

AUSTRALIAN PI – LMX4® (LIDOCAINE (LIGNOCAINE) 4% W/W) TOPICAL ANAESTHETIC CREAM

1 NAME OF THE MEDICINE

LMX4®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of LMX4 is lidocaine 40mg.

Chemical name: 2-diethylaminoaceto-2',6'-xylidide

Molecular formula: C₁₄H₂₂N₂O

Molecular weight: 234.3

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

3 PHARMACEUTICAL FORM

Topical cream. A white to off-white yellowish cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Topical anaesthesia of intact skin prior to superficial skin procedures, including insertion of IV catheters and blood sampling.

4.2 DOSE AND METHOD OF ADMINISTRATION

For cutaneous use only.

Adults, the elderly and children 1 year of age and older:

Apply 1g to 2.5g of cream onto the skin to cover a 2.5cm x 2.5cm area where venous cannulation or venipuncture will occur.

Full term neonates and infants up to 1 year of age:

Apply up to 1g of cream onto the skin where venous cannulation or venipuncture will occur. Not more than 1g of cream should be applied to infants below the age of 1 year.

Adults, the elderly and children 12 years of age and older:

Maximum application time should not exceed 5 hours.

Full term neonates, infants and children under 12 years of age:

Do not leave on skin for longer than 1 hour.

There is insufficient data for neonates under full term age and therefore LMX4® is not recommended in this age group.

1g of cream equates to approximately 5cm of cream squeezed from the 5g tube or 3.5cm from the 30g tube.

The cream should remain undisturbed and the area can be covered with an occlusive dressing to prevent disturbance or interference by the patient or other external factors. Adequate anaesthesia should be obtained after 30 minutes at which time the LMX4® cream should be

removed using a clean gauze swab and the site for venous cannulation or venipuncture prepared in the usual manner. The procedure should be initiated approximately 5 minutes after the cream has been removed.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance, or any of the amide-type local anaesthetics, or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For external use only.

Avoid contact with eyes. Lidocaine coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of lidocaine in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Do not apply to irritated skin or if excessive irritation develops. If condition worsens, or if symptoms persist unaltered for more than seven days or clear up and occur again within only a few days, discontinue use of this product and consult a doctor. Do not use in large quantities, particularly over raw or blistered areas.

LMX4® should not be applied to wounds, mucous membranes or in areas of atopic dermatitis.

Application of lidocaine to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine resulting in serious adverse effects.

Repeated doses of lidocaine may increase blood levels of lidocaine. Lidocaine should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine including acutely ill, debilitated, or elderly patients.

Lidocaine should not be used in any clinical situation in which its penetration or migration beyond the tympanic membrane into the middle ear is possible. Studies in laboratory animals (guinea pigs) have shown that lidocaine has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to lidocaine in the external auditory canal only showed no abnormality.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine; however, lidocaine should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anaesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine. Patients with severe cardiac or renal impairment are also at greater risk.

When lidocaine is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Lidocaine has bactericidal and antiviral properties in concentrations above 0.5%. For this reason, the results of intra-cutaneous injections of live vaccines (such as BCG vaccination) should be monitored.

Paediatric use

Do not use in preterm infants.

Full term infants and children should be closely observed during and after use of topical anaesthetics, as they are at greater risk than adults for adverse events.

When using LMX4® in younger children, especially infants under the age of 12 months, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see Dosage and Administration).

Use in the elderly

Greater sensitivity of some older individuals cannot be ruled out. There are insufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine between geriatric and non-geriatric patients following application of LMX4®.

During IV studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lidocaine should be used with caution in patients receiving Class III and Ib anti-arrhythmic drugs (such as Amiodorone, tocainide and mexiletine) since the toxic effects are additive and generally synergistic.

The risk of additional systemic toxicity should be considered when large doses of LMX4® are applied to patients already using other local anaesthetics.

Drugs that reduce the clearance of lidocaine – for instance, cimetidine or beta blockers - may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long time period. Such interactions should not be of clinical importance following short term treatment of LMX4® at recommended doses.

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy – Pregnancy Category A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Lidocaine should be used during pregnancy only if clearly needed.

Lidocaine is not contraindicated in labour and delivery. Should LMX4® be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Lidocaine crosses the placental barrier.

Use in lactation.

Lidocaine is excreted in human milk. Therefore, caution should be exercised when LMX4® is administered to a nursing mother since the milk: plasma ratio of lidocaine is 0.4.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None known.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Common side effects (>1/100) can include irritation, redness, itching, or rash.

In rare cases local anaesthetics have been associated with allergic reactions including anaphylactic shock.

To the best of our knowledge there have been no reports of methaemoglobinaemia directly associated with LMX4®.

Corneal irritation after accidental eye exposure.

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

In an event of an overdose contact the Poisons Information Centre (telephone 13 11 26 in Australia and 0800 764 766 in New Zealand). Overdose with LMX4® cream is unlikely, but signs of systemic toxicity would be consistent with those of lidocaine.

An indication of systemic toxicity may include blurred vision, dizziness or drowsiness, difficulty breathing, trembling, chest pain, or irregular heartbeat.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Anaesthetics for topical use. Lidocaine is an amide-type local anaesthetic agent which stabilises neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anaesthetic action.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lidocaine applied to intact skin provides dermal analgesia by a release of lidocaine from the cream into the epidermal and dermal layers of the skin, and by the accumulation of lidocaine in the vicinity of pain receptors and nerve endings. The onset, depth and duration of dermal analgesia provided by lidocaine depend primarily on the duration of application. In clinical trials LMX4® has demonstrated an onset of action after an application of 30 minutes.

Clinical trials

In clinical trials with children, venipuncture or venous catheterisation was achieved within 30 minutes of application with lower mean pain scores, higher IV cannulation success rate, less pain, shorter total procedure time and minor dermal changes.

Clinical Trial Data in Children

A pivotal randomised, double-blind, placebo-controlled trial compared the safety and efficacy of LMX4® Lidocaine 4% w/w Cream to placebo prior to venous cannulation procedures in children (Taddio, 2005). One gram of the proposed product or placebo cream (the base cream without the active) with occlusion was applied for 30 minutes to approximately 2.5cm² of each hand.

The study report notes that this corresponds to approximately 0.16g/cm² per hand, which complies with the proposed usage of the product. Both hands were treated to give the nurse the choice of the best hand for cannulation.

Patient accountability

A total of 151 patients aged between 1 month and 17 years old were randomised into the trial, but 9 patients dropped out before cannulation took place. For 5 of these patients their clinical condition had improved and IV cannulation was no longer considered necessary. Of the 142 patients that completed the study, 69 received LMX4®, and 73 received placebo. The average age of the LMX4® patients was 6.7 years, with equal numbers of male and female subjects. The average weight of the LMX4® subjects was 29.0kg.

The primary outcome variable of this study was the cannulation success rate. The procedure duration and the assessment of pain were secondary outcome variables.

Cannulation on the first attempt was significantly higher among children who received LMX4® compared with those who received placebo (74% vs 55% respectively). Additionally, the total procedure time was also shorter for those patients receiving LMX4® compared to those with placebo (6.7 minutes and 8.7 minutes respectively).

Pain was measured using the Faces Pain Scale Revised (FPS-R), with scores ranging from zero (no pain) to five (worst possible pain). The scores were evaluated by three different raters:

1. Pain assessment by the child – this was done only in children ≥5 years of age.
2. Pain assessment by the parents – this was planned for all patients, but the assessment was missing for 4 patients on LMX4® Lidocaine 4% w/w Cream and 6 patients on placebo.
3. Pain assessment by research assistant – assessments were available for all patients.

Pain scores were measured during the first cannulation attempt for each child. Baseline measurements (pain without provocation) were taken 5 minutes before the cream was removed). The primary analysis of pain was pain during cannulation minus the baseline score. The scores from the three different raters were given equal priority.

Mean (sd) FPS-R scores

	Lidocaine	Placebo	p- Value
Child	N=37	N=30	
Baseline	1.3 (1.2)	1.6(1.6)	p=0.29
At Cannulation	2.6 (1.5)	3.9 (1.5)	p=0.001
Change from baseline	1.3 (1.3)	2.3(1.6)	P=0.01
Parents	N=65	N=67	
Baseline	1.2 (1.2)	1.3(1.2)	p=0.696
At Cannulation	2.7 (1.5)	3.6 (1.3)	P<0.0001
Change from baseline	1.5 (1.3)	2.3 (1.2)	p<0.0001
Research Assistant	N=69	N=73	
Baseline	1.1 (1.1)	1.1(1.2)	p=0.912
At cannulation	2.4 (1.4)	3.4 (1.3)	p=<0.0001
Change from baseline	1.3 (1.0)	2.3 (1.2)	p=0.001

The results are consistent across all three groups of pain raters, with the treatment groups being balanced at baseline and clear differences of around one point being evident during cannulation. The differences are similar whether raw scores or change from baseline is considered. The p-values are extreme for the parent and research assistant rating scores. The less extreme values for the child's own ratings are most likely due to the smaller patient numbers, as the point estimates for the difference are very similar.

This trial provides evidence that use of LMX4® Lidocaine 4% w/w Cream for 30 minutes under occlusion reduces pain during IV cannulation.

The authors also reported near-identical incidence levels of transdermal reactions for both the LMX4® and placebo groups (16 vs 17 incidences respectively), and concluded that the risk: benefit ratio for using LMX4® in these age groups was therefore favourable.

5.2 PHARMACOKINETIC PROPERTIES

It has been reported that the amount of lidocaine systemically absorbed is directly related to both the duration of application and to the area over which it is applied. It is not known if it is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The end metabolite, 2,6-xylylidine, has unknown pharmacologic activity but is carcinogenic in rats (Parker *et al* 1996). Following IV administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of administered lidocaine serum concentrations, respectively. The half-life of lidocaine elimination from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, \pm 24 SD, n=13). This half-life may be increased in cardiac or hepatic dysfunction. More than 98% of an absorbed dose of can be recovered in the urine as metabolites or parent drug. The systemic clearance is 10 to 20 mL/min/kg (mean 13, \pm 3 SD, n=13) (Benowitz and Meister, 1978).

When applied topically to intact skin, the absorption of lidocaine is very low. Increased absorption is therefore to be expected when applied to mucosa or previously damaged skin. LMX 4® should not be applied to mucosa or previously damaged skin.

The maximum plasma level of active ingredient was very low (0.3 µg/ml or less) in a study investigating the application of LMX4® in 120 children aged 5-7 years, well below the therapeutic (1.2µg/ml) and toxic (>5µg/ml) plasma level [Eichenfield, 2002].

Another study evaluated the potential absorption and clinical toxicity of either 30g or 60g of occluded LMX4® Lidocaine Cream (removed after 60 minutes) in healthy adult volunteers (Nestor, 2006). Blood levels of lidocaine and monoethylglycinexylidide (MEGX) were measured at 1, 2, 6 and 24 hours post application. Additionally the volunteers were assessed for any clinical signs of lidocaine toxicity. All blood samples showed less than 0.5µg/ml of serum lidocaine and MEGX metabolite. Patients reported no systemic effects and did not show any clinical signs of lidocaine toxicity. This study demonstrates the safety of topically applied 4% Lidocaine Cream, when up to 60g of product is applied under occlusion to an area of up to 600cm² in healthy subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The mutagenic potential of lidocaine hydrochloride has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by mouse micronucleus test *in vivo*. There was no indication in these tests of any mutagenic effects (Benowitz 1978, Nelson 1978). The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results (Parker 1996). The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatic exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/mL). No evidence of genotoxicity induced by 2,6-xylidine was found in the *in vivo* assays measuring unscheduled DNA synthesis in rat hepatocytes (Mirsalis et al 1989).

Carcinogenicity

No chromosome damage by 2,6-xylidine was observed in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts from mice (Kerlaan et al 1985). However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions *in vivo* (Short et al, 1989).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl alcohol, carbomer 940, cholesterol, lecithin – hydrogenated, polysorbate 80, propylene glycol, triethanolamine, dl-alpha tocopheryl acetate, water-purified.

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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LMX4® is a white to off-white yellowish cream packaged in aluminium tubes fitted with a polypropylene cap in pack sizes of 5g, 15g and 30g. The tubes are packed in individual cartons in the sizes below. All tubes and cartons are branded with the LMX4® registered trademark.

The following packaging options are approved but not all of these packaging options may be marketed:

AUST R 126095:

- 1) A carton containing one 5g tube.
- 2) A carton containing five 5g tubes.
- 3) A carton containing one 15g tube.
- 4) A carton containing one 30g tube.

AUST R 208815:

- 5) A carton containing five 5g tubes with 10 occlusive dressings.

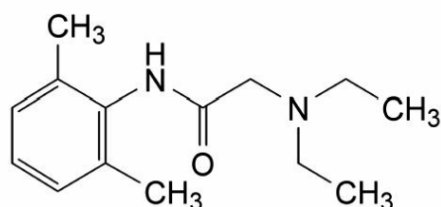
Some packs may not be currently marketed.

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

Chemical structure



CAS number

137-58-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 2 (Pharmacy Medicine)

8 SPONSOR

Dermocosmetica

Unit 8, 14-16 Lens Street,

Coburg North, VIC, 3058, Australia

9 DATE OF FIRST APPROVAL

23 July 2013

10 DATE OF REVISION

03 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor change