AUSTRALIAN PRODUCT INFORMATION
NUMIT 5% CREAM (LIDOCAINE (LIGNOCAINE)/PRILOCAINE EUTECTIC MIXTURE)

1 NAME OF THE MEDICINE

Lidocaine (Lignocaine) and Prilocaine

Lidocaine is the new medicine ingredient name for Lignocaine and is mostly used in this product information.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NUMIT contains lidocaine 2.5% w/w (25mg/g) and prilocaine 2.5% w/w (25mg/g).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

NUMIT is a soft, white cream for topical application.

NUMIT is non-sterile.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NUMIT is indicated for topical anaesthesia of the skin prior to: insertion of IV catheters, mechanical cleansing or debridement of leg ulcers, cleaning ulcers, blood sampling, vaccination; superficial surgical procedures, including split skin grafting, minor surgical cosmetic procedures. Topical anaesthesia of genital skin prior to superficial surgical procedures or infiltration anaesthesia.

4.2 DOSE AND METHOD OF ADMINISTRATION

In order to avoid cross-contamination, infection control procedures and principles should be strictly adhered to during application of NUMIT.

Pharmacokinetic data for application longer than 4 hours is not available in children. In adults, there is no benefit in application times longer than 5 hours, as the analgesic effectiveness of the cream dissipates over time.

Use in elderly

No dosage adjustment is require when NUMIT is applied to intact skin in the elderly

Use in premature infants with a gestational age of less than 37 weeks is not recommended (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Unscrew tube cap and peel off security seal. When used on leg ulcers discard the tube with any remaining NUMIT after each occasion that a patient is treated.

A 1 g dose of NUMIT cream is achieved by squeezing NUMIT from the tube into a circular area with diameter of approximately 20 mm (the size of a 2 dollar coin) to a depth of approximately 4 mm. Keep the tube in close contact with the skin until the correct amount has been applied.

A 1 g dose of NUMIT cream can also be achieved by squeezing a length of NUMIT of approximately 3.5 cm from the tube.

Surface/Age	**Procedure**	**Application**
Skin		A thick layer of cream to the skin, under an occlusive dressing. Following application for 1 – 2 hours, the minimum duration of anaesthesia is 2 hours after removal of the dressing.
Adults		Approx. 1.5 g/10 cm^2
	Minor procedures: needle insertion, cosmetic procedures (on small areas) and surgical treatment of localised lesions.	Up to 2g (Approx. half a 5g tube) for a minimum of 1 hour, maximum 5 hours[1)9)]
	Procedures on larger areas of skin e.g. cosmetic procedures such as hair removal or other superficial surgical procedures (in an outpatient setting).	Maximum dose: 60g. Maximum treatment area: 600cm^2 for a minimum of 1 hour, maximum 5 hours[1)]
	Dermal procedures on larger areas in a hospital setting (e.g. split-skin grafting).	Approx. 1.5 - 2 g/10 cm^2 for a minimum of 2 hours, maximum 5 hours [1)]
Children		Approx. 1.0 g/10 cm^2 Application time: approx. 1 hour
Neonates and infants 0 up to 3 months[3)]	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Up to 1.0 g and 10 cm^2 [2)]

	Circumcision	1 g applied to the prepuce
Infants 3 up to 12 months[3)]	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Up to 2.0 g and 20 cm^2 [4)]
Children 1 up to 6 years	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Up to 10.0 g and 100 cm^2 [8)] for a minimum of 1 hour, maximum 4 hours
Children 6 up to 12 years	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Up to 20.0 g and 200 cm^2 [8)] for a minimum of 1 hour, maximum 4 hours

Surface/Age	Procedure	Application
Male genital skin Adults	Prior to injection of local anaesthetics.	Apply a thick layer of NUMIT Cream (1 g/10 cm^2 under an occlusive dressing for 15 minutes.
Female genital skin Adults	Prior to injection of local anaesthetics.[7]	Apply a thick layer of NUMIT Cream (1 - 2 g/10 cm^2) under an occlusive dressing for 60 minutes.
Leg ulcer Adults	Mechanical cleansing /debridement of leg ulcer(s).	Apply a thick layer of the cream, approx. 1 - 2 g/10 cm^2 up to a total of 10 g to the leg ulcer(s).[5] [6] Cover with an occlusive dressing. Application time: at least 30 minutes. Up to 60 minutes may improve the anaesthesia further. Cleansing should start without delay after removal of the cream.

