and coma followed by clonic convulsions and possibly death due to circulatory collapse.

**Treatment of Overdosage** If these symptoms occur during the course of treatment, depending on severity, dosage should be reduced or treatment should be discontinued. Keep the patient recumbent in a shock position and comfortably warm. Remove the NITRO-DUR Transdermal Delivery System and scrub underlying skin thoroughly. Passive movement of the extremities may aid venous return. Central volume expansion with intravenous infusion of normal saline or similar fluid may be indicated; however, in patients with renal disease or congestive heart failure this is not without hazard and invasive monitoring may be indicated. Adrenaline and related products are ineffective in reversing the severe hypotensive events associated with overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

**PRESENTATION AND STORAGE CONDITIONS**

NITRO-DUR 5: 5mg/24hr (10cm²); NITRO-DUR 7.5 *: 7.5mg/24hr (15cm²) NITRO-DUR 10: 10mg/24hr (20cm²); NITRO-DUR 15: 15mg/24hr (30cm²).

* NITRO-DUR 7.5 is not marketed in Australia

Cartons of 30 units.

**NAME AND ADDRESS OF THE SPONSOR**

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road,
Macquarie Park NSW 2113
Australia

**POISON SCHEDULE OF THE MEDICINE**

Prescription only medicine (Schedule 4)
DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

NITRO-DUR 5, NITRO-DUR 7.5: 2 May 1995

This product information was approved by the Therapeutic Goods Administration on 13 April 1995. The change of trade name was submitted to the TGA on 3 July 1995.

Date of most recent amendment:
3 October 2014