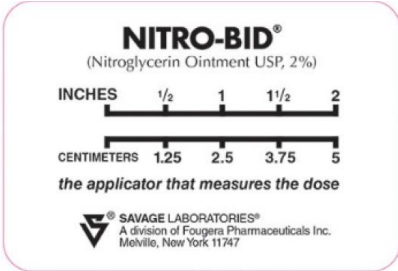



Glyceryl Trinitrate 2% ointment

Newborn use only

2022

Alert	Glyceryl trinitrate (GTN) is also known as nitroglycerin. Methaemoglobin levels should be monitored when GTN is used in very preterm infants. ⁽¹⁾ Rectogesic ointment (0.2% GTN) is not a preferred option for treatment of tissue ischaemia. GTN patches are not suitable preparations due to their slower and erratic drug release. ANMF group recommends to store this drug in the NICU/SCN because of the urgent nature of an ischaemic event.
Indication	Adjuvant therapy for peripheral tissue ischaemia
Action	GTN is converted to nitric oxide (NO) in the vascular smooth muscle, and this activates guanylate cyclase and increases the levels of cyclic guanosine monophosphate (cGMP). ⁽⁵⁾ cGMP causes relaxation of vascular smooth muscle in veins and arteries and consequent dilatation of the collateral circulation. ⁽²⁻⁴⁾ Topical GTN is well absorbed. ^(3, 5)
Drug type	Nitrates
Trade name	NITRO-BID® Nitroglycerin USP (SAS) – Link Pharmaceuticals
Presentation	NITRO-BID® Nitroglycerin USP (SAS) - Glyceryl trinitrate 2% ointment, 1 g foilpac® (unit dose package) Each inch (2.5 cm), as squeezed from the tube, contains approximately 15 mg of nitroglycerin. ⁽⁶⁾ Each box of foilpacs is supplied with a pad of ruled, impermeable, paper applicators.
Dose	Ribbon of 4 mm/kg (2.4 mg/kg) to be applied as a thin film. <u>Peripheral artery catheter related ischaemia</u> Along the anatomic course of artery 1 cm proximal to the site of pallor/cyanosis and the affected areas. Can be applied 8 hourly. ^(2, 4) <u>Umbilical artery/vein catheter associated ischaemia</u> On the affected areas. Can be applied 8 hourly. ⁽⁷⁾ <u>Dopamine and other vasoconstrictor extravasation tissue ischaemia</u> Along the anatomic course of artery 1 cm proximal to the site of pallor/cyanosis and the affected areas. Can be applied 8 hourly. ^(4, 8)
Dose adjustment	Therapeutic hypothermia – No information. ECMO – Not applicable. Renal impairment - No information. Hepatic impairment – No information.
Maximum dose	
Total cumulative dose	
Route	Topical application
Preparation	
Administration	Apply a thin film over affected area. An Opsite dressing can be placed to cover the area. Dose should be measured using the paper applicators supplied (only calibrated to 1.25, 2.5, 3.75 and 5cm). Use ruler to mark the dose on applicator before measuring.  
Monitoring	Blood gas for methaemoglobinaemia – 2-6 hours after topical application. ⁽¹⁾ Blood pressure – 2 hourly for 6 hours after the application and thereafter 6-8 hourly for 24 hours (ANMF consensus). Heart rate – continuous monitoring for 6-24 hours.

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Contraindications	Hypersensitivity to GTN or other ingredients in the product.
Precautions	Hypotension. ⁽⁶⁾ Concomitant use of sildenafil and other nitrates may lead to hypotension.
Drug interactions	Sildenafil – can amplify the vasodilatory effects of GTN resulting in hypotension. ⁽⁶⁾
Adverse reactions	Adverse reactions are generally dose-related. Hypotension, tachycardia. Methaemoglobinaemia (see special comments).
Compatibility	Not applicable
Incompatibility	Not applicable
Stability	
Storage	Store at 20°-25°C. Discard remaining unused contents of foilpac after use. ⁽⁶⁾
Excipients	Lactose, lanolin, white petrolatum and purified water. ⁽⁶⁾
Special comments	Methaemoglobinaemia – Methaemoglobin is formed when the iron in haemoglobin is oxidised from ferrous iron to ferric iron. The functional consequence of this change is that haemoglobin is transformed to methaemoglobin. Methaemoglobin has a higher oxygen-binding capacity than haemoglobin and cannot oxygenate tissues adequately, causing hypoxia and cyanosis. Infants have unique physiology that increases their risk of developing methaemoglobinaemia. Infants have lower NADH cyb5r reductase activity that converts methaemoglobin to haemoglobin and have a higher percentage of foetal haemoglobin, which is easier to convert to methaemoglobin. ^(1, 9) Treatment of choice for methaemoglobinaemia is methylene blue, 1-2 mg/kg intravenously.
Evidence	<p>Background The approach to neonatal peripheral tissue ischaemia consists of conservative treatment (including removal of the device, elevation of the affected limb, and application of warmth to the opposite limb to induce reflex vasodilation). Pharmacologic therapy (antithrombotic and fibrinolytic agents) and surgical management (surgical thrombectomy) in sick newborns is limited because of the high risk of complications.</p> <p>Efficacy A systematic review by Sushko et al identified 23 neonates who received GTN ointment for 25 peripheral tissue ischaemic events. The most commonly used strength and dose in these case reports were 2% GTN ointment at 4mm/kg as a thin film.⁽¹⁰⁾ Time from application to first effect varied from 15 minutes to 23 days. Treatment duration ranged from 1 dose to 36 days; 19 (76%) injuries showed complete recovery.⁽¹⁰⁾</p> <p>Safety Systematic review identified 4 adverse events in 23 neonates treated with GTN ointment: 3 were mild hypotension and tachycardia that resolved without discontinuation of treatment and 1 was an occurrence of swelling bulla.⁽¹⁰⁾ Methaemoglobinaemia was not reported in these cases. However, methaemoglobinaemia was noted when GTN patches were used in 2 neonates. In both cases, 9 cm² patches were used which contained 18.7 mg GTN.⁽¹⁾</p> <p>Pharmacokinetics Skin permeability will influence how much GTN reaches the plasma when an ointment is applied.⁽³⁾ In a study of 7 infants, (age range from 6 days to 9 months), Guran et al evaluated systemic diffusion of topical GTN ointment on a 3 x 3 cm surface of the arm at a dose of 1 mg. It resulted in blood levels of between 0.03 and 3.36 ng/mL.⁽¹¹⁾ The skin of prematurely born infants has increased permeability compared with term born infants which might lead to greater absorption of topical treatments. Adult data suggest that large inter- and intra-individual variations in plasma concentrations occur with ointment preparations. The shape of the plasma concentration-time curve differs from study to study. While in some studies more or less constant concentrations were found over the period of application, in others an early peak followed by steadily declining concentrations were seen and others found steadily increasing concentrations over 6 hours.⁽³⁾</p>
Practice points	
References	1. Mintoft A, Williams E, Harris C, Kennea N, Greenough A. Methemoglobinemia during the use of glyceryl trinitrate patches in neonates: two case reports. American Journal of Perinatology Reports. 2018;8(04):e227-e9.

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