1) After a longer application time the anaesthesia decreases.
2) An application time longer than 1 hour has not been documented.
3) Until further clinical data is available, NUMIT should not be used in infants between 0 - 12 months of age receiving treatment with methaemoglobin-inducing agents.
4) Non clinically significant increase in methaemoglobin levels has been observed after an application time of up to 4 hours on 16cm^2.
5) NUMIT has been used for the treatment of leg ulcers up to 15 times over a period of 1- 2 months with no loss of efficacy or increase in local reactions.
6) The application of a larger dose than 10g has not been studied with regard to plasma levels.
7) On female genital skin, NUMIT alone applied for 60 or 90 min does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.
8) Doses significantly larger than 2 g are applicable to procedures on larger dermal areas.
9) Rates of absorption may be higher for shaved skin compared to unshaved skin due to possible removal of parts of the protective skin barrier during shaving.

4.3 CONTRAINDICATIONS

Hypersensitivity to prilocaine, lidocaine or any local anaesthetics of the amide type.

Hypersensitivity to any of the excipients of NUMIT cream.

Glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Open wounds

NUMIT should not be applied to open wounds other than leg ulcers, due to insufficient data on absorption from these sites.

Atopic dermatitis

Care should be taken when applying NUMIT to skin areas with atopic dermatitis. A shorter application time (15 – 30 minutes) may be sufficient.

Eyes

NUMIT should not be applied to or near to the eyes since it causes corneal irritation. Damage to the eye may also occur from undetected foreign bodies. Special care should be employed to reduce the risk of rubbing the eyes with NUMIT. It is therefore important that the patch or occlusive dressing should be secured against accidental dislocation, especially in young children.

Middle ear

Lidocaine/prilocaine 5% cream is not recommended in any clinical situation in which its penetration into the middle ear is possible. In studies in rodents (guinea pigs) lidocaine/prilocaine 5% cream was found to have an ototoxic effect when instilled directly into the middle ear, however no abnormalities were observed when lidocaine/prilocaine 5% cream was applied to the animals' external auditory canal.

Lidocaine/prilocaine 5% cream caused minor structural damage to the tympanic membrane in rats when applied directly to the membrane. The relevance of these findings to the clinical situation in unknown.

Genital mucosa

Lidocaine/prilocaine 5% cream is presently not recommended for use on genital mucosa. Available data suggest that the anaesthetic efficacy of NUMIT on genital mucosa may be variable.

Vaccination

Lidocaine and prilocaine have bactericidal and antiviral properties in concentrations above 0.5 – 2%. A clinical trial with MMR vaccine administered subcutaneously demonstrated that lidocaine/prilocaine 5% cream does not adversely affect antibody response.

There are no data effects of NUMIT on other live viral vaccines administered subcutaneously. When lidocaine/prilocaine 5% cream is used prior to intradermal BCG vaccination, the results of vaccination should be monitored.

Use in the elderly

No data available.

Paediatric use

Until further clinical data are available, lidocaine/prilocaine 5% cream should not be used in infants between 0 and 12 months of age receiving treatment with methaemoglobin-inducing agents such as sulphonamides (see also OVERDOSE) or in preterm infants with a gestational age less than 37 weeks.

Studies have been unable to demonstrate the efficacy of lidocaine/prilocaine 5% cream for heel lancing in neonates.

Lidocaine/prilocaine 5% cream should not be applied to the genital mucosa of children owing to insufficient data on absorption. However, when used in neonates for circumcision (genital skin), a dose of 1.0 g lidocaine/prilocaine 5% cream on the prepuce has proven to be safe.

In children/neonates younger than 3 months of age, a transient increase in methaemoglobin is commonly observed up to 12 hours after an application of lidocaine/prilocaine 5% cream.

Caution is required in those at risk of methaemoglobinaemia. Repeated applications of lidocaine/prilocaine 5% cream in neonates and infants have not been studied and should be avoided.

Use in premature infants with a gestational age of less than 37 weeks is not recommended.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anti-arrhythmic drugs class III

Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and EG monitoring considered, since cardiac effects may be additive. Specific interaction studies with lidocaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised.

Drugs reducing clearance of lidocaine

Drugs that reduce the clearance of lidocaine (for example, cimetidine or beta blockers) may cause potentially toxic plasma concentrations when lidocaine (e.g. NUMIT) is given in repeated high doses over a long time period. Such interactions should therefore be of no clinical importance following short term treatment with lidocaine (e.g. NUMIT) at recommended doses.

Methaemoglobinaemia-inducing agents

NUMIT may accentuate the formation of methaemoglobin in patients treated with other drugs known to induce methaemoglobinaemia (e.g. sulphonamides).

Other local anaesthetic agents

With large doses of NUMIT, the risk of additional systemic toxicity should be considered in patients receiving other local anaesthetics or agents structurally related to local anaesthetics e.g. Mexiletine.

Drugs reducing clearance of lidocaine

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4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category A

Category A: Drugs which have been taken by a large number of pregnant women and women of child bearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Use in lactation

No information is available on the excretion of lidocaine, prilocaine or their metabolites into breast milk following the administration of NUMIT.

Following parenteral administration, lidocaine is excreted into breast milk. Because of low maternal systemic absorption following application of recommended doses of NUMIT, the amount of lidocaine and prilocaine that may be ingested by the breast-fed infant would be extremely small.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Intact skin

Common events (≥1% and <10%)	*Skin:* Transient local reactions at the application site such as, paleness, erythema (redness) and oedema.
Uncommon events (≥0.1% and <1%)	Skin sensations (an initial mild burning sensation, itch or warmth at the application site).
Rare events (<0.1%)	*General:* In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock). Rare cases of discrete local lesions at the application site, described a purpuric or petechial, have been reported, especially after longer application times in children with atopic dermatitis or mollusca contagiosa. Increased methaemoglobin level. Methaemoglobinaemia and/or cyanosis. Corneal irritation after accidental eye exposure.

Leg ulcer

Common events (≥1% and <10%)	*Skin:* Transient local reactions at the application site such as, paleness, erythema (redness) and oedema. Skin sensations (an initial mild burning sensation, itch or warmth at the application site).
Uncommon events (≥0.1% and <1%)	*Skin:* Skin irritation (at the application site).
Rare events (<0.1%)	*General:* In rare cases, local anaesthetic preparations have been associated with allergic reactions (in most sever instances anaphylactic shock).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important.

It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at

www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare cases of methaemoglobinaemia have been reported.

Prilocaine in high doses may cause an increase in the methaemoglobin level particularly in conjunction with methaemoglobinaemia-inducing agents (e.g. sulphonamides). Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylene blue.

In the unlikely event of systemic toxicity following epidermal application of NUMIT, the signs and symptoms anticipated would be similar in nature to those observed following other routes of administration of local anaesthetics. Owing to slow absorption into the circulation from intact skin, a patient with signs of toxicity should be observed for several hours after treatment.

Systemic toxicity to amide type local anaesthetics is initially manifested as CNS excitation and may result in a slow onset of nervousness, dizziness, blurred vision and tremors followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest.

Toxic cardiovascular reactions to local anaesthetics are usually depressant in nature, may occur rapidly and with little warning and can lead to peripheral vasodilation, hypotension, myocardial depression, bradycardia and possible cardiac arrest. Sever neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and administration of anticonvulsive drugs.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lidocaine and prilocaine are both amide-type local anaesthetic agents. Both agents stabilise the neuronal membrane preventing the initiation and conduction of nerve impulses thereby effecting local anaesthetic action.

NUMIT provides dermal anaesthesia. The depth and quality of anaesthesia depends upon the application time and the applied dose.

Local anaesthesia with NUMIT is achieved after 60 minutes application. NUMIT cream should

be applied under an occlusive, impermeable dressing. Following the application of NUMIT cream for 1 - 2 hours, the duration of anaesthesia is at least 2 hours after removal of the occlusive dressing.

Reliable anaesthesia for the cleansing of leg ulcers is achieved after an application time of 30 minutes in most patients. An application time of 60 minutes may improve the anaesthesia. The cleansing procedure should start within 10 minutes of removal of the cream. There is no clinical data regarding cleaning started after 10 minutes of cream removal.

A reduced number of cleansing sessions are required to achieve a clean ulcer when NUMIT is used compared to a placebo.

No negative effects on ulcer healing or bacterial flora have been observed.

NUMIT may cause transient local peripheral vasoconstriction or vasodilation, observed as transient paleness or redness, at the treated area.

Clinical trials

In clinical trials with lidocaine/prilocaine 5% cream, venepuncture or venous catheterisation was pain-free in 50 - 59% patients, slightly painful in 35 - 40% and painful in 3 - 6%. Anaesthesia may be less for skin structures below the deep fascia.

In clinical trials in adults assessing pain associated with intramuscular influenza vaccination and intramuscular and subcutaneous injections of saline solution, lidocaine/prilocaine 5% cream significantly reduced injection pain relative to placebo.

In clinical trials in infants and children assessing pain associated with subcutaneous and intramuscular vaccination, lidocaine/prilocaine 5% cream significantly reduced injection pain behaviours and pain scores relative to placebo.

In clinical trials assessing the effects of lidocaine/prilocaine 5% cream on intramuscular and subcutaneous, live and non-live vaccines, it was demonstrated that lidocaine/prilocaine 5% cream does not adversely affect antibody response. A clinical trial assessing the effect of lidocaine/prilocaine 5% cream application prior to intracutaneous BCG injection demonstrated that lidocaine/prilocaine 5% cream did not affect the immunisation response.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Systemic absorption and anaesthetic efficacy of lidocaine and prilocaine is dependent upon the characteristics of the leg ulcer, the applied dose, total application area, application time, thickness of the skin (which varies between different areas of the body), other conditions such as skin diseases, and shaving.

Intact skin

The extent of systemic absorption was approximately 10% following application to the face (10 g/100 cm^2 for 2 hours). Maximum plasma levels (mean 0.16 and 0.06 µg/mL of lidocaine and prilocaine respectively) were reached after approximately 2.5 hours.

After application to the thigh in adults (60 g cream/400 cm^2 for 3 hours) the extent of absorption was approximately 5% of lidocaine and prilocaine. Maximum plasma concentrations (mean 0.12 and 0.07 µg/mL) were reached approximately 2 - 6 hours after the application.

In adults, a thick layer of lidocaine/prilocaine 5% cream (corresponding to approximately 150 g) has been applied to intact skin areas of up to 1,300 cm^2 for application times of up to 7 hours. The highest individual plasma levels observed to date were 1.1 µg/mL lidocaine and 0.2 µg/mL prilocaine. These levels were below those at which symptoms of toxicity would be expected to occur (5 - 10 µg/mL either agent; see also ADVERSE EFFECTS).

Leg ulcers

Following a single application for 30 minutes of 5 to 10 g of lidocaine/prilocaine 5% cream to leg ulcers, the maximum plasma levels of lidocaine (range 0.05 - 0.25 µg/mL, one individual value of 0.84 µg/mL) and of prilocaine (0.02 - 0.08 µg/mL) were reached within 1 - 2.5 hours.

After an application time of 24 hours the maximum plasma levels of lidocaine (0.19 - 0.71 µg/ml) and of prilocaine (0.06 - 0.28 µg/ml) were usually reached within 2 - 4 hours.

Following repeated applications for 30 - 60 minutes of 2 - 10 g lidocaine/prilocaine 5% cream 3 - 7 times a week, for up to 15 doses, during a period of one month, there was no apparent accumulation in plasma of lidocaine and its metabolites monoglycinexylidide and 2,6-xylidine or of prilocaine and its metabolite ortho-toluidine. The maximum observed plasma levels for lidocaine, monoglycinexylidide and 2,6-xylidine were 0.41, 0.03 and 0.01 µg/mL respectively. The maximum observed plasma levels for prilocaine and ortho-toluidine were 0.08 µg/mL and 0.01 µg/mL respectively.

Children

Following the application of 1.0 g of lidocaine/prilocaine 5% cream in neonates below 3 months of age, to approximately 10 cm^2 for one hour, the maximum plasma concentrations of lidocaine and prilocaine were 0.135 µg/mL and 0.107 µg/mL respectively.

Following the application of 2.0 g of lidocaine/prilocaine 5% cream in infants between 3 and 12 months of age, to approximately 16 cm^2 for four hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.155 µg/mL and 0.131 µg/mL respectively.

Following the application of 10.0 g of lidocaine/prilocaine 5% cream in children between 2 and 3 years of age, to approximately 100 cm^2 for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.315 µg/mL and 0.215 µg/mL respectively.

Following the application of 10.0 – 16.0 g of lidocaine/prilocaine 5% cream in children between 6 and 8 years of age, to approximately 100 - 160 cm^2 for two hours, the maximum plasma concentrations of lidocaine and prilocaine were 0.299 µg/mL and 0.110 µg/mL respectively.

Pharmacokinetic data for application longer than 4 hours is not available in children. In adults, there is no benefit in application times longer than 5 hours, as the analgesic effectiveness of the cream dissipates over time.

5.3 PRE-CLINICAL SAFETY DATA

Genotoxicity

Genotoxicity tests with lidocaine are inconclusive. In genotoxicity studies, a metabolite of lidocaine, 2,6-xylidine, showed evidence of activity in some tests but not in other tests.

Carcinogenicity

A metabolite of lidocaine, 2,6-xylidine has been shown to have carcinogenic potential (nasal and subcutaneous tumours) in preclinical toxicological studies evaluating chronic

exposure. A metabolite of prilocaine, o-toluidine, has also shown evidence of mutagenic activity in some genotoxicity tests but not others. o-toluidine has also been shown to have carcinogenic potential (e.g. renal, bladder, spleen, subcutaneous tumours) in preclinical toxicological studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each gram of NUMIT Cream contains ethoxylated hydrogenated castor oil, purified water, carbomer 934P and sodium hydroxide as excipients.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

5g laminate tube*, 10g laminate tube and 30g laminate tube, packed into a carton.

* Not currently marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

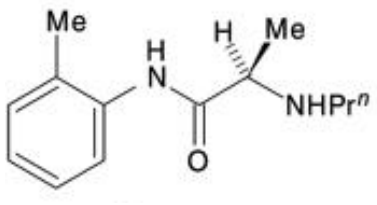
6.7 PHYSICOCHEMICAL PROPERTIES

NUMIT cream is a 1:1 oil/water emulsion of an eutectic mixture of lidocaine and prilocaine.

When lidocaine and prilocaine are mixed in equal amount, the solid pure bases of lidocaine and prilocaine form an oil at temperatures above 16°C (i.e. a eutectic mixture). By avoiding the need for non-aqueous solvent, higher concentrations of local anaesthetic in the cream can be achieved and maintained during application.

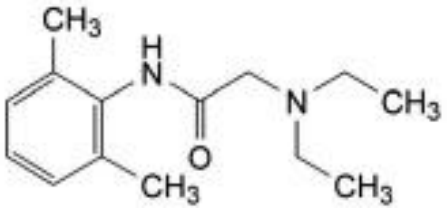
Chemical structure

Lidocaine



$C_{14}H_{22}N_2O$ molecular weight 234.3

Prilocaine



$C_{13}H_{20}N_2O$ molecular weight 220.3

CAS numbers

137-58-6, 721-50-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 (Pharmacy Medicine)

8 SPONSOR

Ego Pharmaceuticals Pty Ltd.
21-31 Malcolm Road, Braeside, Victoria 3195
AUSTRALIA (ACN 005 142 361)

9 DATE OF FIRST APPROVAL

This product information was approved by the Therapeutic Goods Administration in December 2015.

10 DATE OF REVISION

12 July 2019

10.1 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat